



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 138

## **Medication Therapy Management Interventions in Outpatient Settings**



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## **Medication Therapy Management Interventions in Outpatient Settings**

**Prepared for:**

Agency for Healthcare Research and Quality  
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540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

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**Prepared by:**

RTI International–University of North Carolina Evidence-based Practice Center  
Research Triangle Park, NC

**Investigators:**

Meera Viswanathan, Ph.D.  
Leila C. Kahwati, M.D., M.P.H.  
Carol E. Golin, M.D.  
Susan Blalock, M.P.H., Ph.D.  
Emmanuel Coker-Schwimmer, M.P.H.  
Rachael Posey, M.S.L.S.  
Kathleen N. Lohr, Ph.D., M.Phil., M.A.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

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We welcome comments on this systematic review. They may be sent by mail to Christine Chang, M.D., M.P.H., at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Richard G. Kronick, Ph.D.  
Director  
Agency for Healthcare Research and Quality

David Meyers, M.D.  
Acting Director  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director  
EPC Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Carmen Y. Kelly, Pharm.D., M.P.H., R.Ph.  
Task Order Officer  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

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## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Jamie C. Barner, Ph.D.  
College of Pharmacy  
The University of Texas at Austin  
Austin, TX

Brian Isetts, Ph.D., B.C.P.S., FAPhA  
College of Pharmacy  
University of Minnesota  
Minneapolis, MN

Steve Handler, M.D., Ph.D.  
Department of Biomedical Informatics and  
Division of Geriatric Medicine  
University of Pittsburgh  
Pittsburgh, PA

Michelle Ketcham, Pharm.D., M.B.A.  
Medicare Drug Benefit Group  
Centers for Medicare & Medicaid Services  
Baltimore, MD

Joseph Hill, M.A.  
American Society of Health-System  
Pharmacists  
Bethesda, MD

Julie Kuhle, R.Ph.  
Senior Director, Performance Measurement  
Pharmacy Quality Alliance, Inc.  
Springfield, VA

James Owen, Pharm.D., B.C.P.S.  
Practice & Science Affairs  
American Pharmacists Association  
Washington, DC

## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Jamie C. Barner, Ph.D.  
College of Pharmacy  
The University of Texas at Austin  
Austin, TX

Steve Handler, M.D., Ph.D.  
Department of Biomedical Informatics and Division of Geriatric Medicine  
University of Pittsburgh  
Pittsburgh, PA

Joseph Hill, M.A.  
American Society of Health-System Pharmacists  
Bethesda, MD

Brian Isetts, Ph.D., B.C.P.S., FAPhA  
College of Pharmacy  
University of Minnesota  
Minneapolis, MN

Michelle Ketcham, Pharm.D., M.B.A.  
Medicare Drug Benefit Group  
Centers for Medicare & Medicaid Services  
Baltimore, MD

Julie Kuhle, R.Ph.  
Senior Director, Performance Measurement  
Pharmacy Quality Alliance, Inc.  
Springfield, VA

James Owen, Pharm.D., B.C.P.S.  
Practice & Science Affairs  
American Pharmacists Association  
Washington, DC

## Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Rowena Dolor, M.D., M.H.S.  
Primary Care Research Consortium  
Duke Clinical Research Institute  
Duke University  
Durham, NC

William Doucette, Ph.D.  
College of Pharmacy  
University of Iowa  
Iowa City, IA

C. Bernie Good, M.D., M.P.H.  
Center for Health Equity Research and Promotion  
VA Pittsburgh Healthcare System  
Pittsburgh, PA

Steve Handler, M.D., Ph.D.  
Department of Biomedical Informatics  
and Division of Geriatric Medicine  
University of Pittsburgh  
Pittsburgh, PA

Brian Isetts, Ph.D., B.C.P.S., FAPhA  
College of Pharmacy  
University of Minnesota  
Minneapolis, MN

Julie Kuhle, R.Ph.  
Senior Director, Performance Measurement  
Pharmacy Quality Alliance, Inc.  
Springfield, VA



Andrew Masica, M.D., M.S.C.I.  
Baylor Scott & White Health  
Dallas, TX

James Owen, Pharm.D., B.C.P.S.  
Practice & Science Affairs  
American Pharmacists Association  
Washington, DC

Alan Zilich, Pharm.D.  
Research Scientist, Roudebush VA Medical Center, Center of Health Information and  
Communication  
Indianapolis, IN  
Associate Professor, Purdue University College of Pharmacy  
West Lafayette, IN

# Medication Therapy Management Interventions in Outpatient Settings

## Structured Abstract

**Objectives.** To describe intervention components and implementation features (Key Question [KQ]1) for outpatient medication therapy management (MTM) interventions with comprehensive medication review, followup, education, and care coordination; assess the effectiveness of these MTM interventions on intermediate, patient-centered, or resource utilization outcomes (KQ 2); identify intervention features (KQ 3) and patient characteristics (KQ 4) that moderate the effect of an intervention on outcomes; and assess harms associated with interventions (KQ 5).

**Data sources.** MEDLINE<sup>®</sup>, Cochrane Library, International Pharmaceutical Abstracts, gray literature, additional studies from reference lists and technical experts.

**Review methods.** Two trained reviewers selected, extracted data from, and rated the risk of bias of relevant trials and cohort studies. We used random-effects models to estimate pooled effects for outcomes with three or more similar studies with a low or medium risk of bias. For other outcomes, we synthesized the data qualitatively.

**Results.** We included 44 eligible studies (21 randomized controlled trials, 4 controlled clinical trials, and 19 cohort studies) reported in 61 articles, described in detail in the report (KQ 1). Evidence was insufficient on the effect of outpatient MTM interventions on most outcomes (KQ 2). In a few instances, described below, the evidence led us to conclude benefit or lack of benefit. Specifically, we found evidence that MTM results in improvement when compared with usual care for some measures of medication adherence and appropriateness; medication dosing; health plan expenditures on medication costs; and, for patients with diabetes, the proportion hospitalized and costs of hospitalization. Similarly, we conclude, based on a low strength of evidence, that MTM confers no benefit for patient satisfaction and most measures of health-related quality of life.

We found evidence on five intervention components and intervention features (KQ 3). One study provided information on each feature and yielded insufficient evidence for most outcomes, with the following two exceptions. An MTM program with pharmacist access to brief clinical summaries from the medical record reduces the mean number of adverse drug events when compared with a basic MTM program without such access (low strength of evidence). Community pharmacists increase the generic dispensing ratio more than call-center-based pharmacists (low strength of evidence). We found no relevant studies on patient characteristics moderating the effect of MTM interventions (KQ 4). Similarly, the evidence on harms associated with MTM was limited to one study on inconvenience and was rated as insufficient (KQ 5).

**Conclusions.** The evidence base offers low evidence of benefit for a limited number of intermediate and health utilization outcomes. We graded the evidence as insufficient for most other outcomes because of inconsistency in direction, magnitude, and precision, rather than lack of evidence. Wide variations in populations and interventions, both within and across studies,

likely explain these inconsistencies. Given the widespread implementation of MTM and urgent need for actionable information, optimal investments in new research require a process of research prioritization in which the value of information from each proposed study is carefully considered. Studies designed to identify causal relationships between MTM interventions and their outcomes require adequate controls for confounding but may offer limited information on the factors that explain program success or failure. Studies designed to explore the reasons for program success or failure using qualitative or single-arm designs may offer hypotheses-generating rather than hypotheses-confirming insights on MTM effectiveness. New research, regardless of specific focus, will likely continue to find inconsistent results until underlying sources of heterogeneity are accounted for.

# Contents

<b>Executive Summary</b> .....	ES-1
<b>Introduction</b> .....	1
Context.....	1
Populations.....	2
Interventions and Comparators .....	3
Outcomes .....	5
Settings.....	5
Timing.....	6
Contextual Factors .....	6
Scope and Key Questions .....	7
Scope of the Review .....	7
Relevance of Research Question to Clinical Decisionmaking or Policymaking .....	7
Key Questions .....	7
Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) .....	9
Organization of the Report.....	12
<b>Methods</b> .....	13
Topic Refinement and Review Protocol .....	13
Literature Search and Identification Strategy .....	13
Search Strategy .....	13
Inclusion/Exclusion Criteria .....	14
Study Selection .....	15
Data Extraction .....	15
Assessment of Risk of Bias of Individual Studies .....	17
Data Synthesis.....	17
Grading Strength of Evidence for Individual Comparisons and Outcomes .....	18
Assessing Applicability .....	19
Peer Review and Public Commentary .....	19
<b>Results</b> .....	20
Introduction.....	20
Results of Literature Searches .....	20
Key Question 1: Components and Implementation Features of MTM Interventions .....	22
Overall Descriptors of Study Interventions .....	23
Study-Level Descriptors of Interventions .....	25
Key Question 2: Effect of Medication Therapy Management Interventions on Intermediate, Patient-Centered, and Resource Utilization Outcomes .....	27
Key Points: Intermediate Outcomes .....	27
Detailed Synthesis: Intermediate Outcomes .....	28
Key Points: Patient-Centered Outcomes.....	58
Detailed Synthesis: Patient-Centered Outcomes .....	58
Resource Utilization.....	76
Detailed Synthesis: Resource Utilization.....	77

Key Question 3: Outcomes of Medication Therapy Management by Intervention	
Features .....	114
Key Points .....	114
Detailed Synthesis: Intervention Features .....	114
Key Question 4. Outcomes of MTM by Patient Characteristics .....	117
Key Question 5. Harms of Medication Therapy Management Interventions .....	117
Key Points .....	117
Detailed Synthesis: Inconvenience .....	117
<b>Discussion</b> .....	118
Key Findings and Strength of Evidence .....	118
KQ 1: Intervention Components and Implementation Features .....	118
KQ 2: Overall Effectiveness .....	118
KQ 3: Effectiveness of MTM by Intervention Features .....	125
KQ 4: Effectiveness of MTM by Patient Characteristics .....	126
KQ 5: Harms of MTM Interventions .....	126
Findings in Relation to What Is Already Known.....	126
Applicability of the Findings .....	127
Implications for Clinical Practice and Policymakers.....	128
Limitations of the Comparative Effectiveness Review Process .....	129
Limitations of the Evidence .....	131
Research Gaps.....	131
Conclusions.....	133
<b>References</b> .....	134
<b>Tables</b>	
Table A. Populations, interventions, comparators, outcomes, timing, and settings .....	ES-5
Table B. Definitions of the grades of overall strength of evidence .....	ES-12
Table C. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions .....	ES-15
Table D. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions.....	ES-17
Table E. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions.....	ES-19
Table 1. MTM services .....	2
Table 2. Populations, interventions, comparators, outcomes, timing, and settings .....	9
Table 3. Literature search terms for medication therapy management studies.....	14
Table 4. Inclusion/exclusion criteria for medication therapy management studies.....	16
Table 5. Definitions of the grades of overall strength of evidence .....	19
Table 6. Characteristics of included studies .....	22
Table 7. Characteristics of medication therapy management interventions .....	23
Table 8. Characteristics of medication therapy management studies by type of patient population (broad focus or narrow focus on conditions or diagnoses).....	24
Table 9. Anticoagulation: Strength of evidence .....	28
Table 10. Hemoglobin A1c: Summary of results .....	29
Table 11. Hemoglobin A1c: Strength of evidence.....	30

Table 12. LDL cholesterol: Summary of results.....	31
Table 13. LDL cholesterol: Strength of evidence.....	33
Table 14. Blood pressure: Summary of results.....	34
Table 15. Improvement in blood pressure: Strength of evidence.....	37
Table 16. Drug therapy problems identified: Summary of results.....	38
Table 17. Drug therapy problems identified: Strength of evidence.....	38
Table 18. Total number of drug therapy problems resolved: Summary of results.....	39
Table 19. Specific drug therapy problems resolved: Summary of results.....	40
Table 20. Drug therapy problems resolved: Strength of evidence.....	41
Table 21. Medication adherence: Summary of results grouped by type of adherence outcome.....	42
Table 22. Adherence outcome Type 1—proportion of patients adherent based on a threshold of percentage of pills taken: Strength of evidence.....	50
Table 23. Adherence outcome Type 2—absolute measure of adherence as percentage of prescribed doses taken: Strength of evidence.....	51
Table 24. Adherence outcome Type 3—self-reported scales: Strength of evidence.....	52
Table 25. Adherence outcome miscellaneous: Strength of evidence.....	52
Table 26. Medication appropriateness scales: Summary of results.....	53
Table 27. Medication appropriateness for individual medications: Summary of results.....	55
Table 28. Medication appropriateness scales: Strength of evidence.....	57
Table 29. Medication appropriateness for individual medications: Strength of evidence.....	57
Table 30. Medication dosing: Strength of evidence.....	58
Table 31. Adverse events: Summary of results.....	59
Table 32. Adverse drug events: Strength of evidence.....	61
Table 33. Cognitive, affective, and physical function: Summary of findings.....	62
Table 34. Cognitive and physical function: Strength of evidence.....	63
Table 35. Affective function: Strength of evidence.....	63
Table 36. All-cause mortality: Summary of results.....	64
Table 37. All-cause mortality: Strength of evidence.....	64
Table 38. Gastrointestinal bleeding events: Strength of evidence.....	65
Table 39. Scores on SF-36 measures: Summary of effects from meta-analyses.....	65
Table 40. SF-36: Strength of evidence.....	68
Table 41. Condition-specific quality of life: Summary of results.....	70
Table 42. Condition-specific quality of life: Strength of evidence.....	70
Table 43. Patient satisfaction: Summary of results.....	71
Table 44. Patient satisfaction: Strength of evidence.....	76
Table 45. Use of generic medications: Summary of results.....	78
Table 46. Use of generics for MTM versus usual care: Strength of evidence.....	79
Table 47. Measures used in studies of costs of medications.....	80
Table 48. Patient copayments: Summary of results.....	83
Table 49. Patient copayments: Strength of evidence.....	84
Table 50. Total expenditures on medications by insurers: Summary of results.....	85
Table 51. Health plan expenditures: Strength of evidence.....	88
Table 52. Total outlays on medications: Summary of results.....	88
Table 53. Total outlays on medications: Strength of evidence.....	91
Table 54. Medication and other costs: Summary of results.....	91

Table 55. Medication and other costs: Strength of evidence .....	93
Table 56. Number of outpatient visits: Summary of results .....	94
Table 57. Number of outpatient visits: Strength of evidence .....	96
Table 58. Costs of outpatient visits: Summary of results .....	96
Table 59. Costs of outpatient resource utilization: Strength of evidence .....	98
Table 60. Number of laboratory and diagnostic tests: Summary of results .....	99
Table 61. Number of laboratory and diagnostic tests: Strength of evidence .....	99
Table 62. Costs of laboratory tests: Summary of results .....	100
Table 63. Costs of laboratory tests: Strength of evidence .....	100
Table 64. Emergency department visits: Summary of results .....	101
Table 65. Emergency department visits: Strength of evidence.....	103
Table 66. Costs of emergency department visits: Summary of results.....	104
Table 67. Cost of emergency department visits: Strength of evidence.....	105
Table 68. Hospitalizations: Mean number, risk and rates.....	105
Table 69. Mean number of hospitalizations: Strength of evidence .....	110
Table 70. Risk of hospitalization: Strength of evidence .....	110
Table 71. Rate of hospitalization: Strength of evidence .....	111
Table 72. Costs of hospitalization: Summary of results .....	111
Table 73. Cost of hospitalization: Strength of evidence .....	113
Table 74. Length of hospitalization: Summary of results.....	113
Table 75. Length of hospital stay: Strength of evidence .....	114
Table 76. Access to patient records (basic MTM versus enhanced MTM): Strength of evidence .....	115
Table 77. Intensity of care coordination and followup following comprehensive medication review: Strength of evidence.....	115
Table 78. Pharmacy intensity of adoption: Strength of evidence .....	116
Table 79. Community pharmacy versus call center: Strength of evidence.....	116
Table 80. Type of payer: Strength of evidence.....	117
Table 81. Confusion: Strength of evidence.....	117
Table 82. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions .....	119
Table 83. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions.....	121
Table 84. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions.....	123

## Figures

Figure A. Analytic framework for outpatient medication therapy management .....	ES-4
Figure B. Disposition of articles on medication therapy management (PRISMA figure).....	ES-13
Figure 1. Analytic framework for outpatient medication therapy management.....	8
Figure 2. Disposition of articles on medication therapy management (PRISMA figure) .....	21

## Appendixes

Appendix A. Literature Search Strategies
Appendix B. Abstract and Full-Text Review Form Templates
Appendix C. Studies Excluded After Full-Text Level Review
Appendix D. Evidence Tables

Appendix E. Risk of Bias Evaluations and Rationale  
Appendix F. Meta-Analyses



# Executive Summary

## Background

Used appropriately, medications can alleviate distressing symptoms that compromise physical and psychological well-being, help prevent the onset of many acute and chronic illnesses, and improve patient health outcomes. Too often, however, medications are not used appropriately.<sup>1-3</sup> In the United States in 2001, adverse drug events led to an estimated 4.3 million ambulatory visits.<sup>4</sup> In addition to problems involving adverse drug events, many patients do not receive optimal pharmaceutical prescriptions. Even when optimal therapy is prescribed, patient inability to adhere closely to medication regimens may lead to poor health outcomes.<sup>5</sup>

Medication-related problems are especially pronounced among older adults.<sup>6</sup> Individuals 65 years or older constitute 13 percent of the U.S. population, but they consume more than 30 percent of all prescription medications.<sup>6,7</sup> A 2006 report found that nearly 60 percent of people in this age group were taking 5 or more medications and that nearly 20 percent were taking 10 or more medications,<sup>8</sup> placing them at increased risk for experiencing adverse drug events.

Medication therapy management (MTM) services are intended to address issues of polypharmacy, preventable adverse drug events, medication adherence, and medication misuse.<sup>9</sup> MTM is the current term that represents a suite of health care services that have evolved out of the philosophy and processes described in the early 1990s as “pharmaceutical care.”<sup>9</sup> The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)<sup>10</sup> expanded patient access to MTM services and established the requirements that Medicare Part D Prescription Drug Benefit Plan sponsors have to meet with respect to cost and quality and the requirements for MTM programs sponsored by Part D drug benefit plans. The Centers for Medicare & Medicaid Services (CMS) requirements for Part D MTM programs have evolved since their implementation in 2006.

Within a year of the passage of Medicare Part D, 11 national pharmacy organizations established a consensus definition of MTM,<sup>11</sup> and in 2008 a subset of national pharmacy organizations established five core elements for an MTM service model.<sup>12</sup> These elements include a medication therapy review, a personal medication record, a medication action plan, intervention and/or referral, and documentation and followup.<sup>9</sup> Also in 2008, Current Procedural Terminology (CPT<sup>®</sup>) for MTM services became available and further defined MTM and service-level expectations.<sup>13-15</sup>

The evolution from isolated research interventions studying the impact of pharmaceutical care interventions to large-scale commercial MTM programs or collaborative medication management within primary care represents a journey along a continuum of practice settings, patient populations, and intervention components and features. Over time, the practice and standards for these services have evolved, as have standards for describing and conducting research studies involving these interventions. A broadly defined scope for this review risks including studies that may be too different from each other to allow for meaningful comparison and synthesis. A narrowly defined scope for this review risks the omission of studies that met the definition of MTM but that predated the Part D era, were conducted in other countries, or used patient eligibility criteria that are less restrictive than Part D.

## Scope and Key Questions

MTM is a complex intervention that could have different components depending on the goals and scope of the MTM program. This review seeks to catalog outpatient-based MTM intervention components, assess the overall effectiveness of outpatient-based MTM in comparison with usual care, examine the factors under which outpatient-based MTM is effective and optimally delivered, assess what types of patients are likely to benefit from outpatient-based MTM services, and clarify what types of patients may be at risk of harms from such programs. This review does not address (1) MTM services provided within inpatient settings or shortly after hospital discharge, (2) disease management services provided by pharmacists, or (3) interventions designed as a single episode of contact. The rationale for limiting the scope to exclude some types of MTM interventions is to ensure that included studies are reasonably comparable with respect to intended purpose and design of the MTM intervention.

The Key Questions (KQs) addressed in this review are—

**KQ 1:** What are the components and implementation features of MTM interventions?

**KQ 2:** In adults with one or more chronic diseases who are taking prescription medications, is MTM effective in improving the following:

- a. Intermediate outcomes, including biometric and laboratory measures, drug therapy problems identified, drug therapy problems resolved, medication adherence, goals of therapy met, and patient engagement in medication management?
- b. Patient-centered outcomes, such as disease-specific morbidity, disease-specific or all-cause mortality, adverse drug events, health-related quality of life, activities of daily living, patient satisfaction with health care, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking?

c. Resource utilization, such as prescription drug costs, other health care costs, and health care utilization?

**KQ 3:** Does the effectiveness of MTM differ by MTM components and implementation features?

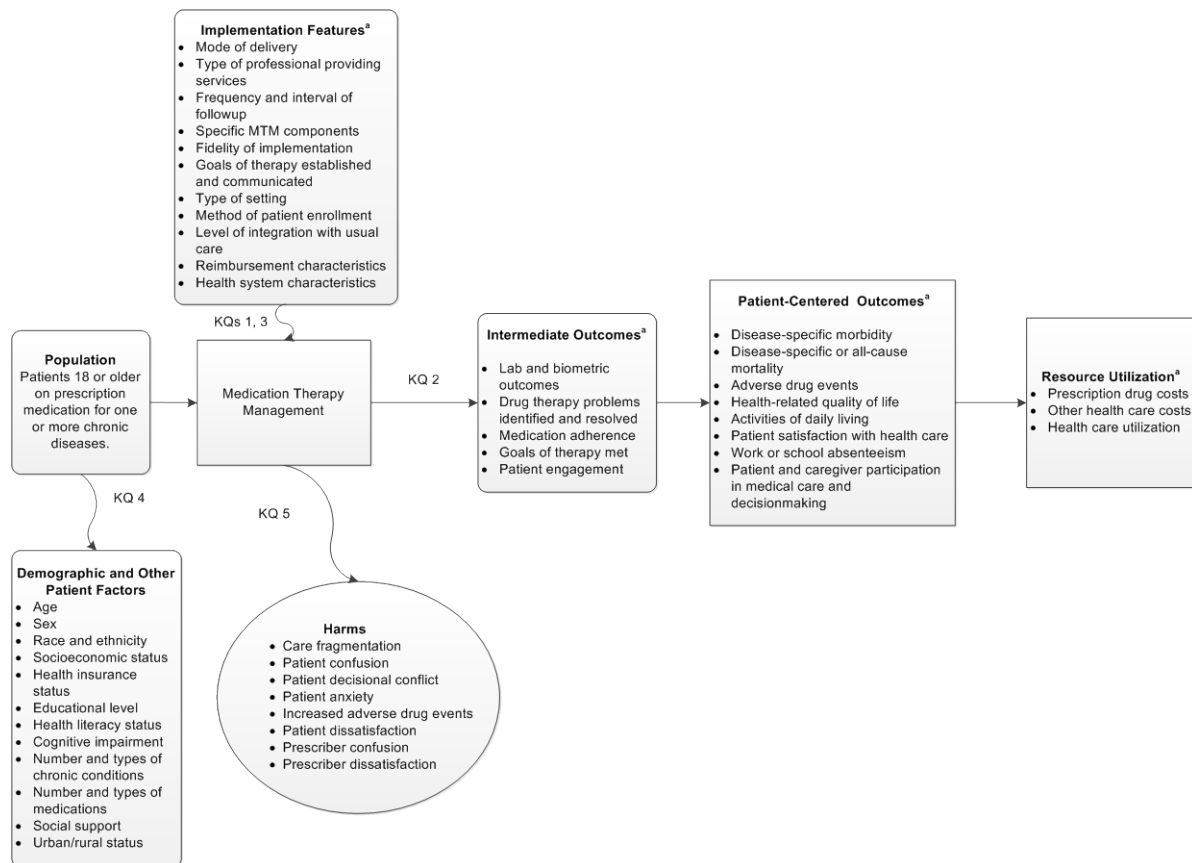
**KQ 4:** Does the effectiveness of MTM differ by patient characteristics, including but not limited to patient demographics and numbers and types of conditions and medications?

**KQ 5:** Are there harms of MTM, and if so, what are they?

### **Analytic Framework**

The KQs are placed in relation to one another and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) in the analytic framework (Figure A). Specific details regarding patient population, intervention components, and outcomes are provided in the next section.

**Figure A. Analytic framework for outpatient medication therapy management**



<sup>a</sup>The population, intervention, outcomes, and setting are described in detail in the text.

KQ = Key Question; MTM = medication therapy management.

## Populations, Interventions, Comparators, Outcomes, Timing, and Setting

Table A lays out the PICOTS for this review. For this review, we took a broad perspective on the population and interventions evaluated; we did not require CMS Part D MTM eligibility criteria. Specifically, we did not require multiple chronic conditions or a minimum number or level of expenditures on prescription drugs. We included randomized and controlled clinical trials, systematic reviews, and prospective and retrospective cohort studies. We included observational studies because we anticipated, from our topic refinement work, that a review limited to trials alone would fail to yield evidence on our wide range of prespecified benefits and harms for MTM interventions as a whole and for studies evaluating the modifying effects of specific intervention and patient characteristics on outcomes of MTM interventions.

**Table A. Populations, interventions, comparators, outcomes, timing, and settings**

<b>PICOTS</b>	<b>Inclusion and Exclusion Criteria and Relevant Factors for Study Abstraction</b>
Populations	<p data-bbox="354 380 548 415"><i>Inclusion criteria:</i></p> <ul data-bbox="365 415 1377 468" style="list-style-type: none"><li data-bbox="365 415 1377 468">• Patients age 18 or older with one or more chronic conditions requiring the use of prescription medication to manage symptoms or prevent progression of chronic disease</li></ul> <p data-bbox="354 468 548 499"><i>Exclusion criteria:</i></p> <ul data-bbox="365 499 1401 552" style="list-style-type: none"><li data-bbox="365 499 1401 552">• Patients in long-term or acute care settings without access or control over their own medication administration.</li></ul> <p data-bbox="354 552 548 583"><i>Relevant factors:</i></p> <ul data-bbox="365 583 1417 655" style="list-style-type: none"><li data-bbox="365 583 1417 655">• Patient characteristics that may influence intervention effectiveness: age, sex, race and ethnicity, socioeconomic status, health insurance status, educational level, health literacy status, cognitive impairment, number and types of chronic conditions, social support, and urban/rural status</li></ul>

**Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

<b>PICOTS</b>	<b>Inclusion and Exclusion Criteria and Relevant Factors for Study Abstraction</b>
Interventions	<p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"><li>• A bundle of medication-related services described by the term “MTM,” “pharmaceutical care,” “clinical pharmacy services,” or a similar phrase that include <i>at a minimum</i> the following 3 elements:<ul style="list-style-type: none"><li>○ Comprehensive medication review covering all prescription and nonprescription drugs, herbs, and supplements taken by the patient (i.e., a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them with the patient, caregiver, and/or prescriber)</li><li>○ Patient-directed education and counseling or other resources to enhance understanding of the use of medication</li><li>○ Coordination of care, including prescriber-directed interventions; documentation of MTM services for use by the patient’s other providers; and referral to other providers, clinicians, or resources when appropriate<sup>16</sup></li></ul></li></ul> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"><li>• Medication reconciliation interventions that did not include all 3 elements described above were excluded</li><li>• The following types of interventions may include MTM services, but MTM may represent only 1 component of the overall intervention:<ul style="list-style-type: none"><li>○ Disease-management interventions<sup>17</sup></li><li>○ Case- or care-management interventions<sup>17</sup></li><li>○ Patient-centered medical home models of care</li><li>○ Fully integrated collaborative care models involving multiple disciplines and specialties</li></ul></li></ul> <p>These types of interventions were excluded unless studies contained the same level of overall medical care or services among different study arms such that the effect of MTM could be isolated. For example, a study with 2 arms that has 1 arm with a care-management intervention that includes MTM services and another arm that has the care-management intervention without MTM services could be included. In contrast, a study that includes a care-management intervention with MTM in 1 arm and usual medical care (no care-management intervention) in the other arm would not be included.</p> <p><i>Relevant factors:</i></p> <ul style="list-style-type: none"><li>• Implementation features that may influence intervention effectiveness include the following:<ul style="list-style-type: none"><li>○ Mode of delivery: telephone, face to face, virtual (Web/online/Internet), and remote video</li><li>○ Type of professional providing initial and followup MTM service: pharmacist, nurse, physician, other clinician</li><li>○ Frequency and interval of followup for MTM services</li><li>○ Specific MTM components used</li><li>○ Fidelity in implementing MTM components: extent to which services were delivered as designed or intended</li><li>○ Establishing and communicating goals of drug therapy to patients and among care providers</li><li>○ Method of identifying patients for enrollment (e.g., population health data, provider referral for services, enrollment during a transition in care, targeting highly activated patients, targeting patients at time of high risk for event such as when prescribing a new drug)</li><li>○ Level of integration of MTM with usual care, which includes access to real-time clinical information and laboratory values, and regular and consistent communication among prescribers and others providing MTM services</li><li>○ Reimbursement characteristics (e.g., who is paying for cost of MTM services, who is reimbursed for MTM services, whether services are separately reimbursable)</li><li>○ Health system characteristics (e.g., are services being provided within an accountable care organization, patient-centered medical home, or some other unique system setting, such as the Veterans Health Administration, the Indian Health Service, non-U.S. single-payer system)</li></ul></li></ul>

**Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

<b>PICOTS</b>	<b>Criteria</b>
Comparators	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Usual care, as defined by the studies</li><li>• Different bundles of MTM services (e.g., 5 components vs. 3 components)</li><li>• Same MTM services provided by different health care professionals (e.g., pharmacist vs. physician or nurse)</li><li>• Same bundle of MTM services delivered by different modes (e.g., telephone vs. in person)</li><li>• Same bundle of MTM services provided at different intensities, frequencies, or level of integration with prescribers</li></ul>
Outcomes	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Studies must report at least 1 eligible outcome<ul style="list-style-type: none"><li>○ Intermediate outcomes<ul style="list-style-type: none"><li>- Disease-specific laboratory or biometric outcomes (e.g., hemoglobin A1c; blood pressure; total, low-density lipoprotein, or high-density lipoprotein cholesterol; pulmonary function; renal function; left ventricular ejection fraction; or other laboratory or biometric outcome specific to diseases covered)</li><li>- Drug therapy problems identified as defined by primary studies but typically including the following: medications being taken but not indicated; medications indicated but not prescribed; patient adherence issues; supratherapeutic doses; subtherapeutic doses; generic, formulary, or therapeutic substitution issue; complex regimen that can be simplified with same therapeutic benefit; and potential for drug-drug interactions or adverse event</li><li>- Drug therapy problems that are resolved as defined by primary studies but typically including the following: needed drug initiated; unnecessary drug discontinued; change in drug dose, form, or frequency; or generic, formulary, or therapeutic substitution</li><li>- Medication adherence</li><li>- Goals of therapy met</li><li>- Patient engagement (e.g., initial and continuing patient participation in the MTM program)</li></ul></li><li>○ Patient-centered outcomes<ul style="list-style-type: none"><li>- Disease-specific morbidity, including falls and fall-related morbidity, and outcomes specific to the patient's underlying chronic conditions (e.g., PHQ9, disease-specific symptoms, reduced number of disease-specific acute exacerbations or events)</li><li>- Disease-specific or all-cause mortality, including fall-related mortality</li><li>- Reduced (actual) adverse drug events (frequency and/or severity)</li><li>- Health-related quality of life as measured by generally accepted generic health-related quality-of-life measures (e.g., short-form questionnaires, EuroQOL) or disease-specific measures</li><li>- Activities of daily living as measured by generally accepted standardized measures of basic and/or instrumental activities of daily living (e.g., Katz, Lawton, or Bristol instruments) or with instruments that have demonstrated validity and reliability</li><li>- Patient satisfaction with MTM care</li><li>- Work or school absenteeism</li><li>- Patient and caregiver participation in medical care and decisionmaking</li></ul></li><li>○ Resource utilization<ul style="list-style-type: none"><li>- Prescription drug costs and appropriate prescription drug expenditures</li><li>- Other health care costs</li><li>- Health care utilization (hospitalizations, emergency department visits, and physician office visits)</li></ul></li><li>○ Harms<ul style="list-style-type: none"><li>- Care fragmentation</li><li>- Patient confusion</li><li>- Patient decisional conflict</li><li>- Patient anxiety</li><li>- Increased adverse drug events</li><li>- Patient dissatisfaction with care</li><li>- Prescriber confusion</li><li>- Prescriber dissatisfaction</li></ul></li></ul></li></ul>

**Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

PICOTS	Criteria
Timing	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Interventions should have at least 2 separately identifiable episodes of patient-directed MTM services, with any interval of time in between episodes</li><li>• For studies that report outcomes at different points in time, we considered only outcomes measured after the second episode of care and used the longest term outcomes reported by the study</li></ul> <i>Exclusion criteria:</i> <ul style="list-style-type: none"><li>• Interventions designed as single-episode interventions without any provision for followup and monitoring</li></ul>
Setting	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Ambulatory settings (e.g., outpatient clinics or private physician offices), long-term care (e.g., assisted living) settings if residents have control over medication self-administration, or retail pharmacy settings</li><li>• Home setting</li><li>• Interventions conducted in the United States</li><li>• Interventions conducted in non-U.S. countries published in English</li></ul> <i>Exclusion criteria:</i> <ul style="list-style-type: none"><li>• MTM services that are delivered exclusively in inpatient settings</li><li>• MTM services delivered at the time of hospital discharge or shortly after (e.g., within a few weeks)</li></ul> <i>Relevant factors:</i> <ul style="list-style-type: none"><li>• The MTM intervention itself may be delivered by home visits, by telephone, via the Web, or in other non-face-to-face modalities, such as video conferencing</li></ul>

MTM = medication therapy management; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PHQ9 = Patient Health Questionnaire 9.

## Methods

### Topic Refinement and Review Protocol

The topic of this report and preliminary KQs arose through a nomination from the Pharmacy Quality Alliance. Key Informants representing several clinical and scientific disciplines provided input on the initial KQs; we revised them as needed. An initial draft of the revised KQs was posted for public comment from March 6, 2013, through April 2, 2013, on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site. We received comments from 23 professional organizations and individuals and further revised KQs as appropriate.

### Literature Search and Identification Strategy

To identify articles relevant to each KQ, we began with a focused MEDLINE<sup>®</sup> search for MTM interventions using a combination of medical subject headings and title and abstract keywords, and limiting the search to English-language and human-only studies (inception through January 9, 2014). We also searched the Cochrane Library (inception through January 10, 2014) and the International Pharmaceutical Abstracts database (inception through January 10, 2014) using analogous search terms. We selected these databases based on preliminary searches and consultation with content experts. We conducted quality checks to ensure that the searches identified known studies (i.e., studies identified during topic nomination and refinement). Based on these quality checks, we revised and ran additional searches (specifically, using keywords such as “drug therapy management,” “drug therapy problem,” and “medications management”) to avoid missing articles that might prove eligible for this systematic review.



In addition, we searched the gray literature for unpublished studies relevant to this review and included studies that met all the inclusion criteria and contained enough methodological information to assess risk of bias. Specifically, sources of gray literature included ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Health Services Research Projects in Progress (HSRProj), the National Institutes of Health Research Portfolio Online Reporting Tools, the Database of Promoting Health Effectiveness Reviews, the New York Academy of Medicine Grey Literature Report, and CMS.gov. In addition, we reviewed the yield from AHRQ's request for Scientific Information Packets in the Federal Register, posted for 30 days from September 16, 2013 onward.

We reviewed our search strategy with an independent information specialist and the Technical Expert Panel, and supplemented it according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to identify any relevant citations that our electronic searches might have missed.

Two trained members of the research team independently reviewed each of the titles and abstracts against the inclusion/exclusion criteria listed in Table A. We applied the same criteria to systematic reviews and primary studies. Each article that either or both reviewers chose to include based on the abstract review underwent full-text review. Two reviewers reviewed the full text for eligibility against our inclusion/exclusion criteria. During full-text review, if both reviewers agreed that a study did not meet the eligibility criteria (including designation of high risk of bias), we excluded the study. Reviewers resolved conflicts by discussion and consensus or by consulting a third member of the review team.

For studies that met our inclusion criteria, a trained reviewer abstracted information into structured evidence tables; a second senior member of the team reviewed all data abstractions for completeness and accuracy. Reviewers resolved conflicts by discussion and consensus or by consulting a third member of the review team.

## **Assessment of Risk of Bias of Individual Studies**

To assess the risk of bias of individual studies, we used predefined criteria developed by AHRQ.<sup>18</sup> For randomized controlled trials (RCTs), we relied on the risk-of-bias tool developed by the Cochrane Collaboration.<sup>19</sup> We assessed the risk of bias of observational studies using an item bank developed by RTI International.<sup>20</sup>

In general terms, results of a study with low risk of bias are considered valid. Studies marked low risk of bias did not have any major flaws in design or execution. A study with medium risk of bias is susceptible to some bias but probably not sufficient to invalidate its results. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Primary concerns for our review included selection bias, confounding, performance bias, detection bias, and attrition bias. Very high attrition rates, particularly when coupled with a failure to control for confounding or to conduct intention-to-treat analyses, resulted in a rating of high risk of bias for trials and prospective cohort studies. Likewise, we rated studies with an inherently high risk of confounding in design (e.g., observational studies comparing refusers vs. acceptors of MTM interventions) as high risk of bias if they failed to address confounding through design (e.g., matching) or analysis (e.g., regression). Specifically, we evaluated trials on the adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of

outcome measures, and treatment fidelity. For observational studies, we did not assess adequacy of randomization or allocation concealment but assessed for confounding. We also evaluated trials for confounding due to randomization failure through biased selection or attrition. In other words, we evaluated trials with potential randomization failure for the same risks of bias as observational studies.

We excluded studies that we deemed at high risk of bias from our main data synthesis and main analyses. We included them for sensitivity analyses; in cases when we had no other available or credible evidence, we included in the report a brief synopsis of studies assessed as high risk of bias.

## **Data Synthesis**

When we found three or more similar studies for a comparison of interest, we conducted meta-analysis of the data from those studies using Comprehensive Meta-Analysis software (Biostat, Inc, Englewood, NJ). For all analyses, we used random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance;<sup>21</sup> that is, we qualitatively assessed the PICOTS of the included studies, looking for similarities and differences. When we conducted quantitative syntheses (i.e., meta-analysis), we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the  $I^2$  statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of  $I^2$  depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., the p-value from the chi-squared test or a confidence interval for  $I^2$ ). Where relevant, we examined potential sources of heterogeneity using sensitivity analysis.

When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. Whenever possible, we computed confidence intervals for individual outcomes.

Numerous articles did not provide complete information about findings (e.g., 95% confidence intervals, statistical significance values, or between-group data). In many cases, therefore, we had to calculate odds ratios, mean differences or standardized mean differences, the relevant 95-percent confidence intervals, and p-values.

## **Grading Strength of Evidence for Individual Comparisons and Outcomes**

We graded the strength of evidence based on the guidance established for the AHRQ Evidence-based Practice Center program.<sup>22</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: study limitations (includes study design and aggregate quality), consistency (similar magnitude and direction of effect), directness (evidence links interventions directly to outcome of interest for the review), and precision of the evidence (degree of certainty surrounding an effect estimate based on sample size and number of events). In addition, the evidence may be rated as lower strength for bodies of evidence with suspected reporting bias from publication, selective outcome reporting, or selective analysis reporting. Regardless of the specific risk of bias of observational studies, this approach to grading the evidence assigns observational studies a grade of high for study limitations, which

then leads to low strength of evidence. The strength of evidence from observational studies can be rated as higher for scenarios such as a strong dose-response association, plausible confounding that would decrease the observed effect, and a high strength of association (magnitude of effect). We evaluated optimal information size criteria to make judgments about precision based on guidance from Guyatt and colleagues<sup>23</sup> and based our grades on RCTs with low or medium risk of bias or on observational studies unless none were available, based on guidance from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group<sup>24</sup> and the AHRQ Evidence-based Practice Center program.<sup>22</sup>

Table B describes the grades of evidence that can be assigned.<sup>25</sup> Grades reflect the strength of the body of evidence to answer the KQs on the overall effectiveness, comparative effectiveness, and harms of the interventions examined in this review. Two reviewers assessed each domain for each major outcome, and resolved any differences by consensus discussion or referral to a third, senior member of the team. We graded the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature; we did not grade the strength of evidence for KQ 1 (on components and features of MTM services). The grades shown in Table B describe the state of evidence (which may demonstrate benefit, harm, or no effect) and the confidence in the stability of that state. An insufficient grade is not a statement about lack of efficacy or effectiveness; rather it is a statement about the lack of convincing evidence on benefit, harm, or lack of effect.

**Table B. Definitions of the grades of overall strength of evidence**

<b>Grade</b>	<b>Definition</b>
High	<b>High confidence that the evidence reflects the true effect.</b> Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	<b>Moderate confidence that the evidence reflects the true effect.</b> Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	<b>Low confidence that the evidence reflects the true effect.</b> Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

## Assessing Applicability

We assessed applicability of the evidence following guidance from the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”<sup>26</sup> We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age and health status of enrolled populations, health insurance coverage and access to health care, and complexity and intensity of the MTM intervention.

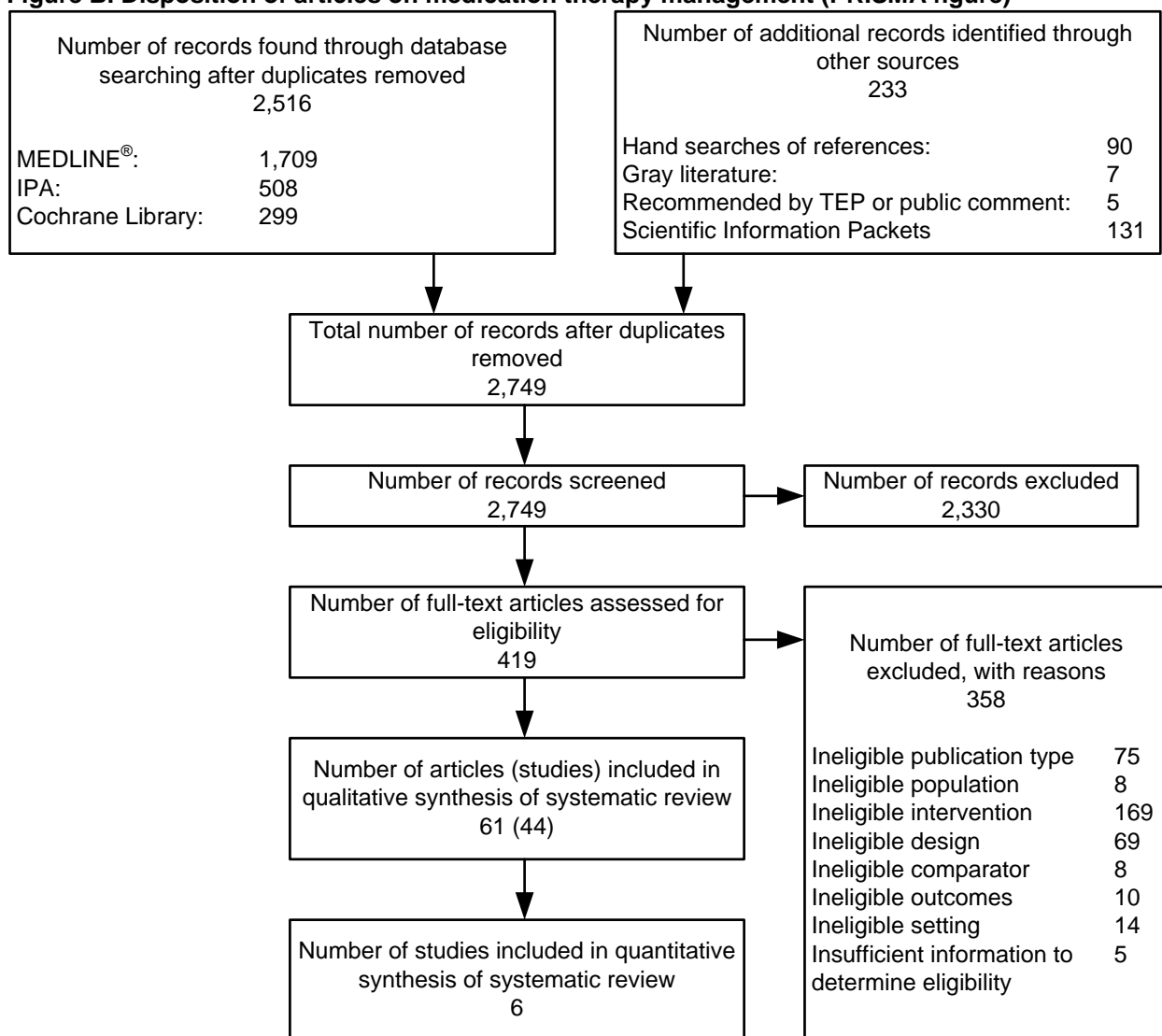
## Results

We provide a summary of results by KQ below. Detailed descriptions of included studies, key points, detailed synthesis, summary tables, and expanded strength-of-evidence tables that include the magnitude of effect can be found in the full report. Our summary of results below presents the strength-of-evidence grades.

## Results of Literature Searches

Figure B presents our literature search results through January 9, 2014. We identified 2,516 unduplicated citations. In addition, we identified 233 publications through gray literature searches, suggestions from Technical Experts or public comments received during topic refinement, hand searches of included studies, and Scientific Information Packets. After applying our eligibility and exclusion criteria to titles and abstracts of all 2,749 identified citations, we obtained full-text copies of 419 published articles. We reapplied our inclusion criteria and excluded 358 of these articles from further review before doing the risk-of-bias assessment. The 61 articles included after full-text review represent 44 studies.

**Figure B. Disposition of articles on medication therapy management (PRISMA figure)**



IPA = International Pharmaceutical Abstracts; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TEP = Technical Expert Panel.

This evidence base consisted of 44 studies (21 RCTs, 4 controlled clinical trials, and 19 cohort studies) reported in 61 articles. Most RCTs compared an MTM intervention with usual

care rather than with a different active intervention; all observational studies were cohort studies. Numerous studies had methods problems that led us to rate them as having a medium or high risk of bias; only a few studies were of low risk of bias. When possible (enough studies similar in intervention, populations, and outcomes measured), we conducted meta-analyses of data from RCTs or cohort studies separately; when relevant, we did two sets of meta-analyses, one with and one without the trials that had high risk of bias.

Because of the wide variation in types of interventions classified as MTM, we first cataloged intervention components and implementation features of MTM interventions (KQ 1). We then evaluated the effect of MTM on intermediate, patient-centered, and resource utilization outcomes (KQ 2). We also reviewed the evidence to identify how these effects might vary by specific intervention components and features (KQ 3) and patient characteristics (KQ 4). Finally, we reviewed the evidence on harms associated with MTM (KQ 5).

Below, we summarize the main findings and strength of evidence, where applicable. We then discuss the findings in relationship to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions.

## **Key Findings and Strength of Evidence**

### **KQ 1: Intervention Components and Implementation Features**

Of the 44 included studies, over three-quarters were broadly focused MTM interventions with patients who had a wide-ranging collection of conditions; the remaining studies were narrowly focused MTM interventions with patients who had a specific condition. All studies used a pharmacist as the interventionist. Services were provided face to face in half of included studies. Included studies provided interventions in a variety of clinical settings, including community pharmacies, centralized pharmacies or pharmacy call centers, and outpatient medical clinics, and some used home visits. Half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.

Whether they used the term “pharmaceutical care” or “MTM,” studies did not describe intervention components and features in a consistent manner or in sufficient detail. These drawbacks were especially prevalent for intervention intensity and frequency of followup, method of patient enrollment for services, level of integration with usual care, and reimbursement characteristics for rendered MTM services. KQ 1 was descriptive in nature, so we did not grade strength of evidence.

### **KQ 2: Overall Effectiveness of MTM**

Of the 44 studies included in this review, we rated 16 as high risk of bias overall; that is, concerns about randomization failure, confounding, or overall attrition increased the risk of bias for all outcomes. In addition, we rated some studies that were otherwise of low or medium risk of bias as high for individual outcomes, chiefly because of measurement or detection bias related to the specific outcome. These instances are specified in the relevant results section in the full report.

We rated the strength of evidence for each outcome from studies with low or medium risk of bias when available. MTM significantly improved objective measures of medication adherence, medication appropriateness assessed in general, and medication dosing (Table C). However, we did not find evidence of benefit for any other intermediate outcomes on which we had data. No studies addressed either goals of therapy or patient engagement.

**Table C. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions**

<b>Intermediate Outcome</b>	<b>Study Design: No. Studies (N Patients Analyzed)</b>	<b>Strength of Evidence</b>	<b>Supporting Judgment</b>	<b>Findings and Direction of Effect</b>
Anticoagulation	RCT: 1 (10)	Insufficient	Medium study limitations, consistency unknown (single study), direct, imprecise	Therapeutic INR achieved, 100% vs. 16.7%; p = 0.048.
HbA1c	RCT: 2 (102)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One trial with significantly greater percentage of patients with HbA1c <7.5% at 12 months.
	Cohort: 2 (2,688)	Insufficient	High study limitations, inconsistent, direct, imprecise	One study: adjusted findings significant at 12 months for percentage with HbA1c <7%, but findings not maintained at 24 months. Other study: no change in mean HbA1c or percentage <7% at 6 months.
Low-density lipoprotein cholesterol	RCT: 1 (38)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Calculated OR, 56.00; 95% CI, 5.583 to 561.753.
	Cohort: 2 (3,062)	Insufficient	High study limitations, inconsistent, direct, imprecise	One study: adjusted difference in difference coefficient, 1.95; 95% CI, 0.81 to 4.84; p = 0.13. Other study: calculated OR for achieving LDL goal, 1.392; 95% CI, 1.160 to 1.670; p <0.001.
BP	RCT: 1 (53)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	MTM group 28 times more likely to achieve BP goals than controls.
	Cohort: 2 (2,507)	Insufficient	High study limitations, consistent within design but inconsistent with RCT, direct, imprecise	MTM group less likely to achieve BP goals than controls.
Drug therapy problems identified	Cohort: 1 (582)	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Risk difference, 6.1%; calculated p = 0.062.
Number of drug therapy problems resolved	Cohort: 1 (120)	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Calculated mean difference, -1.00; 95% CI, -1.967 to -0.033; p = 0.04.

**Table C. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions (continued)**

Intermediate Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication adherence measured as proportion adherent to a threshold	RCT: 1 (69)	Insufficient	Medium study limitations, consistency unknown, direct, precise	100% of intervention patients and 88.9% of controls were adherent; $p = 0.115$ .
	Cohort: 2 (224 to 200,722)	Low for benefit	High study limitations, inconsistent, direct, precise	Two studies with findings in opposite direction; larger study showing range of ORs for medication-specific adherence depending on medication.  For comparison of PDP vs. controls, ORs ranged from 0.99 to 1.43; 95% CIs ranged from (0.90, 1.08) to (1.26, 1.62).  For comparison of MA-PD vs. controls ORs ranged from 1.10 to 1.40; 95% CIs ranged from (0.83, 1.24) to (1.29, 1.52).  For clinic-based MTM vs. usual care for adherence to aspirin, odds of adherence ranged from 5.981 (95% CI, 0.284 to 126.030; $p = 0.250$ ) during the intervention to 1.17 1 year after the intervention (95% CI, 0.072 to 18.903; $p = 0.912$ ).
Medication adherence measured as percentage of prescribed doses taken	Cohort: 2 (120 to 4,500)	Low for benefit for adherence to treatment for hypertension and dyslipidemia  Insufficient for treatment of patients with diabetes, depression, and asthma	High study limitations, inconsistent, direct, imprecise	Calculated mean difference from small study, -0.040; 95% CI, -0.101 to 0.021; $p = 0.201$ .  Larger study found a small (difference in adherence ~4.6%) but statistically significant effect of MTM on adherence to medications for some (2 of 5) conditions but no significant effect for the other conditions.
Medication adherence using self-report measures	RCT: 1 (292)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Calculated mean difference, 0.090; 95% CI, -0.076 to 0.256; $p = 0.289$ .
Medication adherence, miscellaneous measures	RCT: 2 (365)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Two studies with opposite direction of effect, both with nonsignificant differences between groups.
Medication Appropriateness General Index Scores	RCT: 1 (208)	Low for benefit	Low study limitations, consistency unknown, direct, precise	Improvement in MTM group from score of 17.7 to 13.4 at 3 months and 12.8 at 12 months.

**Table C. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions (continued)**

Intermediate Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication-specific appropriateness	RCT: 2 (261)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Significant improvement in appropriateness in the MTM group for some medications but not others.
Medication dosing	RCT: 1 (56)	Low for benefit	Medium study limitations, consistency unknown, indirect, precise	Mean difference, -2.2 doses; calculated 95% CI, -3.738 to -0.662.
Goals of therapy	0	NA	NA	NA
Patient engagement	0	NA	NA	NA

BP = blood pressure; CI = confidence interval; HbA1c = hemoglobin A1c; INR = International Normalized Ratio; LDL = low-density lipoprotein; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NA = not applicable; OR = odds ratio; PDP = Medicare Part D Plan; RCT = randomized controlled trial.

Similarly, we did not have evidence of benefit for most patient-centered outcomes, including adverse drug events or mortality (Table D). MTM did not improve most measures of health-related quality of life (low strength of evidence for no benefit). We graded the “vitality” and “emotional role functioning” domains of the Medical Outcomes Study Short-Form (SF36) questionnaire as insufficient for this domain. For the SF-36, neither the other six domains nor the two component scores (physical health, mental health) showed significant benefit from MTM interventions. The various patient satisfaction items also showed no impact from MTM programs (low strength of evidence for no benefit). We found no evidence on activities of daily living, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking.

**Table D. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions**

Patient-Centered Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Adverse drug events	RCT: 2 (806)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Direction and magnitude of effect differs between the 2 trials.
Cognitive and physical function	RCT: 1 (133)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	No significant differences between arms.
Affective function	RCT: 2 (181)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One study with no significant calculated mean differences in depression or anxiety scores; the other study with significant differences in mean depression and anxiety scores, but no significant difference in percentage achieving a depression remission.



**Table D. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions (continued)**

Patient-Centered Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Mortality	RCT: 1 (181)	Insufficient	Medium study limitations consistency unknown, direct, imprecise	OR, 0.59; 95% CI, 0.12 to 2.49; p = 0.48.
	Cohort: 2 (173,329)	Insufficient	High study limitations, inconsistent (magnitude), direct, imprecise	One study: OR, 0.5; 95% CI, 0.3 to 0.9. Second study: adjusted HR, 0.92; 95% CI, 0.87 to 0.96; p < 0.001.
Gastrointestinal bleeding events	Cohort: 1 (unclear)	Insufficient	High study limitations, consistency unknown, direct, imprecise	RRR, 60%; p = 0.001.
General health-related quality of life domains other than vitality and emotional role functioning	RCT: 3 (1,169)	Low for no benefit	Medium study limitations; consistent for physical role functioning, general health perceptions, and social functioning domains; inconsistent for physical functioning, bodily pain, and mental health domains; direct; precise	Variable mean difference with CIs consistently spanning the null effect.
General health-related quality of life for vitality and emotional role functioning domain	RCT: 3 (1,169)	Insufficient	Medium study limitations, consistent, direct, imprecise (not corrected for multiple comparisons or wide CIs)	Vitality: Mean difference of 2.797; 95% CI, 0.655 to 4.939; p = 0.010. Emotional role functioning: Mean difference of 5.386; 95% CI, -7.244 to 18.013.
Condition-specific health-related quality of life (diabetes)	RCT: 1 (73)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise,	Nonsignificant improvement of 0.1 point on a 5-point scale in the intervention group compared with no change in the control group.
Patient satisfaction	RCT: 3 (1,463)	Low for no benefit	Medium study limitations, consistent, direct, precise	No differences on 17 of 21 items of patient satisfaction; 4 statistically significant differences ranged in magnitude from -0.15 to -0.36, favoring MTM.
Activities of daily living	0	NA	NA	NA
Work or school absenteeism	0	NA	NA	NA
Patient and caregiver participation in medical care and decisionmaking	0	NA	NA	NA

CI = confidence interval; HR = hazard ratio; MTM = medication therapy management; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; RRR = relative risk ratio.

Outcomes related to using health resources were also not much influenced by MTM interventions (Table E). Two exceptions may merit attention: (1) health plan expenditures on medication costs and (2) the proportion and costs of hospitalization for patients with diabetes. MTM trials implemented in settings with a broad range of patients did not show a consistent signal of reduction in the number of hospitalizations, but a single cohort study that partially addressed confounding inherent in studies of refusers and acceptors found a lower mean number

of inpatient visits for patients accepting MTM compared with patients refusing MTM. Overall, we judge the strength of evidence for this outcome to be insufficient owing to lack of consistency across studies.

**Table E. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions**

Resource-Utilization Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Use of generics	Cohort: 1 (63,198 to 200,722)	Insufficient	High study limitations, consistency unknown, direct, imprecise	Odds range from -0.01 to 0.006.
Medication costs: patient copayments	RCT: 1 (NR)	Insufficient	Medium study limitations, consistency unknown, indirect, precision cannot be determined	Calculated mean difference, -64 USD; variance not calculable.
	Cohort: 1 (1,606)	Insufficient	High study limitations, consistency unknown, indirect, precise	Calculated mean difference for MTM vs. same-country control, 80.40 USD; 95% CI, 10.43 to 150.37; p = 0.024.  Calculated mean difference for MTM vs. different country control, 88.60 USD; 95% CI, 24.61 to 152.59; p = 0.007.
Medication costs: health plan expenditures	RCT: 3 (965)	Low for benefit	Medium study limitations, consistent, indirect, imprecise	Mean difference varies from -34 CAD to -293 USD over 6 months.
	NRCT and cohort: 5 (120 to 200,722)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varies from -800 USD over 1 year to 425 USD over 2 years.
Medication costs: total outlays	RCT: 6 (2,636)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Mean difference varies from -20.16 USD to +5.25 USD per month.
	Cohort: 2 (177,565)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varies from -563 USD to +310 USD annually.
Medication costs: medication costs plus other expenditures	RCT: 2 (996)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences in mean costs range from -8.1 CAD to 1,947 USD.
	NRCT and cohort: 3 (5,300)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Differences in mean costs range from -1,039 to 1,100 USD.
Number of outpatient visits	RCT: 3 (2,208)	Insufficient	Medium study limitations, inconsistent, indirect, precise	Standardized mean difference, 0.049; 95% CI, -0.034 to 0.133; p = 0.247; I <sup>2</sup> = 0.
	Cohort: 1 (4,500)	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Calculated mean difference, 2.48; 95% CI, 1.674 to 3.286; p <0.001.

**Table E. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions (continued)**

Resource-Utilization Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Outpatient costs	RCT: 3 (2,050)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Variable estimates.
Number of laboratory tests	RCT: 2 (1,842)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences range from +0.15 to -1.6 tests.
Costs of laboratory tests	RCT: 3 (2,050)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences range from +15 CAD to -140 USD.
Number of emergency department visits	RCT: 3 (1,552)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Mean difference ranges from -0.7 (p not significant) to -0.03 (95% CI, -0.113 to 0.053).
	Observational: 3 (795 to 200,722)	Insufficient	High study limitations, inconsistent, direct, imprecise	Adjusted OR ranges from 0.89 (95% CI, 0.6 to 1.3) to 1.09; mean difference (1 study), 0.04; 95% CI, -0.043 to 0.123; p = 0.346.
Costs of emergency department visits	RCT: 2 (996)	Insufficient	Medium study limitations, consistent, direct, imprecise	Mean difference ranges from -52 USD to -5.6 CAD.
	Cohort: 1 (150,470 to 200,722)	Insufficient	High study limitations, consistency unknown, direct, imprecise	Difference ranges from -16 USD to +12.8 USD.
Hospitalization: number	RCT: 3 (2,208)	Low for no benefit	Medium study limitations, consistent, direct, precise	Mean difference, 0.037; 95% CI, -0.004 to 0.080.
	Cohort: 1 (4,500)	Low for benefit	High study limitations, consistency unknown, direct, precise	Mean difference, -0.21; 95% CI, -0.265 to -0.155; p <0.001.
Hospitalization: risk	RCT: 1 (556)	Insufficient	Low study limitations, consistency unknown, direct, imprecise	OR for basic MTM vs. usual care, 2.069; 95% CI, 1.104 to 3.878; p = 0.02.
				OR for enhanced MTM vs. usual care, 1.345; 95% CI, -0.693 to 2.609; p = 0.381.
	Cohort—CHF, COPD, or unspecified: 3 (795 to 200,722)	CHF, COPD, or unspecified: insufficient	High study limitations, inconsistent, direct, imprecise	Adjusted OR ranges from 0.90 to 1.4.
	Diabetes: 1 (150,470)	Diabetes: low for benefit	High study limitations, consistency unknown, direct, precise	OR ranges from 0.91 to 0.93.

**Table E. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions (continued)**

Resource-Utilization Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Hospitalization: rate (patients with heart failure and home medicine review)	Cohort: 1 (5,717)	Low for benefit	High study limitations, consistency unknown, direct, precise	Adjusted HR, 0.55; 95% CI, 0.39 to 0.77.
Costs of hospitalization	3; 2,151 (2,050)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Inconsistent direction of effect but consistent in lack of significant effect.
	CHF or COPD: 1 (169,099 to 200,722)	Insufficient for CHF or COPD	High study limitations, consistency unknown, direct, imprecise	Differences range from -526 USD to 200 USD for CHF and COPD.
	Diabetes: 1 (150,470)	Low for benefit for diabetes	High study limitations, consistency unknown, direct, precise	Differences range from -363 USD to -399 USD for diabetes.
Length of hospital stay	RCT: 1 (208)	Insufficient	Low study limitations, consistency unknown, direct, imprecise	MTM reduced length of stay 1.8 days.

CAD = Canadian dollar; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; OR = odds ratio; RCT = randomized controlled trial; USD = U.S. dollar.

Over all three categories of outcomes, each of which had a substantial number of individual measures, MTM improved outcomes in only a couple of instances. Study limitations, lack of consistency, and lack of precision of the estimates of effects limited the strength of evidence considerably. As discussed later, even the minimal findings of effectiveness are at best only narrowly applicable.

### **KQ 3: Effectiveness of MTM by Intervention Features**

We found evidence from one study each on five intervention features: (1) access of pharmacists to patient records,<sup>27</sup> (2) intensity of care coordination and followup after comprehensive medication review,<sup>28</sup> (3) community pharmacy versus call center,<sup>29</sup> (4) level of intensity of intervention,<sup>30</sup> and (5) type of payer (private vs. Medicaid).<sup>31</sup> With the exception of the study on pharmacists' access to patient records, we rated these studies as high risk of bias. Evidence was insufficient for most outcomes for the first two intervention features, with the following two exceptions. First, MTM delivered by community pharmacists increased the weighted generic dispensing ratio when compared with call-center pharmacists (low strength of evidence). Second, enhanced MTM with pharmacists' access to patient records reduced the mean number of adverse drug events; this finding suggested benefit when compared with basic MTM (low strength of evidence). We found insufficient evidence for all outcomes for intensity of intervention and type of payer.

### **KQ 4: Effectiveness of MTM by Patient Characteristics**

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

### **KQ 5: Harms of MTM Interventions**

Lack of precision and the limitations of a single study with high risk of bias meant that evidence was insufficient to judge whether MTM resulted in greater inconvenience<sup>32,33</sup> than

usual care. We found no evidence on other prespecified harms, specifically including care fragmentation, patient decisional conflict, patient anxiety, increased (actual) adverse drug events, prescriber confusion, and prescriber dissatisfaction.

## **Discussion**

### **Key Findings**

We included 44 eligible studies (21 randomized controlled trials, 4 controlled clinical trials, and 19 cohort studies) reported in 61 articles, described in detail in the full report (KQ 1). Evidence was insufficient on the effect of MTM on most outcomes (KQ 2). In a few instances, described below, the evidence led us to conclude with a low strength of evidence either a benefit or lack of benefit. Specifically, we found evidence that MTM results in improvement when compared with usual care for some measures of medication adherence and appropriateness; medication dosing; health plan expenditures on medication costs; and, for patients with diabetes, the proportion and costs of hospitalization. Similarly, we conclude based on a low strength of evidence that MTM conferred no benefit for patient satisfaction and most measures of health-related quality of life.

We found evidence on five intervention components and intervention features (KQ 3): one study provided information on each feature and yielded insufficient evidence for most outcomes, with the two following exceptions. MTM programs with pharmacist access to brief clinical summaries from the medical record reduced the mean number of adverse drug events when compared with basic MTM programs without such access (low strength of evidence). Community pharmacists increased the generic dispensing ratio more than pharmacists based in call centers (low strength of evidence). We found no relevant studies on patient characteristics moderating the effect of MTM interventions (KQ 4). Similarly, the evidence on harms associated with MTM was limited to one study on inconvenience and was rated as insufficient (KQ 5).

### **Findings in Relation to What Is Already Known**

Our findings contrast with conclusions that Chisholm-Burns and colleagues reached in a recent systematic review.<sup>34</sup> In that review, the authors concluded on page 923: “Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states.”<sup>34</sup> Several differences between the Chisholm-Burns review and the current review may account for the discrepant conclusions. First, the Chisholm-Burns review included all studies that cited evidence of pharmacist involvement in direct patient care. The interventions examined included chronic disease management and prospective and retrospective drug utilization review; we excluded these types of efforts because of the clinical heterogeneity those interventions would have introduced into the review. Notably, the Chisholm-Burns review did not use the term “medication therapy management” to categorize the interventions in the articles they reviewed. Second, approximately 30 percent of the studies in the Chisholm-Burns review were conducted entirely in institutional settings. In contrast, we did not identify any studies within institutional settings that met our MTM intervention definition criteria. Third, the Chisholm-Burns review included a total of 298 articles and did not omit from the analyses studies with a high risk of bias; in contrast, we based our strength-of-evidence grades in this review on only those studies with no more than medium risk of bias. Thus, a direct comparison of findings between these two reviews would be ill advised.

The striking differences between the conclusions reached in these two reviews emphasize two important needs for efforts to systematically review MTM programs. The first is for researchers to specify the MTM intervention based on existing definitions, taxonomies, or service models. The second is to develop consensus guidelines for describing intervention features and fidelity of intervention delivery in publications reporting findings from evaluation studies. Progress on these two steps would enable systematic reviews to differentiate better between different types of services and avoid the problem of overgeneralizing review results.

## **Applicability of the Findings**

This body of evidence has significant clinical and methodological heterogeneity, which limits the ability to make any universal statements about effectiveness. However, the range of study designs, which includes RCTs, nonrandomized trials, and cohort studies, enhances the applicability of findings for real-world settings.<sup>26</sup> Included studies ranged from relatively small interventions in single clinics provided by a single interventionist to evaluations of MTM services delivered on a large scale through integrated health systems or health plans as a Medicare Part D or other drug plan benefit. This diversity of studies enhanced the applicability of findings to a wide variety of settings, including outpatient clinics, community pharmacies, and centralized pharmacy call centers. A few studies conducted outside the United States included MTM as part of a home visits program; findings from this model may not be directly applicable within the United States.

The studies in this review are broadly applicable to a range of chronically ill adult patient populations. A majority of interventions were directed at populations with multiple and common chronic conditions, such as diabetes, chronic heart failure, and hypertension. Several specifically targeted adults age 65 years or older. Few studies reported sociodemographic characteristics beyond age and sex; thus, the applicability of findings to specific populations (e.g., rural, low socioeconomic status, cognitively impaired, uninsured) is unknown. The nature of the MTM intervention, which includes involving patients as active participants in the process, limits the extent to which findings can be generalized beyond patients who agree to participate in such interventions. Patients who agree to participate may be systematically different from those who decline to be in such a program. For that reason, the impact of such interventions at a population or health-plan level may be limited by the degree of uptake among interested patients.

The intervention used across most studies can be characterized as complex and moderately resource intensive. Components involve identifying applicable patients; initially assessing patients; providing counseling, education, and care coordination; and following patients over time. These services were provided per protocol in some studies and as needed or ad hoc in others. Most studies described intervention components in terms of “pharmaceutical care model” components or Medicare Part D MTM program criteria, but few provided detailed descriptions or measurement of implementation fidelity.

The comparator arm in all studies was usual medical or pharmacy care. This does not typically include distinct MTM services by health care providers other than prescribing providers (not common for the time period covered by most of the studies). Models of collaborative health care delivery are evolving, and the changing roles and training of pharmacists increase the potential applicability of MTM interventions in future models of health care.

The broad sets of outcomes evaluated across this body of evidence spanned a substantial range of both intermediate and health outcomes as well as outcomes related to resource use. Proximal and intermediate outcomes included number of drugs, identification of drug therapy

problems, appropriateness of medication prescribing, and laboratory or biometric markers of disease control (e.g., hypertension, hemoglobin A1c, low-density lipoprotein cholesterol). Patient-centered outcomes focused on numerous measures of quality of life as well as adverse drug events. Many studies also reported outcomes involving health care resource use and expenditures (e.g., number and costs of hospitalizations, emergency department visits, outpatient visits).

Most studies did not, however, clearly indicate the expected, desired, or intended direction of effect on most resource use outcomes, making the applicability of using these interventions to reduce drug-related health care costs or expenditures difficult to assess. For example, it is not clear whether one should expect the number of medications prescribed for heart failure to increase or decrease under the careful scrutiny of an MTM intervention because the desired impact will be based on the goal of therapy for each individual.

The focus of outcome measurement in many studies was the short-term identification and characterization of drug therapy problems and their resolution; these endpoints are thought to be the outcomes most sensitive to change as a result of receiving MTM services. However, because identification of drug therapy problems is, by design, a part of the MTM intervention itself, differences between the nature of the intervention and that of the control programs mean that measuring these outcomes cannot be as rigorous in a usual-care comparison group as it is in the intervention group. In fact, many studies were able to measure changes in this outcome only in the intervention group. Hence, many studies failed to demonstrate a direct analytic link between the resolution of drug therapy problems as a result of MTM and impact on intermediate outcomes, patient-centered outcomes, and resource utilization. Thus, the applicability of studies that demonstrate an impact on the resolution of drug therapy problems is limited.

## **Implications for Clinical Practice and Policymakers**

Although we found the evidence insufficient in general to draw definitive conclusions about the comparative effectiveness of MTM for most outcomes that we evaluated, our findings suggest some implications for practice and policy. MTM is already in widespread practice and is now shaped in the United States largely by Medicare Part D policy; this presents both challenges and opportunities. MTM programs sponsored and administered by Part D drug benefit plans are often centrally administered and delivered primarily by phone, and may be less integrated into routine health care than some of the interventions included in our review. MTM programs of the future have the potential to be more integrated into routine health care through participation in accountable care organizations or patient-centered medical home models. We were unable to answer definitively whether level of integration matters for effectiveness, but policymakers may need to consider expectations about the impact that MTM might have on patient-centered outcomes and resource use in the context of other health care delivery transformation activities or quality improvement initiatives that are also occurring. More integration of MTM services with other activities may be effective; however, the more integrated MTM becomes within routine medical care, the more difficult it becomes to isolate it as a discrete intervention for evaluation.

Policymakers could thus consider whether MTM services should be positioned as a *contributor* to overall improvement in processes of care, health status, and costs or positioned as an intervention to which effects can be discretely *attributed*. As noted earlier, improvements in medication appropriateness or drug therapy regimens may not always translate into improvements in health or costs, and even if they do, secular trends in related quality

improvement (e.g., medication adherence interventions, regulatory requirements for medication reconciliation, meaningful use incentives for electronic health records) may make measuring outcomes *attributable* to MTM very challenging.

Future training of MTM providers would benefit from a better understanding of which MTM components really matter. At the moment, such information is lacking. Policymakers and funders who wish to understand the comparative effectiveness of different MTM components could encourage rigorous program evaluation designs that fit within the context of the real-world implementation of these programs. For example, positive deviance analyses<sup>35</sup> with rigorous measurement of implementation features or stepped wedge trial designs<sup>36</sup> may be useful approaches.

A typical approach for evaluating complex interventions is to identify the “core” components for standardization, while allowing for flexibility for peripheral components or variations in implementation. In complex practice-based innovations, such flexibility may reflect desirable (or unavoidable) adaptations to local circumstances. Policy governing MTM programs may warrant modifications to permit investigators to conduct rigorous and innovative evaluative designs to identify core components or effectiveness-enhancing modifications. As future research and evaluation elucidate these components or enhancements, policy will need to evolve to keep pace with best practices.

Finally, consideration of both patients’ and prescribers’ perspectives in future design and delivery of MTM services may be needed. In our current analytic framework, MTM interventions require a significant element of engagement by both patients and prescribers if the interventions are to have a reasonable likelihood of improving outcomes. Although “opt in” strategies may increase the reach of such interventions, keeping patients (and their prescribing providers) engaged in the intervention over a reasonable amount of time may be the key to translating the potential of MTM interventions into actual improvements. Further refinement of eligibility criteria based on evidence to provide interventions to those most at risk from drug-related problems, and therefore most likely to benefit, may also be warranted.

## **Limitations of the Comparative Effectiveness Review Process**

The constraints for populations, interventions, and settings that we imposed on this systematic review may limit its applicability, as discussed above. During topic refinement and based on Technical Expert Panel inputs and public comment, we expanded the scope by removing an exclusion criterion that would have required MTM interventions to have been directed at a patient population with two or more chronic conditions. As a result, we included studies that focused on one chronic condition. Because of the prevalence of certain chronic conditions in the adult population, and particularly among Medicare beneficiaries, we think this decision was sensible and permitted us to examine a broader evidence base than would otherwise have been the case.

Although we tried to distinguish MTM from disease or case-management interventions, making this distinction was challenging. We created a threshold for the intervention components that were required to be present for this distinction. Specifically, we elected to emphasize whether the intervention entailed a comprehensive review of all medications; for that reason, we did not constrain studies of interest to those that targeted a single medication or drug regimen or that focused on a single condition such as diabetes or hypertension.

When we were unable to determine which medications the interventionist had reviewed, we wrote to the authors for additional information. We chose to pursue authors in an effort to permit



us to use studies that had been designed as MTM but did not describe the comprehensive medication review component in detail.

Our approach may have been overly inclusive because it led us to include studies that addressed a single disease, as long as the pharmacist reviewed all medications. For example, 10 of the 44 studies were relatively narrowly focused; 2 of these addressed patients with chronic heart failure and 2 addressed patients with either hypertension or hypertension and diabetes. The remaining six studies focused on patients with diabetes, HIV, glucocorticoid-induced osteoporosis, or hemodialysis. The fact that we did not require patients to have more than one clinical condition resulted in an approach that was inclusive of these more narrowly focused (albeit often termed “MTM”) studies and may render our results less applicable to MTM interventions targeted to patients with a wide range of chronic conditions.

Also based on feedback during the process of setting out the scope of this review, we chose to include interventions that were broader than the Medicare Part D MTM-defined interventions. Put another way, we broadened our view of patient populations and intervention criteria, and we allowed studies not conducted in the United States into the evidence base. This decision led us to include interventions described as “pharmaceutical care,” which were generally based on the pharmaceutical care model principles;<sup>9</sup> it also permitted us to examine investigations with elements of pharmaceutical care or MTM that did not specifically label the intervention as either MTM or pharmaceutical care. These studies were often described as “clinical pharmacist interventions.”

Furthermore, all the non-U.S. studies involved interventions within single-payer health systems. Hence, the interventions in this review constitute a more heterogeneous group than if we had allowed only those labeled as Medicare Part D MTM programs. This is both a limitation and a strength. Although our approach makes results more challenging to interpret, it enhances our ability not to miss interventions that include MTM components but lack the descriptor term “MTM.”

Studies did not often explicitly describe certain MTM components. In cases when we could not determine whether investigators had provided certain MTM components (such as patient education and counseling or coordination with other health care providers), we contacted the authors to gain additional information that would allow us to make an informed decision. We were fairly permissive in interpreting the presence of the MTM intervention components other than comprehensive medication review. The main reason is that we recognized that terms describing some components have evolved over time and may have been absent from the lexicon in earlier years or implicitly conveyed by authors by simply using the terms “MTM” or “pharmaceutical care” to describe their intervention.

Our approach to categorizing interventions for KQ 1 relied primarily on the short descriptions in published manuscripts and those we were able to obtain via email inquiries. Their similarities or differences substituted for any overarching taxonomy, because none that we considered seemed to fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for clinical heterogeneity among interventions. This approach limits our ability to make definitive statements about the effectiveness of various intervention components. We believe that the clusters and categorizations we used are useful heuristics, but some may regard them more as hypothesis generating than as reflecting settled principles of classification.

Finally, our search process was complicated by having to ensure coverage of all terms that could be used to describe MTM interventions over time. Adding to this challenge was our effort

to examine the gray literature, where we thought we might find studies tilted toward effectiveness and real-world program evaluation. As it turned out, studies of these types of interventions were not indexed similarly; for that reason, we needed to rely heavily on hand searches of citation lists from key background articles to identify possibly relevant studies for inclusion. Thus, we may have missed some studies that might have qualified for inclusion. Given the considerable diversity in the evidence base we did have, however, we do not think that any potentially missed studies would have changed our conclusions in any material way. No meta-analyses included more than five studies; as a result, we did not examine included studies for publication bias quantitatively.

## Limitations of the Evidence

As a body of evidence, the MTM literature evaluated in this review has measured numerous outcomes. As indicated in previous sections, very few outcomes, with the exception of harms, remain completely unexamined. Of the 44 studies in this review, we rated 28 as having medium, low, or mixed risk of bias. The 44 studies included 21 trials and 4 nonrandomized controlled studies. In other words, the literature on this topic is *not* marked by failure to consider important outcomes, universally high risk of bias, or pervasively weak designs.

Despite these advantages, we were unable to identify sufficient evidence on the majority of hypothesized outcomes of MTM. In several instances, our inability to rate evidence as higher than insufficient came from inconsistent and imprecise evidence or from a body of evidence with high study limitations. The choice of outcome measures in this body of evidence limited our ability to come to conclusions in some instances. For example, some studies did not focus on changes that proponents might expect MTM services to produce. Because effective MTM can either increase or decrease expenditures or use of services based on the needs of the patient, studies that did not prespecify the expected direction of change had no way to interpret their results as an appropriate change. Studies that demonstrated inconsistent results in direction of change (i.e., some showing an increase in resource use and others showing a decrease) may well have been consistent in terms of appropriate change, but because they generally failed to establish a priori the direction in which they expected to find an effect, we rated such evidence as indirect and inconsistent.

Similarly, studies often used nonstandardized or idiosyncratic measures for outcomes such as adverse events, adherence, and expenditures or costs; this tendency limited our ability to meta-analyze results. When studies focused on specific outcomes, they were often significantly underpowered to detect differences between groups (i.e., they did not meet optimal information size criteria). As a result, we rated several studies as imprecise.

MTM intervention studies are largely practice based and incorporate substantial heterogeneity in specific intervention elements and in patient populations targeted. Yet the evidence is sharply constrained in its ability to inform questions about the effectiveness of specific MTM components or intervention features (KQ 3 in our review) because study designs did not often capitalize on variants in MTM programs for a prospective evaluation of outcomes by those variants. Neither did they measure fidelity to intended MTM elements for post hoc evaluation. Similarly, the relatively untargeted nature of the MTM interventions meant that, in many studies, only small numbers of patients had any one specific condition, and most studies did not measure patient characteristics beyond age and sex, thus limiting our ability to address KQ 4 in our review. For this reason, the evidence we identified for this review was most relevant for KQ 2.

## Research Gaps

In many bodies of research, questions regarding the *comparative* effectiveness of specific intervention components or implementation features are best answered after clear evidence of the overall effectiveness of the intervention relative to usual care has been established. Our review largely indicates insufficient evidence on the primary question of effectiveness relative to usual care. By definition, this limited what we could say about comparative effectiveness.

Nonetheless, the widespread implementation of MTM coexists with the urgent need for actionable information for policy, program policies, and training. This clinical and policy environment means that new research cannot afford to address causal claims relative to usual care first, followed by comparative effectiveness of the intervention elements in a relatively controlled environment, and finally, program evaluation of real-world implementation, all in sequential order.

In prioritizing among various research goals, therefore, funders may wish to consider the relative value of new evidence on overall effectiveness, effectiveness of implementation features, and program implementation and accountability. Trial research in narrow clinical settings can address questions of effectiveness but may lack applicability to real-world implementation. Likewise, evaluations of real-world programs with variable fidelity to interventions can answer questions about process and implementation, but they offer limited information on effectiveness. Research prioritization exercises will also need to account for already commissioned MTM intervention studies.

For new studies focusing on causal claims, a critical gap relates to the failure to specify the expected direction of effect. New research requires a strong theoretical foundation to help specify causal mechanisms and hypothesized effects. Without such an edifice, future research will continue to produce inconsistent and uninterpretable results.

Heightened attention to causal mechanisms will also help researchers convey their understanding of what outcomes these types of interventions are likely to influence. For instance, how should researchers wishing to establish direct causal links between MTM programs and outcomes evaluate distal outcomes such as patient-centered outcomes and resource utilization? This effort requires a better understanding of the relationship between proximal outcomes such as “drug therapy problems identified and resolved” and distal outcomes. For instance, MTM may reduce outpatient visits to address side effects. MTM may also result in the need for further testing and evaluation for some patients, which could, in turn, result in more rather than fewer outpatient visits. Unless the nature of change resulting from MTM is specified in relation to goals of drug therapy, studies cannot assert benefit or harm. Further, drug therapy problems are diverse and may not all have the same causal relationship to health, quality of life, patient satisfaction, or resource use outcomes. Furthermore, a causal model of these distal outcomes may need to take into account the competing or complementary contributions of MTM, new models of health care delivery (e.g., patient-centered medical homes), and other quality improvement interventions.

Investigators embarking on new studies focusing on causal links between MTM and outcomes may wish to consider the limitations of studies based on secondary data from existing MTM programs that use opt-in/opt-out patient enrollment mechanisms. Although these studies may provide invaluable information on process measures such as patient engagement, underlying issues of confounding severely limit the validity of causal claims from such studies.

Regardless of the goal of their future research, investigators should consider issues of sample size to ensure precision of their results. This issue is particularly relevant when evaluating

outcomes likely to occur in smaller subgroups defined by patient risk, context, or highly adapted intervention features. Innovative designs (e.g., stepped wedge trials, statistical process control, time-series analysis, simulations, and factorial experiments) may permit both rigor and adequate sample size within the context of real-world implementation. With careful attention to fidelity, new studies may also inform questions about the effectiveness of intervention components and implementation features. Mixed-methods approaches may allow more information on variations in context and implementation. Such designs may also help inform our understanding of critical training elements for MTM service providers.

Regarding research gaps for specific outcomes such as patient satisfaction, measures specific to the types of services provided through MTM (e.g., patient education about medications) or to the proximal outcomes that MTM is intended to achieve (e.g., reduced medication side effects, improved disease control) may offer better insights into the effects of MTM. Similarly, a medication-related instrument may better measure patients' concerns that are directly related to medication use (e.g., experience of side effects, intrusiveness of the medication regimen) than generic tools do.

## **Conclusions**

The evidence base offers low evidence of benefit for a limited number of intermediate and health utilization outcomes. We graded the evidence as insufficient for most outcomes because of inconsistency in direction, magnitude, and precision, rather than lack of evidence. Wide variations in populations and interventions, both within and across studies, likely explain these inconsistencies. Given the widespread implementation of MTM and urgent need for actionable information, optimal investments in new research require a process of research prioritization in which the value of information from each proposed study is carefully considered. Studies designed to identify causal relationships between MTM interventions and their outcomes require adequate controls for confounding but may offer limited information on which factors explain program success or failure. Studies designed to explore the reasons for program success or failure using qualitative or single-arm designs may offer hypothesis-generating rather than hypothesis-confirming insights on MTM effectiveness. New research, regardless of specific focus, will likely continue to find inconsistent results until underlying sources of heterogeneity are accounted for.

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# Introduction

## Context

Used appropriately, medications can alleviate distressing symptoms that compromise physical and psychological well-being, help prevent the onset of many acute and chronic health illnesses, and improve patient health outcomes. Too often, however, medications are not used appropriately. The Institute of Medicine and other prominent organizations have recognized that medication-related problems plague our health care system.<sup>1-3</sup> In the United States in 2001, an estimated 4.3 million ambulatory visits were for adverse drug events.<sup>4</sup> A cohort study of Medicare enrollees estimated the overall rate of adverse drug events at 50.1 per 1,000 person-years.<sup>5</sup> The study rated more than one-third of the adverse drug events as serious, life-threatening, or fatal; more than 40 percent of these more severe adverse drug events were classified as preventable. Another study found that more than 12 percent of hospitalized patients experienced an adverse drug event within 3 weeks following hospital discharge.<sup>6</sup>

In addition to problems involving adverse drug events, many patients are not prescribed optimal treatment for chronic conditions such as high blood pressure and hyperlipidemia that increase their risk of cardiovascular disease and its complications. Moreover, even when optimal therapy is prescribed, patient inability to adhere closely to medication regimens may lead to poor health outcomes.<sup>7</sup>

Medication-related problems are especially pronounced among older adults.<sup>5</sup> Individuals 65 years or older constitute 13 percent of the U.S. population, but they consume more than 30 percent of all prescription medications.<sup>5,8</sup> A 2006 report found that nearly 60 percent of people in this age group were taking five or more medications and that nearly 20 percent were taking 10 or more medications,<sup>9</sup> placing them at increased risk for experiencing adverse drug events. Moreover, these figures reflect a substantial increase in the prevalence of polypharmacy since 1998.<sup>9</sup>

Medication therapy management (MTM) services are intended to address issues of polypharmacy, preventable adverse drug events, medication adherence, and medication misuse.<sup>10</sup> MTM services are designed to be distinct from medication-dispensing services; in particular, they employ a patient-centric and comprehensive approach, rather than an individual product or episodic perspective.<sup>11</sup>

MTM is the current term that represents a suite of health care services that have evolved out of the philosophy and processes described in the early 1990s as “pharmaceutical care.”<sup>10</sup> Similar to the concept of medical care or nursing care, pharmaceutical care is a term that describes professional pharmacy practice, not a discrete intervention. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)<sup>12</sup> expanded patient access to MTM services and identified the following as goals for MTM services within Medicare Part D: (1) educate and counsel to improve patient understanding of their medications, (2) improve adherence, and (3) detect adverse drug reactions and improper medication use. This law also established the requirements that Medicare Part D Prescription Drug Benefit Plan sponsors have to meet with respect to cost, quality, and the requirements for MTM programs sponsored by Part D drug benefit plans. The law established oversight for Part D MTM programs by the Centers for Medicare & Medicaid Services (CMS) and provided a general framework for MTM programs but allowed Part D Plan sponsors flexibility in design, including the patient eligibility criteria for services. The CMS requirements for Part D MTM programs have evolved since their implementation in 2006.



Within a year of the passage of Medicare Part D, 11 national pharmacy organizations established a consensus definition of MTM.<sup>13</sup> “MTM is a distinct service or group of services that optimize therapeutic outcomes for individual patients.”<sup>13, p. 572</sup> This definition further describes MTM as “a broad range of professional activities and responsibilities within the licensed pharmacist’s, or other qualified healthcare provider’s scope of practice.”<sup>13, p. 72</sup> Table 1 lists the types of services that can be considered under the umbrella MTM definition.

**Table 1. MTM services**

<b>Services defined as MTM<sup>14</sup></b>
Medication therapy reviews
Pharmacotherapy consults
Disease management coach/support
Pharmacogenomic applications
Anticoagulation management
Immunizations
Health, wellness, and public health
Medication safety surveillance
Other clinical services

The pharmacy profession has developed or supported additional efforts to standardize and establish the infrastructure for MTM service delivery. In 2008, a subset of national pharmacy organizations published the second version of core elements for an MTM service model. This model established five core elements for use in practice, including a medication therapy review, a personal medication record, a medication-related action plan, intervention and/or referral, and documentation and

followup.<sup>10,15</sup> Also in 2008, Current Procedural Terminology (CPT<sup>®</sup>) codes were established to provide a mechanism for reimbursement for services related to medication management. These CPT codes define MTM as “services provided by a pharmacist to optimize the response to medications for the management of treatment-related medication problems or complications.” More recently, the Patient-centered Primary Care Collaborative established its definition of comprehensive medication management to describe MTM in the context of a patient-centered medical home, which includes elements of the CPT definition.<sup>16,17</sup> The evolution from isolated research interventions studying the impact of pharmaceutical care interventions to large-scale, commercial MTM programs or collaborative medication management within primary care represents a journey along a continuum of practice settings, patient populations, and intervention components and features. Over time, the practice and standards for these services have evolved, as have standards for describing and conducting research studies involving these interventions. Thus, establishing the scope of this review was very challenging. A broadly defined scope (all clinical pharmacist interventions regardless of setting or patient population) risks including studies that may be too different from each other to allow for meaningful comparison and synthesis. A narrowly defined scope (e.g., a focus exclusively on Medicare Part D-defined MTM programs) risks the omission of studies that met the definition of MTM, but that predated the Part D era, were conducted in other countries, or used patient eligibility criteria that are less restrictive than Part D. In the next section, we describe background related to population, intervention, comparison, outcomes, timing, and setting (“PICOTS”) that we relied on to establish the scope of this review. Throughout this review, we will use the term MTM to describe the general class of intervention. However, when describing individual studies included in this review, we will defer to the terms used by the study author to describe the intervention they were evaluating (e.g., pharmaceutical care, clinical pharmacy services, or MTM).

## Populations

Adult patients with multiple chronic conditions who take many different prescription or nonprescription medications, herbal products, or diet supplements (and combinations of these) are the target population for most outpatient-based MTM services.<sup>11</sup> Because older adults are

more likely to take multiple medications, MTM services generally target them. However, MTM interventions may also target patients taking a single high-risk medication (e.g., Coumadin) or may target patients at high risk for an adverse drug event, for example, during a transition in care from a hospital to home setting. Although some children with complex medication regimens may benefit from MTM, these program are typically designed and delivered to adults.

As part of Medicare Part D implementation, CMS required that MTM programs target Medicare Part D enrollees, who have multiple chronic diseases, are taking multiple Part D drugs, and are likely to incur annual costs for covered Part D drugs that exceed a predetermined level (“annual cost threshold”). To be eligible for CMS reimbursement, MTM programs originally had to offer services for at least four of seven core chronic diseases: hypertension, chronic heart failure, diabetes, dyslipidemia, respiratory disease (e.g., asthma, chronic obstructive pulmonary disease), bone disease (e.g., osteoporosis, osteoarthritis, rheumatoid arthritis), and mental health diseases. As of January 2013, this criterion specifies at least five of nine core chronic conditions—Alzheimer’s disease and end-stage renal disease were the added conditions. Programs may require no more than eight Part D drugs, although they may set the maximum at any number between two and eight. CMS set the annual cost threshold at \$4,000 in 2006, lowered it to \$3,000 in 2010, and increased it by an annual percentage each year beginning in 2012. The cost threshold for 2013 is \$3,144. CMS reimburses for MTM services for both community-dwelling beneficiaries and beneficiaries in long-term care settings. Although initial Part D MTM programs were designed as “opt-in,” more recently, MTM programs must enroll eligible beneficiaries using an “opt-out” approach.

Health care systems, pharmacy benefit management organizations, large self-insured employers, community pharmacies, or individual medical practices may also provide MTM services to beneficiaries who do not have Medicare Part D or who do not meet the CMS Part D criteria. For example, the Veterans Health Administration (VHA) includes MTM as one of several clinical activities provided to VHA health beneficiaries by VHA pharmacy services.<sup>18</sup> The VHA does not specify patient eligibility criteria for MTM services. Non-Part D MTM programs and research studies of MTM interventions may define their own patient eligibility criteria, which may or may not be similar to current CMS criteria, for example, requiring only one chronic condition to be eligible for services.

## **Interventions and Comparators**

As discussed, several pharmacy organizations have proposed core elements for an MTM service model.<sup>10,11</sup> These features can be summarized as follows:

- A comprehensive medication review (CMR) to identify and resolve medication-related problems.
- The generation of a personal medication report, which is a written list of the patient’s prescription and nonprescription drugs, herbal products, and dietary supplements.
- A patient-directed medication action developed in collaboration with the patient.
- Education, counseling, and resources to enhance patients’ understanding about using the medication and to improve adherence.
- Coordination of care, including documenting MTM services and providing that documentation to the patient’s other providers and referring patients to other providers as needed.

CMS requires that each beneficiary enrolled in a Part D MTM program be offered a minimum level of MTM services. These include:

- Interventions for both beneficiaries and prescribers;
- An annual CMR with written summaries in CMS’s standardized format:
  - The beneficiary’s CMR must include an interactive, person-to-person, or telehealth consultation that is performed by a pharmacist or other qualified provider (e.g., a nurse or a physician) and may result in a recommended medication action plan.
  - If a beneficiary is offered the annual CMR and is unable to accept the offer to participate, the pharmacist or other qualified provider may perform the CMR with the beneficiary’s prescriber, caregiver, or other authorized individual; and
- Quarterly targeted medication reviews with followup interventions when necessary.

CMS expects the CMR to meet the following professional service definition: “a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, and developing a prioritized list of medication-related problems, and creating a plan to resolve them with the patient, caregiver, and/or prescriber.”<sup>19, p. 6</sup> In addition, CMS expects the CMR to be “an interactive person-to-person or telehealth medication review and consultation conducted in real time between the patient and/or other authorized individual, such as [a] prescriber or caregiver, and the pharmacist or other qualified provider. It is designed to improve patients’ knowledge of their prescriptions, over-the-counter medications, herbal therapies, and dietary supplements; identify and address problems or concerns that patients may have; and empower patients to self-manage their medications and their health conditions.”<sup>19, p. 6</sup> Written summaries of the CMR are to be provided in CMS’s standardized written format that includes a beneficiary cover letter, medication action plan, and personal medication list.<sup>19</sup>

The service-level expectations of a CMR align closely with the definition of MTMs contained in the official health-reporting nomenclature of CPT.<sup>@20,21</sup> The CPT MTM codes define three components that may each vary in complexity or time required to complete. These components are (1) assessment of drug-related needs, (2) identification of drug therapy problems, and (3) complexity of care planning and followup evaluation. Recently, transitional management CPT codes have been established for use within the first 29 days of patient discharge from an acute care facility. These codes also include elements of medication management, specifically medication reconciliation. MTM CPT codes cannot be used by the same professional in the same time frame as transitional care management codes, suggesting that the medication management activities during transitions of care are a distinct category of MTM services.<sup>22</sup>

Disease-management, case-management, and self-management interventions have components that overlap with MTM components—for example, provision of education and counseling to increase medication adherence or coordination of care. Our preliminary literature search yielded many pharmacist-led interventions that were termed as one of these three types of interventions (e.g., a pharmacist-led diabetes disease management intervention). We relied on the descriptions in the Robert Wood Johnson Foundation Research Synthesis Report “Care management of patients with complex health care needs” for guidance to make distinctions between MTM and care management, case management, and disease management interventions.<sup>23</sup> We determined that our inclusion and exclusion criteria related to the intervention needed to define specific MTM intervention components, such that we would

identify relevant studies whether they were called “MTM” or not. We also considered the topic nominator’s original request, which was to consider different models for assisting patients in managing their medications for chronic disease among patients with multiple conditions. Thus, we synthesized our findings from the preliminary literature search; our exploration of case management, care management, and disease management definitions; and the topic nominator’s original request to determine that our intervention criteria needed to narrowly define multiple intervention components related to medication management, but that these components needed to be applied broadly to patients across their entire medication regimen. As a result, MTM services such as pharmacist-led single-disease management programs or anticoagulation clinics would not be considered for inclusion in our review. By bounding the review in this way, we end up with a more homogenous set of studies to synthesize.

## **Outcomes**

MTM is thought to influence a wide variety of outcomes. Two of the most common outcomes measured in MTM studies are drug therapy problems identified and drug therapy problems resolved. Taxonomies to describe drug therapy problems exist, but our preliminary literature search revealed many different approaches to measuring and reporting these outcomes. Other MTM outcomes relate to intermediate health outcomes measured typically by laboratory or other biometric tests for common chronic conditions; these may include hemoglobin A<sub>1c</sub>, blood pressure, cholesterol (e.g., total, low-density lipoprotein, and high-density lipoprotein cholesterol), and cardiac or pulmonary function (e.g., left ventricular ejection fraction, spirometry). Finally, still other MTM services relate to patient-centered outcomes (e.g., morbidity, mortality, adverse drug events, missed days of work or school, patient satisfaction with care, health-related quality of life).<sup>24</sup> The impact of MTM on health care utilization, intermediate health outcomes, and patient-centered outcomes may derive from identification and resolution of drug therapy problems, including improved medication adherence, fewer drug-related adverse events, and more efficient coordination of care.

## **Settings**

MTM services can be delivered in a variety of settings. These include inpatient facilities, ambulatory care settings (e.g., outpatient clinics, physician practices), retail pharmacies in the community, and long-term care settings such as assisted living or skilled nursing facilities. In addition, telephone-based MTM services may be provided to community-dwelling adults by professional staff (often pharmacists) employed by pharmacy benefits management companies or other commercial health care companies that have centralized call centers. The setting in which MTM is delivered depends on the type of provider delivering the service and the goals and scope of the MTM program. Because MTM refers to a wide variety of services, a review of such interventions needs to be bounded to ensure that the interventions synthesized in the review are reasonably comparable. For example, studies focused on MTM services provided during and shortly after an acute hospital stay may not be comparable to MTM services provided to outpatients because the goals of therapy and the acuity of the patient’s status are very different. Based on our preliminary literature search, we found that most studies in inpatient settings were focused either on single-medication reconciliation interventions during or at discharge or focused on integrated clinical pharmacy management in acute settings. We also considered the topic nominator’s proposed research questions, which were decidedly focused on MTM provided to outpatients.

## **Timing**

Because MTM is used to define a broad range of services, MTM services can be provided as one-time interventions or longitudinally during multiple episodes of care depending on the specific type of MTM service and care setting. For example, medication reconciliation or immunization is a type of MTM service that is typically done during a single episode of care. The pharmacy profession consensus definition for MTM includes monitoring and evaluation of a patient's response to therapy, and the MTM Core Service Model includes followup as a component. Similarly, CPT codes for MTM services include a component involving complexity of care planning and followup. Requirements for Medicare Part D MTM programs include a followup component at least quarterly following an initial comprehensive medication review. Thus, we determined that we needed to establish inclusion criteria to distinguish interventions designed to support longitudinal medication management as opposed to studies of one-time interventions.

## **Contextual Factors**

Our preliminary literature search identified pharmacists as the typical interventionist for providing MTM services. CMS guidelines require that MTM be delivered by a pharmacist or other qualified health care provider. Professional pharmacy organizations have been actively involved in proposing delivery models, standards, and recommendations for MTM services. Pharmacist training varies considerably. Before the 1990s, individuals could become registered pharmacists with a bachelor of science (B.S.) degree that required a minimum of 5 years of study. Current regulations require that individuals have a doctor of pharmacy (Pharm.D.) degree, which requires a minimum of 6 years of study and provides more clinical training than B.S. programs. In addition, many Pharm.D. graduates pursue advanced training through residency, fellowship, and certificate programs. Some of these programs focus on areas such as MTM. The influence that interventionist type (e.g., physician, nurse pharmacist), education, and MTM-specific training have on MTM effectiveness is unknown.

Numerous factors other than clinical specialty may affect the quality of MTM services. Mode, frequency, and interval of delivery may influence MTM success, as may specific MTM components and the fidelity of their implementation. One key factor is how well an MTM provider understands the patient-specific goals of medication therapy. Integrating MTM services with usual care may help ensure that the goals of MTM are achieved. Integration of services and usual care refers to the ability of the MTM provider to bidirectionally communicate with patients and multiple prescribers and ease of MTM interventionist access to patients' medical records.

Health care reimbursement systems may also influence the delivery of MTM services. Not all private insurers cover MTM services. The degree to which MTM component services differ for Medicare beneficiaries when compared with non-Medicare beneficiaries is not known.

Finally, certain patient populations may have considerable difficulty accessing or participating in MTM services. Examples include individuals who are homebound, individuals who have physical or cognitive disabilities, patients without health insurance, and patients living in rural areas.

## **Scope and Key Questions**

### **Scope of the Review**

MTM is a complex intervention, which could have different components depending on the goals and scope of the MTM program. This review seeks to catalog outpatient-based MTM interventions, assess the overall effectiveness of outpatient-based MTM in comparison with usual care, examine the factors under which outpatient-based MTM is effective and optimally delivered, assess what types of patients are likely to benefit from outpatient-based MTM services, and assess what types of patients may be at risk of harms from such programs. This review does not address (1) MTM services provided within inpatient settings or shortly after hospital discharge, (2) disease management services provided by pharmacists, or (3) interventions designed as a single episode of contact. The rationale for limiting the scope to exclude some types of MTM interventions is to ensure that included studies are reasonably comparable with respect to intended goals and purpose of the MTM intervention.

### **Relevance of Research Question to Clinical Decisionmaking or Policymaking**

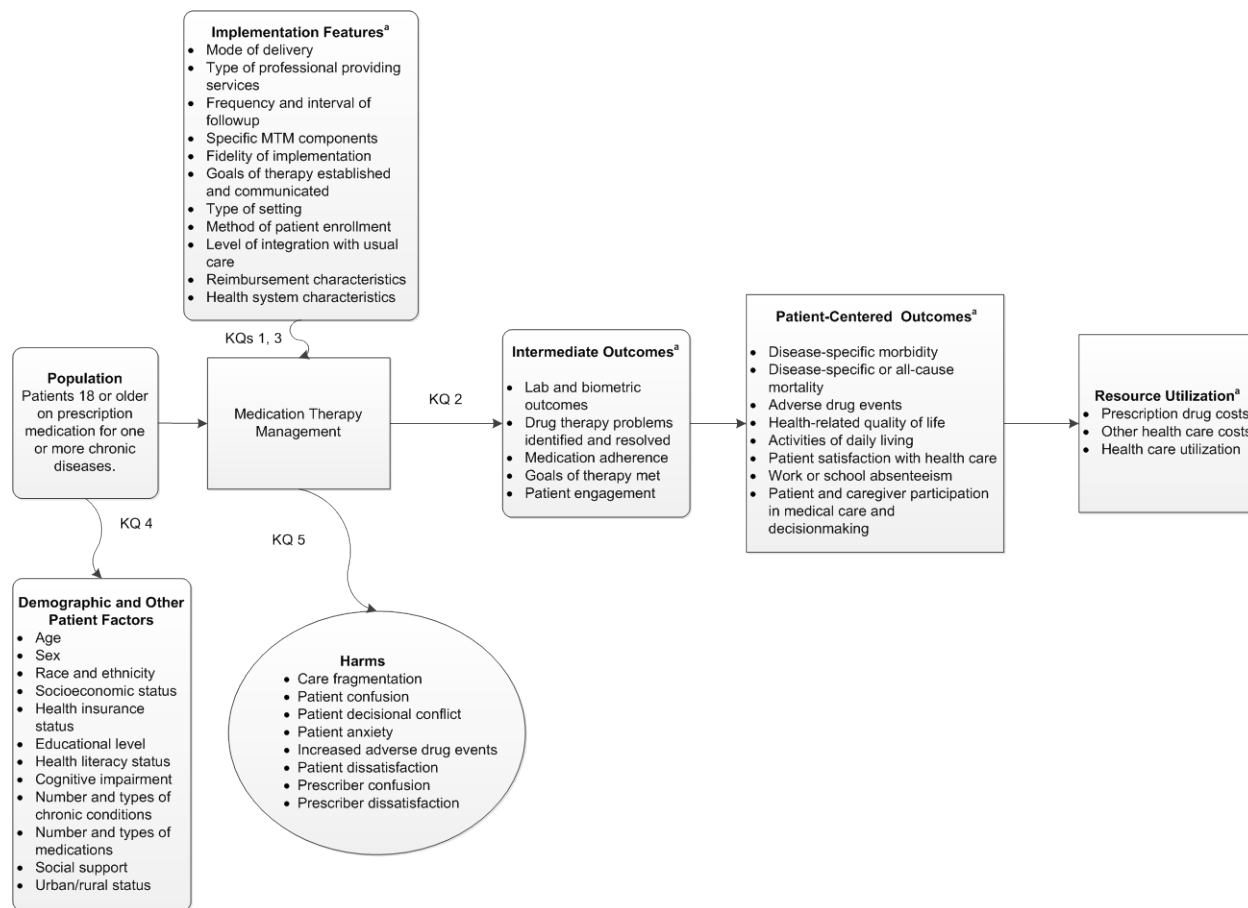
The Key Questions (KQs) we address are highly relevant to both clinical decisionmaking and policies regarding MTM services. Identifying demonstrably effective models and components of MTM services will help patients and their health care providers achieve important intermediate and long-term health-related outcomes. Our findings will help providers of MTM services, particularly pharmacists and pharmacy benefit managers, understand what works well in which settings and with which patients; the findings will have the potential to improve the efficiency of delivery and thus improve the value of MTM services. Lastly, a better understanding of the comparative effectiveness of MTM services will assist CMS with future revisions or enhancements to the policies governing coverage for MTM services.

### **Key Questions**

The KQs are listed below and placed in relation to another and the PICO in the analytic framework (Figure 1). Specific details regarding patient population, intervention components, and outcomes are provided in the section that follows the analytic framework.

# Analytic Framework

Figure 1. Analytic framework for outpatient medication therapy management



<sup>a</sup> The population, intervention, outcomes, and setting are described in detail in the text.

Abbreviations: KQ = Key Question; MTM = medication therapy management.

**KQ 1:** What are the components and implementation features of outpatient MTM interventions?

**KQ 2:** In adults with one or more chronic diseases who are taking prescription medications, is MTM effective in improving the following:

- Intermediate outcomes, including biometric and laboratory measures, drug therapy problems identified, drug therapy problems resolved, medication adherence, goals of therapy met, and patient engagement in medication management?
- Patient-centered outcomes, such as disease-specific morbidity, disease-specific or all-cause mortality, adverse drug events, health-related quality of life, activities of daily living, patient satisfaction with

health care, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking?

- c. Resource utilization, such as prescription drug costs, other health care costs, and health care utilization?

**KQ 3:** Does the effectiveness of MTM differ by MTM components and implementation features?

**KQ 4:** Does the effectiveness of MTM differ by patient characteristics, including but not limited to patient demographics and numbers and types of conditions and medications?

**KQ 5:** Are there harms of MTM, and if so, what are they?

## **Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS)**

Table 2 lays out the PICOTS for this review. For this review, we take a broad perspective on the population evaluated; we do not limit the review to populations meeting CMS Part D MTM eligibility criteria. Specifically, we did not require multiple chronic conditions or a minimum number or level of expenditures on prescription drugs. For the intervention, we required a comprehensive medication review, patient-directed education or counseling, an element of provider followup, and care coordination as the minimum intervention criteria. We established several eligible comparators and detailed intermediate process or health outcomes, patient-centered outcomes, and health care utilization outcomes. We also identified some potential harm outcomes, including patient confusion or decision conflict. Lastly, we established exclusion criteria related to studies conducted in inpatient settings or shortly after an inpatient stay and required the intervention to be designed such that followup to patients was available, regardless of whether the patient actually received any followup.

**Table 2. Populations, interventions, comparators, outcomes, timing, and settings**

<b>PICOTS</b>	<b>Inclusion and Exclusion Criteria and Relevant Factors for Study Abstraction</b>
Populations	<p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• Patients ages 18 or older with one or more chronic conditions requiring the use of prescription medication to manage symptoms or prevent progression of chronic disease</li> </ul> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"> <li>• Patients in long-term or acute care settings without access or control over their own medication administration.</li> </ul> <p><i>Relevant factors:</i></p> <ul style="list-style-type: none"> <li>• Patient characteristics that may influence intervention effectiveness:               <ul style="list-style-type: none"> <li>○ Age, sex, race and ethnicity, socioeconomic status, health insurance status, education level, health literacy status, cognitive impairment, number and types of chronic conditions, social support, and urban/rural status</li> </ul> </li> </ul>



**Table 2. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

PICOTS	Criteria
Interventions	<p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"><li>• A bundle of medication-related services described by the term “MTM” or “pharmaceutical care” or “clinical pharmacy services” or a similar phrase, that include <i>at a minimum</i> the following three elements:<ul style="list-style-type: none"><li>○ Comprehensive medication review covering all prescription and nonprescription drugs, herbs, and supplements taken by the patient</li><li>○ Patient-directed education and counseling or other resources to enhance understanding of the use of medication</li><li>○ Coordination of care, including prescriber-directed interventions; documentation of MTM services for use by the patient’s other providers; and referral to other providers, clinicians, or resources when appropriate<sup>19</sup></li></ul></li></ul> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"><li>• The following types of interventions will be excluded:<ul style="list-style-type: none"><li>○ Medication reconciliation interventions that did not include all three elements as described above</li></ul></li><li>• The following types of interventions may include MTM services, but MTM may represent only one component of the overall intervention:<ul style="list-style-type: none"><li>○ Disease-management interventions<sup>23</sup></li><li>○ Case- or care-management interventions<sup>23</sup></li><li>○ Patient-centered medical home models of care</li><li>○ Fully integrated, collaborative care models involving multiple disciplines and specialties</li></ul></li><li>• These types of interventions will be excluded unless studies contain the same level of overall medical care or services among different study arms such that the effect of MTM can be isolated. For example, a study with two arms that has one arm with a care management intervention that includes MTM services and the other arm that has the care management intervention without MTM services could be included. By contrast, a study that includes a care management intervention with MTM in one arm and usual medical care (no care management intervention) in the other arm would not be included.</li></ul> <p><i>Relevant factors:</i></p> <ul style="list-style-type: none"><li>• Implementation features that may influence intervention effectiveness include the following:<ul style="list-style-type: none"><li>○ Mode of delivery: telephone, face-to-face, virtual (Web/online/Internet), and remote video</li><li>○ Type of professional providing initial and followup MTM service: pharmacist, nurse, physician, other clinician</li><li>○ Frequency and interval of followup for MTM services</li><li>○ Specific MTM components used</li><li>○ Fidelity in implementing MTM components: to what extent were services delivered as designed or intended</li><li>○ Establishing and communicating goals of drug therapy to patients and among care providers</li><li>○ Method of identifying patients for enrollment (e.g., population health data, provider referral for services, enrollment during a transition in care, targeting highly activated patients, targeting patients at time of high risk for event [e.g., when prescribing a new drug])</li><li>○ Level of integration of MTM with usual care, which includes access to real-time clinical information and laboratory values, and regular and consistent communication among prescribers and persons providing MTM services</li><li>○ Reimbursement characteristics (e.g., who is paying for cost of MTM services, who is reimbursed for MTM services, whether services are separately reimbursable)</li><li>○ Health system characteristics (e.g., are services being provided within an accountable care organization, patient-centered medical home, or some other unique system setting, such as the Veterans Health Administration, the Indian Health Service, non-U.S. single-payer system)</li></ul></li></ul>

**Table 2. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

<b>PICOTS</b>	<b>Criteria</b>
Comparators	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Usual care, as defined by the studies</li><li>• Different bundles of MTM services (e.g., five components vs. three components)</li><li>• Same MTM services provided by different health care professionals (e.g., pharmacist vs., physician or nurse)</li><li>• Same bundle of MTM services delivered by different modes (e.g., telephone vs. in person)</li><li>• Same bundle of MTM services provided at different intensities, frequencies, or level of integration with prescribers</li></ul>
Outcomes	<i>Inclusion criteria:</i> <ul style="list-style-type: none"><li>• Studies must report at least one eligible outcome:<ul style="list-style-type: none"><li>○ Intermediate outcomes:<ul style="list-style-type: none"><li>- Disease-specific laboratory or biometric outcomes (e.g., hemoglobin A<sub>1c</sub>; blood pressure; total, low-density lipoprotein, or high-density lipoprotein cholesterol; pulmonary function; renal function; left ventricular ejection fraction; or other laboratory or biometric outcome specific to diseases covered)</li><li>- Drug therapy problems identified as defined by primary studies but typically include the following: medications being taken but not indicated; medications indicated but not prescribed; patient adherence issues; suprathreshold doses; subtherapeutic doses; generic, formulary, or therapeutic substitution issue; complex regimen that can be simplified with same therapeutic benefit; and potential for drug-drug interactions or adverse event.</li><li>- Drug therapy problems that are resolved as defined by primary studies but typically include the following: needed drug initiated; unnecessary drug discontinued; change in drug dose, form, or frequency; or generic, formulary, or therapeutic substitution</li><li>- Medication adherence</li><li>- Goals of therapy met</li><li>- Patient engagement (e.g., initial and continuing patient participation in the MTM program)</li></ul></li><li>○ Patient-centered outcomes<ul style="list-style-type: none"><li>- Disease-specific morbidity, including falls and fall-related morbidity, and outcomes specific to the patient's underlying chronic conditions (e.g., Patient Health Questionnaire 9 [PHQ9], disease-specific symptoms, reduced number of disease-specific acute exacerbations or events)</li><li>- Disease-specific or all-cause mortality, including fall-related mortality</li><li>- Reduced (actual) adverse drug events (frequency and/or severity)</li><li>- Health-related quality of life as measured by generally accepted generic health-related quality-of-life measures (e.g., short-form questionnaires, EuroQOL) or disease-specific measures</li><li>- Activities of daily living as measured by generally accepted standardized measures of basic and/or instrumental activities of daily living (e.g., Katz, Lawton, or Bristol instruments) or with instruments that have demonstrated validity and reliability</li><li>- Patient satisfaction with MTM care</li><li>- Work or school absenteeism</li><li>- Patient and caregiver participation in medical care and decisionmaking</li></ul></li><li>○ Resource utilization<ul style="list-style-type: none"><li>- Prescription drug costs and appropriate prescription drug expenditures</li><li>- Other health care costs</li><li>- Health care utilization (hospitalizations, emergency department visits, and physician office visits)</li></ul></li><li>○ Harms<ul style="list-style-type: none"><li>- Care fragmentation</li><li>- Patient confusion</li><li>- Patient decisional conflict</li><li>- Patient anxiety</li><li>- Increased (actual) adverse drug events</li><li>- Patient dissatisfaction with care</li><li>- Prescriber confusion</li><li>- Prescriber dissatisfaction</li></ul></li></ul></li></ul>

**Table 2. Populations, interventions, comparators, outcomes, timing, and settings (continued)**

<b>PICOTS</b>	<b>Criteria</b>
Timing	<p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"><li>• Interventions should have at least two separately identifiable episodes of patient-directed MTM services, with any interval of time in between episodes.</li><li>• For studies that report outcomes at different points in time, we only considered outcomes measured after the second episode of care and will use the longest-term outcomes reported by the study.</li></ul> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"><li>• Interventions designed as single-episode interventions without any provision for followup and monitoring.</li></ul>
Setting	<p><i>Inclusion criteria:</i></p> <ul style="list-style-type: none"><li>• Ambulatory settings (e.g., outpatient clinics or private physician offices), long-term-care (e.g., assisted living) settings if residents have control over medication self-administration, or retail pharmacy settings</li><li>• Home setting</li><li>• Interventions conducted in the United States</li><li>• Interventions conducted in non-U.S. countries published in English</li></ul> <p><i>Exclusion criteria:</i></p> <ul style="list-style-type: none"><li>• MTM services that are delivered exclusively in inpatient settings.</li><li>• MTM services delivered at the time of hospital discharge or shortly after (e.g., within a few weeks)</li></ul> <p><i>Relevant factors:</i></p> <ul style="list-style-type: none"><li>• The MTM intervention itself may be delivered by home visits, by telephone, via the Web, or in other non-face-to-face modalities, such as video conferencing.</li></ul>

Abbreviations: MTM = medication therapy management; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; PHQ9 = Patient Health Questionnaire 9.

## Organization of This Report

The remainder of this report describes our methods, presents the results of our synthesis of the literature, discusses our conclusions, and provides other information relevant to the interpretation of this work. The Methods section describes our scientific approach for this systematic review in detail. The Results section presents our findings for all five of the KQs and includes summary and strength-of-evidence tables. In the Discussion section, we summarize the findings and discuss the implications for clinical practice and further research. A complete list of references, acronyms, and abbreviations follows the Discussion section.

This report contains the following appendixes: Appendix A contains the exact search strings we used in our literature searches. Appendix B documents the title and abstract and full-text review forms. Studies excluded at the stage of reviewing full-text articles with reasons for exclusion are presented in Appendix C. Evidence tables appear in Appendix D. Appendix E lists studies rated high risk of bias and reasons for excluding them from relevant KQ analyses. Quantitative analyses are presented in Appendix F.

## Methods

The methods for this comparative effectiveness review (CER) on medication therapy management (MTM) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>). We specified methods and analyses a priori in a protocol posted on the AHRQ website,<sup>25</sup> following a standard framework for specifying population, interventions, comparators, outcomes, and settings (PICOTS). The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.<sup>26</sup> We describe below instances in which our a priori methods required further specification during the project.

### Topic Refinement and Review Protocol

The topic of this report and preliminary Key Questions (KQs) arose through a nomination from the Pharmacy Quality Alliance. Key Informants representing several clinical and scientific disciplines provided input on the initial KQs; we revised them as needed. An initial draft of the revised KQs was posted for public comment from March 6, 2013, through April 2, 2013, on the AHRQ Effective Health Care program Web site. We received comments from 23 professional organizations and individuals and further revised KQs as appropriate. Specifically, we

1. added a new KQ (KQ 1) to describe the components and implementation features of MTM interventions,
2. included additional intermediate outcomes in KQ 2,
3. reworded KQ 3 to include MTM components,
4. specified MTM components and implementation features for KQ 3 in the PICOTS,
5. specified additional patient characteristics for KQ 4 in the PICOTS, and
6. rephrased KQ 5 to make the response conditional on identifying whether any harms of MTM exist.

### Literature Search and Identification Strategy

#### Search Strategy

To identify articles relevant to each KQ, we began with a focused MEDLINE<sup>®</sup> search for MTM interventions using a combination of medical subject headings (MeSH<sup>®</sup>) and title and abstract keywords and limiting the search to English-language and human-only studies (Table 3) (inception through January 9, 2014). We also searched the Cochrane Library (inception through January 10, 2014) and the International Pharmaceutical Abstracts database (inception through January 10, 2014) using analogous search terms. (Appendix A). We selected these databases based on preliminary searches and consultation with content experts. We conducted quality checks to ensure that the searches identified known studies (i.e., studies identified during topic nomination and refinement). Based on these quality checks, we revised and ran additional searches (specifically, drug therapy management, drug therapy problem, and medications management) to avoid missing articles that might prove eligible for this CER.

In addition, we searched the gray literature for unpublished studies relevant to this review and included studies that met all the inclusion criteria and contained enough methodological information to assess risk of bias. Specifically, sources of gray literature included ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform, Health Services Research Projects in Progress (HSRProj), the National Institutes of Health Research Portfolio Online Reporting Tools, the Database of Promoting Health Effectiveness Reviews, the New York Academy of Medicine Grey Literature Report, and CMS.gov. AHRQ’s Scientific Resource Center managed the process of submitting requests for scientific information packets, which contain information about MTM programs and services of interest from relevant providers.

We reviewed our search strategy with an independent information specialist and the Technical Expert Panel and supplemented it according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to identify any relevant citations that our electronic searches might have missed.

We conducted an updated literature search (of the same databases searched initially) concurrent with the peer review process. We also investigated any literature the peer reviewers or the public suggest and, if appropriate, incorporated additional studies into the final review. The appropriateness of those studies was determined using the methods and criteria described above.

We planned to include pooled estimates of effect or other relevant results from systematic reviews that meet our inclusion/exclusion criteria and to evaluate the quality of included systematic reviews using the AMSTAR tool.<sup>27</sup> If appropriate and feasible, we had planned to update the results of these reviews quantitatively or qualitatively. We also planned to review reference lists of systematic reviews that used exclusion and inclusion criteria that differed from ours to ensure that we include all relevant studies.

## Inclusion/Exclusion Criteria

We specified our inclusion and exclusion criteria based on the population, intervention, outcome, timing, and settings identified through the topic refinement exercise. We excluded studies published in languages other than English. We excluded study designs without control groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes.

**Table 3. Literature search terms for medication therapy management studies**

Populations	None; no population terms were used to avoid restricting the search yield
Interventions	(“Medication Therapy Management”[Mesh] OR “medication therapy management” OR “comprehensive medication review” OR “personal medication record” OR (“medication” AND “action plan”) OR “medication therapy review” OR “Medication Reconciliation”[Mesh] OR (med* AND reconciliation) OR “medication-related problems” OR MTMP OR prescriber intervention* OR “drug utilization management” OR “chronic care improvement” OR “drug therapy services” OR (“utilization management strategies” OR “utilization management strategy”) OR “medication counseling” OR “pharmaceutical case management” OR “drug therapy management”
Outcomes	“optimized treatment outcomes” OR (patient OR patients) AND “medication understanding”) OR (“drug therapy outcome” OR “drug therapy outcomes”)
Study designs	None; no study design terms were used to avoid restricting the search yield
Limits	Humans; English language

In conducting the review, we found that we needed to define the intervention with greater specificity than originally thought so that we could include MTM interventions but exclude disease management interventions. Specifically, we required that included studies had conducted a *comprehensive*, rather than condition-specific, medication review, as required in our PICOTS criteria. Although we had not planned to contact study authors routinely for additional information, the lack of clarity regarding intervention elements in numerous published studies necessitated our contacting authors. For these studies, we based our decisions on inclusion or exclusion based on email communication. (Appendix D specifies the studies or publications for which we sought such information but received no response from authors as of the time the draft report was submitted for peer review.)

## **Study Selection**

Pairs of trained members of the research team reviewed each title and abstract independently against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. For studies that lack adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination.

We retrieved and reviewed the full text of all included titles during the title/abstract review phase. Two trained members of the team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria specified in Table 4. If both reviewers agreed that a study did not meet the eligibility criteria, they excluded the study. If the reviewers disagreed, they discussed differences to achieve a consensus. If they could not reach consensus, a third senior member of the review team resolved the conflict. We tracked all results in an EndNote<sup>®</sup> (Thomson Reuters, New York, NY) database. We recorded the reason that each excluded full-text publication did not satisfy the eligibility criteria. Appendix C lists all studies excluded at this stage together with the reason(s) for exclusion.

## **Data Extraction**

For studies that met our inclusion criteria, we abstracted relevant information into evidence tables (Appendix D). We piloted our approach with a sample of studies and revised the form thereafter. We designed data abstraction forms to gather pertinent information from each article, including the characteristics of the study populations, interventions, comparators, outcomes, timing, settings, study designs, methods, and results. A second member of the team reviewed all data abstractions for completeness and accuracy. (Relevant forms can be found in Appendix B.)

**Table 4. Inclusion/exclusion criteria for medication therapy management studies**

<b>Category</b>	<b>Inclusion</b>	<b>Exclusion</b>
Population	Patients aged 18 or older with one or more conditions requiring the regular use of prescription medication to manage symptoms or prevent progression of chronic disease	<ul style="list-style-type: none"> <li>• Children under age 18</li> <li>• Adults with acute conditions</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>• Those specified in the PICOTS criteria listed in Table 1 (Introduction)</li> <li>• More complex interventions with an MTM component that are compared with identical interventions without an MTM component (including care management and disease management)</li> </ul>	<ul style="list-style-type: none"> <li>• Drug therapy services for a single drug (e.g., warfarin clinics, statin clinics)</li> <li>• Interventions in which the effect of the MTM component cannot be isolated (e.g., case management or disease management with an MTM component)</li> <li>• Self-management programs</li> <li>• Isolated medication reconciliation interventions</li> <li>• Integrated pharmacy services within inpatient settings</li> <li>• One-time corrective interventions related to medication management</li> </ul>
Control interventions	<ul style="list-style-type: none"> <li>• Those specified in the PICOTS criteria listed in Table 1 (Introduction)</li> </ul>	
Outcomes	<ul style="list-style-type: none"> <li>• Those specified in the PICOTS criteria listed in Table 1 (Introduction)</li> </ul>	<ul style="list-style-type: none"> <li>• Studies that do not include at least one of the outcomes listed under the inclusion criteria</li> </ul>
Timing of intervention and followup	<ul style="list-style-type: none"> <li>• Interventions should have at least two separately identifiable episodes of MTM services (either patient directed or provider directed or both) with or without specifying any certain amount of time between those episodes</li> <li>• For studies that report outcomes at different points in time, we considered only outcomes measured after the second episode of care.</li> </ul>	<ul style="list-style-type: none"> <li>• Studies that measure outcomes only after one episode of MTM care</li> </ul>
Settings	<ul style="list-style-type: none"> <li>• Ambulatory (e.g., outpatient clinics, private physician offices, or retail pharmacy settings) and long-term care settings</li> <li>• May be delivered by telephone, via the Web, or in other non-face-to-face modalities, such as video conferencing</li> <li>• Interventions conducted in the United States and other countries will be included</li> </ul>	<ul style="list-style-type: none"> <li>• Inpatient settings, if delivery of MTM services occurs almost exclusively in the inpatient setting</li> </ul>
Geography	<ul style="list-style-type: none"> <li>• No limits</li> </ul>	<ul style="list-style-type: none"> <li>• Not applicable</li> </ul>
Dates of search	<ul style="list-style-type: none"> <li>• No limits; searches will be updated while the draft report is out for peer review</li> </ul>	<ul style="list-style-type: none"> <li>• Not applicable</li> </ul>
Study designs	<ul style="list-style-type: none"> <li>• Original research</li> <li>• Eligible study designs include: <ul style="list-style-type: none"> <li>- Randomized controlled trials</li> <li>- Nonrandomized controlled trials</li> <li>- Prospective controlled cohort studies</li> <li>- Retrospective controlled cohort studies</li> <li>- Case-control studies</li> <li>- Systematic reviews and meta-analyses</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Case series</li> <li>• Case reports</li> <li>• Nonsystematic reviews</li> <li>• Studies without a control group</li> </ul>
Study duration	No limits	Not applicable
Publication language	English	All other languages
Publication type	Any publication reporting primary data	Publications not reporting primary data

Abbreviations: MTM = medication therapy management; PICOTS = populations, interventions, comparators, outcomes, timing, and setting.

## Assessment of Risk of Bias of Individual Studies

To assess the risk of bias of individual studies, we used predefined criteria developed by AHRQ.<sup>28</sup> For randomized controlled trials (RCTs), we relied on the risk-of-bias tool developed by the Cochrane Collaboration.<sup>29</sup> We assessed the risk of bias of observational studies using an item bank developed by RTI International.<sup>30</sup>

In general terms, results of a study with low risk of bias are considered valid. Studies marked low risk of bias did not have any major flaws in design or execution. A study with medium risk of bias is susceptible to some bias but probably not sufficient to invalidate its results. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Primary concerns for our review included selection bias, confounding, performance bias, detection bias, and attrition bias. Very high attrition rates, particularly when coupled with a failure to control for confounding or conduct intention-to-treat analyses, resulted in a rating of high risk of bias for trials and prospective cohort studies. Likewise, we rated studies with an inherently high risk of confounding in design (e.g., observational studies comparing refusers versus acceptors of MTM interventions) as high risk of bias if they failed to address confounding through design (e.g., matching) or analysis (e.g., regression). Specifically, we evaluated trials on the adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity. For observational studies, we did not assess adequacy of randomization or allocation concealment but did assess for confounding. We also evaluated trials for confounding due to randomization failure through biased selection or attrition. In other words, we evaluated trials with potential randomization failure for the same risks of bias as observational studies.

We excluded studies that we deemed at high risk of bias from our main data synthesis and main analyses. We included them for sensitivity analyses; in cases when we had no other available or credible evidence, we included in the report a brief synopsis of studies assessed as high risk of bias.

## Data Synthesis

When we found three or more similar studies for a comparison of interest, we conducted meta-analysis of the data from those studies using Comprehensive Meta-Analysis software. For all analyses, we used random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance;<sup>31</sup> that is, we qualitatively assessed the PICOTS of the included studies, looking for similarities and differences. When we conducted quantitative syntheses (i.e., meta-analysis), we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the  $I^2$  statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of  $I^2$  depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., the p-value from the chi-squared test or a confidence interval for  $I^2$ ). Where relevant, we examined potential sources of heterogeneity using sensitivity analysis.

When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized



the data qualitatively. Whenever possible, we computed confidence intervals for individual outcomes.

Numerous articles did not provide complete information about findings (e.g., 95 percent confidence intervals; statistical significance values, or between-group data). In many cases, therefore, we had to calculate odds ratios, mean differences, or standardized mean differences, the relevant 95 percent confidence intervals, and p-values. In all such cases in which we calculated data, we specify this in the Results chapter; information not specifically called out as “calculated” is taken from the original articles.

## **Grading Strength of Evidence for Individual Comparisons and Outcomes**

We graded the strength of evidence based on the guidance established for the AHRQ Evidence-based Practice Center program.<sup>32</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: study limitations (includes study design and aggregate quality), consistency (similar magnitude and direction of effect), directness (evidence links interventions directly to outcome of interest for the review), and precision of the evidence (degree of certainty surrounding an effect estimate based on sample size and number of events). In addition, the evidence may be rated as lower strength for bodies of evidence with suspected reporting bias from publication, selective outcome reporting, or selective analysis reporting. Regardless of the specific risk of bias of observational studies, this approach to grading the evidence assigns observational studies a grade of high study limitations, which then leads to low strength of evidence. The strength of evidence from observational studies can be rated as higher for observational studies for scenarios such as a strong dose-response association, plausible confounding that would decrease the observed effect, and a high strength of association (magnitude of effect). We evaluated optimal information size criteria to make judgments about precision based on guidance from Guyatt and colleagues<sup>33</sup> and based our grades on low or medium risk-of-bias RCTs or observational studies unless none were available.

Our approach is consistent with current strength of evidence guidance developed by GRADE and AHRQ EPCs. The GRADE guidance explicitly discourages the inclusion and averaging of risk of bias across studies with different underlying risk-of-bias criteria. Rather, it suggests considering including only studies with a lower risk of bias.<sup>34</sup> Likewise, the AHRQ EPC guidance notes that reviewers may focus “strength of evidence on the subset of studies that provide the least limited, most direct, and most reliable evidence for an outcome or comparison, after analysis of all the evidence.”<sup>32, p. 20</sup>

Table 5 describes the grades of evidence that can be assigned.<sup>35</sup> Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions examined in this review. Two reviewers assessed each domain for each key outcome resolved any differences by consensus discussion or referral to a third, senior member of the team. We graded the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature; we did not grade the strength of evidence for KQ 1 (on components and features of MTM services). The grades described in Table 5 describe the state of evidence (which may demonstrate benefit, harm, or no effect) and the confidence in the stability of that state. An insufficient grade is not a statement about lack of efficacy or effectiveness; rather it is a statement about the lack of convincing evidence on benefit, harm, or lack of effect.

**Table 5. Definitions of the grades of overall strength of evidence**

<b>Grade</b>	<b>Definition</b>
High	<b>High confidence that the evidence reflects the true effect.</b> Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	<b>Moderate confidence that the evidence reflects the true effect.</b> Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	<b>Low confidence that the evidence reflects the true effect.</b> Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

## Assessing Applicability

We assessed applicability of the evidence following guidance from the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”<sup>36</sup> We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age and health status of enrolled populations, health insurance coverage and access to health care, and complexity and intensity of the MTM intervention.

## Peer Review and Public Commentary

This report received extensive external peer review and was posted for public comment December 2, 2013, to January 6, 2014. Comments were received from five peer reviewers and four TEP members. In addition, we received public comments from eight individuals and professional organizations. We addressed all comments in the final report, making revisions as needed; a disposition of comments report will be publicly posted 3 months after release of the final report.

# Results

## Introduction

This section of this comparative effectiveness review (CER) on medication therapy management (MTM) first presents the results of the literature searches. We then document the results for each Key Question (KQ). KQ 1 describes MTM intervention characteristics. KQ 2 presents evidence on the effectiveness of MTM interventions, focusing on intermediate outcomes, then patient-centered (health) outcomes, and then use of health care resources or costs. The presentation of KQ 3 summarizes the evidence by intervention components and implementation features; KQ 4 summarizes evidence by patient characteristics. KQ 5 examines the evidence on harms of MTM programs. Appendix E has two parts pertaining to these KQs: the first part has the lengthy descriptions of the design of all included studies (for KQ 1); the second presents the evidence tables, organized by outcome, for the remaining KQs.

Generally, for KQs 2 through 5, the text gives key points and the related strength of evidence grades, followed by a detailed synthesis of the relevant studies. We also present pairs of tables for each outcome. One gives basic summary information about the results of included studies, indicating whether the quantitative data had been what the investigators reported or were calculated by us. The other table in these sets documents the strength of evidence grades for major outcomes (showing the ratings for required domains and, in a small number of cases, any ratings for optional domains). Appendix F contains the tables documenting how we arrived at risk-of-bias assessments for individual studies.

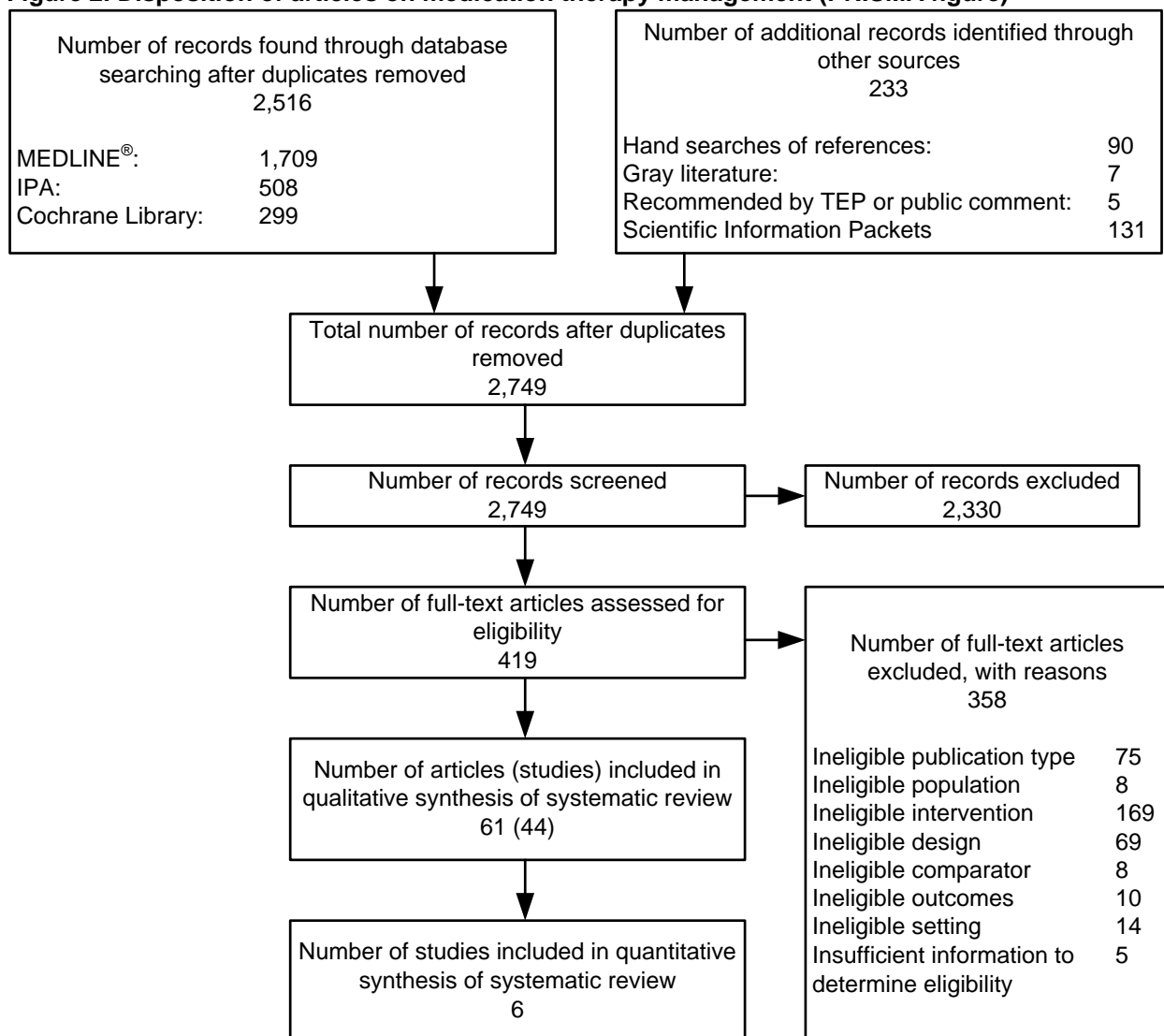
Most data can be found in tables and are not repeated in text. As noted in Methods, we focus on studies of low or medium risk of bias; when we need to summarize information for studies of high risk of bias, we note the principal problems leading to that rating.

Finally, our inclusion criteria for study designs were expansive and included randomized controlled trials (RCTs) and a variety of observational studies (nonrandomized controlled trials, cohort studies and the like). We use “studies” to refer to all types of investigations; we specify RCTs (or non-RCTs) as appropriate.

## Results of Literature Searches

Figure 2 presents our literature search results. Literature searches through January 9, 2014, for the final report, identified 2,516 unduplicated citations. Appendix A provides a list of all search terms used and the results of each literature search. In addition, we identified 233 publications through grey literature searches, suggestions from technical experts or public comments received during topic refinement, or hand searches of included studies, or Scientific Information Packets (SIPs). After applying our eligibility and exclusion criteria to titles and abstracts of all 2,749 identified citations, we obtained full-text copies of 419 published articles. We reapplied our inclusion criteria and excluded 358 of these articles from further review before doing the risk-of-bias assessment. Appendix C provides a list of excluded studies and reasons for exclusion at the full-text stage. The 61 articles included after full-text review represent 44 studies. Evidence tables for these 44 studies are provided in Appendix D.

**Figure 2. Disposition of articles on medication therapy management (PRISMA figure)**



Abbreviations: IPA = International Pharmaceutical Abstracts; PICOTS = populations, interventions, comparators, outcomes, timing, settings; TEP = technical expert panel.

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Scientific Resource Center placed the request for scientific information packets (SIPs) in the *Federal Register* on September 16, 2013; it posted them for 30 days. We included relevant data from responses to this request.

Table 6 summarizes study characteristics of included studies. Overall, 28 (77.8 percent) of included studies were conducted in the United States, and 16 (44.4 percent) were conducted prior to the 2003 Medicare Modernization Act, which established the framework for Medicare Part D MTM programs. Just over half of included studies used an RCT design (either parallel or cluster group), 3 (8.3 percent) used a nonrandomized controlled trial design, and the remaining studies (38.9 percent) used a cohort study design. Only 3 studies used an active treatment comparison group. Intermediate outcomes were the most commonly reported outcomes. Of the 36 studies, 1 was considered low risk of bias (2.3 percent), 19 were considered medium risk of bias (43.2

percent), 16 (36.4 percent) were considered high risk of bias, and 8 (18.2 percent) had mixed risk of bias ratings, depending on outcome.

**Table 6. Characteristics of included studies**

<b>Study characteristic</b>	<b>N (%)</b>
<b>Country</b>	
U.S.	35 (79.5)
Non-U.S.	9 (20.5)
Multiple	1 (2.3)
<b>Conducted prior to 2003 Medicare Modernization Act</b>	19 (43.2)
<b>Study design</b>	
RCT-parallel group	16 (36.4)
RCT-cluster group	5 (11.4)
Non-RCT	4 (9.1)
Cohort study	19 (43.2)
<b>Used an active treatment comparison arm</b>	5 (11.4)
<b>Outcomes measured</b>	
Intermediate outcomes (e.g., disease specific lab values, medication adherence, drug therapy problems)	32 (72.7)
Patient-centered outcomes (e.g., health outcomes, quality of life, patient satisfaction)	21 (47.7)
Utilization and economic outcomes	33 (75.0)
<b>Risk of bias</b>	
Low	1 (2.3)
Medium	19 (43.2)
High	16 (36.4)
Mixed	8 (18.2)

Abbreviations: N = number; RCT = randomized controlled trial; U.S. = United States.

## **Key Question 1: Components and Implementation Features of MTM Interventions**

KQ 1 was designed to synthesize descriptive findings regarding MTM intervention components and implementation features, which have been identified as important factors related to effectiveness of these interventions. Because this report is a CER, our study inclusion criteria included a requirement for a control or comparison arm. For that reason, our synthesis of descriptive findings related to MTM components and implementation features is limited to investigations that comparatively evaluated MTM; that is, it does not include all studies of MTM interventions, many of which we had excluded because of the lack of a comparison arm. Thus, our findings represent a somewhat circumscribed lens for the descriptive part of this review.

Synthesizing intervention components and implementation features across this body of evidence was challenging. Mainly, studies did not consistently describe the intervention characteristics or implementation features in sufficient detail to allow us to determine the extent to which certain components were used, at which intervals, and at what intensity. Even studies published after the 2003 Medicare Modernization Act, which formalized some aspects of pharmaceutical care, lacked sufficient reporting detail in many cases.

## Overall Descriptors of Study Interventions

Table 7 specifies the components and implementation features from our analytic framework (Figure 1 in Introduction). It also gives our assessment of the suitability or feasibility of synthesis, based on information available in the included studies across the entire evidence base.

**Table 7. Characteristics of medication therapy management interventions**

<b>Characteristic of the MTM Intervention (Specified in Analytic Framework in Introduction)</b>	<b>Summarize in Tables and Synthesize With Counts</b>	<b>Summarize in Table but Not Synthesize With Counts</b>	<b>Neither Summarize in Tables nor Synthesize With Counts</b>
Mode of delivery	Yes	NA	NA
Type of professional providing services	Yes	NA	NA
Frequency and interval of followup	Yes	NA	NA
Specific MTM components	NA	NA	Yes
Fidelity of implementation	NA	NA	Yes
Goals of therapy established and communicated	NA	NA	Yes
Type of setting	Yes	NA	NA
Method of patient enrollment	NA	Yes	NA
Level of integration with usual care	NA	Yes	NA
Reimbursement characteristics	Yes	NA	NA
Health system characteristics	Yes	NA	NA

Abbreviation: MTM =medication therapy management, NA = not applicable.

In the best case, we can summarize data in tables and synthesize the information with actual counts across the body of evidence. This is true for mode of delivery, type of professional giving the services, details about followup, settings, modes of reimbursement, and characteristics of health systems. Somewhat less can be done with methods for enrolling patients and level of integrating MTM with usual care, so information is just included in study-level summary tables (but not synthesized with actual counts across the body of evidence). Finally, information on specific MTM components, fidelity of implementation, and MTM goals was so inconsistent or sparse that we could not either synthesize or include information in summary tables.

Table 8 summarizes the intervention characteristics and features that were reported consistently enough to be synthesized with counts and frequencies—namely, those in Table 7 with an X in the first column. It also notes whether the investigators used the phrase “pharmaceutical care” or the phrase “medication therapy management” to refer to the program tested. For details about intervention frequency and interval of followup, the information in Table 8 is “as designed” (i.e., however, the investigators described their initial intentions).

**Table 8. Characteristics of medication therapy management studies by type of patient population (broad focus or narrow focus on conditions or diagnoses)**

<b>MTM Intervention</b>	<b>Characteristic of the Intervention</b>	<b>Overall (N =44) N (%)</b>	<b>Broad Focus (N=34) N (%)</b>	<b>Narrow Focus (N=10) N (%)</b>
Phrase used to describe intervention	Medication therapy management	20 (46)	18(53)	2 (20)
	Pharmaceutical care	14 (32)	9 (27)	5 (50)
	Other	10 (23)	7 (21)	3 (30)
Mode of delivery	Face-to-face only	22 (50)	14 (41)	8 (80)
	Telephone only	9 (21)	9 (27)	0
	Mixture of face-to-face and telephone	11 (25)	10 (29)	1 (10)
	Not reported	2 (5)	1 (3)	1 (10)
Professional	Pharmacist as interventionist	44 (100)	34 (100)	10 (100)
Frequency of followup as designed	One time with followup as needed	8 (18)	8 (24)	0
	Two times	7 (16)	7 (21)	0
	Three times	7 (16)	5 (15)	2 (20)
	Every 4 to 8 weeks for between 4 and 24 months	6 (14)	1 (3)	5 (50)
	Varied based on trigger (e.g., refill, physician visit, continuous enrollment for certain duration)	3 (7)	2 (6)	1 (10)
	Not reported	13 (30)	11 (32)	2 (20)
Clinical settings	Community pharmacy	7 (16)	3 (9)	4 (40)
	Centralized pharmacy	10(23)	10 (29)	0
	Outpatient medical clinic	16 (36)	11 (32)	5 (50)
	Home visits	1 (2)	1 (3)	0
	Integrated health system	2 (5)	2 (6)	0
	Multiple settings	8 (18)	7(21)	1 (10)
Reimbursement characteristics	Services provided through Medicare Part D benefit	10 (23)	10 (29)	0
	Services provided through some other health plan benefit	5 (11)	3 (9)	2 (20)
	Services provided through study-related funding	3 (7)	3 (9)	0
	Reimbursement details not reported	26 (59)	18 (53)	8 (80)
Health system characteristics	Single payer system (outside U.S.)	8 (18)	5 (15)	3 (30)
	Academic medical center	5 (11)	3 (9)	2 (20)
	Integrated health system	13 (30)	13 (38)	0
	Health plan	9 (21)	7 (21)	2 (20)
	Pharmacies independent of medical care system or health plans	3 (7)	0	3 (30)
	Other	6 (14)	6 (18)	0

Abbreviations: N = number; U.S. = United States.

During our abstraction process, we identified two distinct categories of interventions. One category, of 34 studies, used a broad pharmaceutical care approach or MTM intervention in serving their patient populations; that is, they were not designed to focus specifically on any one disease or clinical condition as part of the intervention. We refer to these studies in the review and Table 8 as “broadly focused.” Many of the studies in this category used retrospective designs of existing MTM programs. In these studies, the focus of the MTM intervention may have been broad, but the study may have restricted the evaluation of the MTM program to a patient population with a specific condition or disease. The other category, with 10 studies, involved interventions evaluated in the context of a single chronic condition (e.g., chronic heart failure, diabetes) or provided in a highly specialized setting (e.g., specialized HIV/AIDS community pharmacies). In these studies, the investigators implemented a pharmaceutical care approach or MTM intervention that attended to the patient’s complete drug therapy regimen, but the focus of component interventions (e.g., education, counseling, care coordination) and outcomes measured

may have been specific to certain diseases or conditions. We refer to these studies as “narrowly focused.”

In many cases, to distinguish narrowly focused MTM studies from case- or disease-management interventions, we had to contact study authors to clarify that their intervention included a comprehensive drug therapy assessment and drug therapy intervention beyond the single target condition of interest. The distinction between these broad-focus and narrow-focus categories may be important for interpretation of the effectiveness of these types of interventions.

Studies included in this review used “medication therapy management” to describe the intervention (Table 8) in only 18 of the 44 studies. With respect to mode of delivery (Table 8), 9 broadly focused studies used only telephone contact;<sup>37-48</sup> by contrast, no narrowly focused studies used only telephone contact. Eleven studies (10 broad, 1 narrow) used a mixture of face-to-face and telephone contact.<sup>49-62</sup> The studies using a mixture of modes often used face-to-face delivery for the initial consultation and did followup contacts by telephone. Except for the 2 studies that did not report mode of delivery,<sup>63-65</sup> the remaining studies used only face-to-face delivery in pharmacies, clinics, or homes.

All included studies used a pharmacist as the interventionist (Table 8). In some studies, however, the interventionist was described as a community pharmacy resident or ambulatory care pharmacy resident, and in a few studies nonpharmacist staff performed initial intervention components, such as interviewing patient or reviewing records to compile drug history for the pharmacist.

Table 8 also summarizes the intervention frequency and interval of followup *as designed*, not as may have actually occurred, and these features also differed across studies. Of the 44 included studies, however, 13 (30 percent) did not report the designed frequency of contact and interval of followup. Only 5 studies reported on the *actual* frequency and interval of followup.<sup>49,51-54,58,66-69</sup> Studies evaluating real-world experience with these types of interventions often included a minimum contact threshold for inclusion of patients in the data analysis, but the intervention duration and interval of followup was open-ended and determined by clinical need, as is typical in real-world practice.

Included studies provided interventions in a variety of clinical settings including community pharmacies, centralized pharmacies or call centers, outpatient medical clinics, and some used home visits (Table 8). Half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.<sup>59,70-75</sup>

Concerning reimbursement, of the 44 studies in the evidence base, 26 (59 percent) did not report on reimbursement for MTM services at all. Of the remaining studies, 15 reported that pharmaceutical care or MTM was a covered benefit to patients; pharmacist services were reimbursed through an existing mechanism (e.g., Medicare Part D or other health care benefit).<sup>37-44,46-48,51-54,57,62,76-80</sup> Three studies clearly indicated that pharmacist services were reimbursed through pilot, grant, health system, or study-related funding.<sup>49,58,81</sup>

Finally, the context of the MTM services also varied in terms of features of the health system or organization in which they were provided. Academic medical centers, integrated health care delivery systems, health plans, and single payer health care systems outside the United States were all represented in this evidence base.

## Study-Level Descriptors of Interventions

In Appendix D, we have provided study-level summaries to describe the included interventions. Those tables (Table D-3 and D-4) document: interventions and the amount of



integration with usual practice; method of identifying patients for receipt of MTM services; setting, mode of delivery, frequency and interval of followup; and health care system and reimbursement context. Table D-3 describes the 34 broad-focus studies; Table D-4 describes the remaining 10 narrow-focus studies (and additionally specifies the particular focus). We summarize the main elements in text below.

Of the 10 narrow-focus studies, 2 addressed chronic heart failure and 3 addressed hypertension or hypertension and diabetes. The remaining studies focused on patients with depression and anxiety, diabetes alone, glucocorticoid-induced osteoporosis, HIV/AIDS, and end-stage renal disease on hemodialysis.

The 14 studies described as pharmaceutical care were generally based on the pharmaceutical care model as initially described by Strand and associates and further refined by the profession of pharmacy practice.<sup>51-54,63-65,70-74,79,82-89</sup> Interventions termed medication therapy management (i.e., MTM) were often based on criteria defined for the Medicare Part D program, which includes elements of the pharmaceutical care model.<sup>37-49,57,58,60,62,66-69,76,77,80,81,90</sup> The remaining interventions included elements of pharmaceutical care or MTM but did not specifically label the intervention as either one or the other.<sup>50,55,56,59,61,75,78,91-93</sup> These studies were often described as “clinical pharmacist interventions.”

We defined the level with which pharmaceutical care or MTM services were integrated with usual care as having two main elements: (1) the degree of access that the interventionist had to clinical information in the patient’s medical record, such as laboratory results, diagnoses, and progress notes and (2) the ease of access and method and process of communication between the interventionist and prescribers. Providing MTM services within an outpatient medical clinic, presumably where the patient is also receiving medical care, is one such marker of integration, particularly when the study indicated that the pharmacist was part of a multidisciplinary care team. Some studies, however, described the pharmacy or pharmacist simply as co-located in a medical clinic. In these instances, we do not know whether the level of integration with medical care would be any higher than if the pharmacist had been located in a community pharmacy. Thus, we could not rely solely on clinical setting as a marker of integration with usual care.

Because many studies did not provide sufficient details regarding specific components of the intervention, whether termed pharmaceutical care, MTM, or clinical pharmacist intervention, we were unable to synthesize the use of specific intervention components beyond the components we required for study inclusion.

Only four studies used an active treatment comparator group.<sup>57,58,69,88</sup> All other studies (regardless of focus) compared pharmaceutical care or MTM with usual medical or pharmacy care or both. This factor also impeded our assessing the effectiveness of individual intervention components. Furthermore, almost no study reported on the fidelity with which intervention components were delivered (relative to the original design or intention), including whether goals of drug therapy were established and communicated.

The methods by which patients were identified and offered pharmaceutical care or MTM services has been proposed as a moderator of effectiveness; the aim is to target patients most likely to benefit. These factors may include, for example, patients using drugs with narrow therapeutic windows, complex drug regimens, or patient characteristics such as age, cognitive status, or social situation. With respect to data sources that studies used to identify and then enroll patients for services, pharmacy prescription records (at a community pharmacy, clinic, or health plan) were the most common source. Except for the studies evaluating Medicare Part D MTM programs, few studies used the same criteria for identifying patients for enrollment. Most

required either some degree of regimen complexity, such as the number of drugs taken or use of one or more drugs considered high risk for adverse events. Most studies using pharmacy data or claims mailed or telephoned eligible patients to provide information about enrollment in an MTM program. For Medicare Part D MTM programs, “opt out” is another variation of enrollment for these services. Patients meeting eligibility criteria are enrolled for services unless they specifically “opt-out.” Some studies relied solely on provider referral, patient self-referral, or routine medical record screening at time of a provider visit to identify patients for services.

Tables E-1 and E-2 also provide study-level detail on intervention setting, mode of delivery, frequency and interval of followup and health care system and reimbursement characteristics, which were summarized overall in Table 8 and in the preceding section.

## **Key Question 2: Effect of Medication Therapy Management Interventions on Intermediate, Patient-Centered, and Resource Utilization Outcomes**

We present below key findings and a detailed synthesis of intermediate, patient-centered, and resource utilization outcomes separately. (These outcomes were specified in Table 1 of the Introduction.) When possible (a minimum of three reasonably similar studies for a given intervention or outcome), we pooled study results and document those findings below. When studies were too heterogeneous to pool, we present effect sizes for individual studies whenever possible in summary tables for each outcome that was reported in two or more studies. We also provide strength of evidence tables to support our findings.

Because in many cases the investigators did not report a full set of findings that compared changes over time between intervention and comparisons groups or other details that would permit full analysis, we calculated various statistics ourselves. In these cases, we present in the tables below only these calculated findings and related statistical levels, and we note this explicitly in the tables or text (as “calculated”). The underlying data from the study article(s) can be found in the evidence tables in Appendix D.

### **Key Points: Intermediate Outcomes**

- Evidence was insufficient to evaluate the effect of MTM on anticoagulation after 12 months due to an imprecise, single RCT body of evidence with medium limitations.
- Evidence was insufficient to evaluate the effect of MTM on hemoglobin A1C after 6 to 12 months due to an inconsistent and imprecise body of evidence from two RCTs with medium limitations and two observational studies with high study limitations.
- Evidence was insufficient to evaluate the effect of MTM for decreasing low-density lipoprotein (LDL) cholesterol after 6 to 24 months due to an imprecise, single RCT body of evidence with medium limitations and an imprecise observational body of evidence of two studies with high limitations.
- Evidence was insufficient to evaluate the effect of MTM for reducing blood pressure (BP) after 4 to 12 months based on direct, but inconsistent and imprecise, findings from a single RCT and two cohort studies with medium limitations.
- Several studies did not report outcomes such as drug therapy problems identified and resolved for both intervention and control groups. As a result, limited evidence addresses the effectiveness of MTM compared with usual care in improving these important intermediate outcomes. Study limitations, inconsistency, and lack of precision led us to

conclude that the evidence is insufficient to judge the effectiveness of MTM in improving these outcomes when compared with usual care.

- We found low strength of evidence that MTM had an effect on the percentage of people adherent to at least 80 percent of prescribed doses and on the absolute percentage of prescribed doses taken. Although these conclusions are based on inconsistent evidence with primarily nonsignificant findings of effects and high study limitations, two large cohort studies showed consistent effects of MTM on adherence although with high study limitations.
- Evidence was insufficient to evaluate the effect of MTM on medication adherence (as measured by self-report) as a result of inconsistent and imprecise evidence. The number of trials, consistency, and study limitations varied by specific adherence measure.
- MTM increases the appropriate use of medications as measured by overall scores on appropriateness indices (low strength of evidence).
- Evidence was low for benefit of MTM on medication dosing as a result of indirect, and precise evidence from one trial with medium study limitations.

## Detailed Synthesis: Intermediate Outcomes

### Anticoagulation

One RCT (medium risk of bias) reported on the effects of a pharmaceutical care intervention on anticoagulation among patients in family medicine clinics in a rural community after 12 months of followup.<sup>85</sup> This intervention was conducted with 81 patients at high risk for medication-related problems; however, this outcome was reported only for the four patients in the intervention arm and the six patients in the control arm who were taking anticoagulants. The percentage of subjects who achieved a therapeutic international normalized ratio (INR) differed significantly between the intervention and control arms (100 percent versus 16.7 percent ( $p=0.048$ ); calculated odds ratio [OR], 32.94; 95% confidence interval [CI], 1.06 to 1,021.35). Because of imprecision (wide confidence intervals) and unknown consistency, we graded the evidence as insufficient to evaluate the effectiveness of MTM on improving therapeutic anticoagulation (Table 9).

**Table 9. Anticoagulation: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (10)	Medium	Consistency unknown-single study	Direct	Imprecise	Therapeutic INR achieved: 100% vs. 16.7%, $p=0.048$	Insufficient

Abbreviations: INR = international normalized ratio; RCT = randomized controlled trial; vs. = versus.

### Hemoglobin A1c

Two RCTs and three cohort studies reported on outcomes related to hemoglobin A1c (HbA1c) among patients with diabetes (Table 10). One RCT (medium risk of bias) reported no significant difference in mean HbA1c between intervention (pharmaceutical care) and control patients in an Australian outpatient hospital diabetes clinic at 6 months.<sup>72</sup> The other RCT

(medium risk of bias) reported on changes in the percentage of patients with diabetes who achieved a HbA1c of less than or equal to 7.5 percent at 12 months among patients at high risk for medication-related problems seen in family medicine practices in a rural community.<sup>85</sup> The percentage of patients at goal did not differ significantly between intervention and control arms at baseline (23.1 versus 56.3, calculated  $p=0.08$ ) but was significantly different at followup (100 versus 26.7, calculated OR, 56.455; 95% CI, 2.811 to 1,133.912.  $p=0.008$ ).

**Table 10. Hemoglobin A1c: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed <sup>a</sup>	Outcome Reported by Study and Time Period	Results
Clifford et al., 2002 <sup>72</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 48 G2: 25	Mean HbA1c at 6 months.	Calculated mean difference: -0.20 95% CI: -0.927 to 0.527 $p=0.590$
Taylor et al., 2003 <sup>85</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 13 <sup>a</sup> G2: 16 <sup>a</sup>	Percentage with HbA1c at goal (defined as less than or equal to 7.5%) at baseline and at 12 months.	Calculated OR: 56.455 95% CI: 2.811 to 1,133.912, $p=0.008$
Brummel et al., 2013 <sup>66</sup> ; Soliman, er al., 2013 <sup>67</sup> ; Ramalho de Oliveira et al., 2010 <sup>68</sup> Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage with HbA1c at goal (defined as less than 7%) after 12 months of demonstration	At 12 months unadjusted: Calculated OR: 1.038 95% CI 0.574 to 1.879, $p=0.901$ Adjusted difference-in-difference coefficient: 2.44 95% CI 1.22 to 4.86, $p=0.01$
			Percentage with HbA1c at goal (defined as less than 7%) after 24 months of demonstration (i.e., 12 months after end of demonstration)	At 24 months unadjusted: Calculated OR: 0.502 95% CI 0.294 to 0.855, $p=0.011$ Adjusted difference-in-difference coefficient: NR
Jeong et al., 2009 <sup>38</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program (opted into MTM program) G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects	G1: 1,323 <sup>a</sup> G2: 1,141 <sup>a</sup>	Mean change (SD) in HbA1c at 6 months	Calculated mean difference: -0.020 (0.041) 95% CI: -0.101 to 0.061 $p=0.628$
			Percentage with HbA1c less than 7% at 6 months	Calculated OR: 1.142 95% CI: 0.969 to 1.347 $p=0.114$
Pindolia et al., 2009 <sup>42</sup> Cohort study/High	G1: Opted into a telephone-based MTM program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR	Change in percentage of patients with HbA1c less than 7% at 6 months	G1: + 3 G2: + 7 Between-group $p$ : inferred to be NS, exact $p$ : NR Within-group $p$ : NR

<sup>a</sup> The study included more subjects than the number analyzed and reported in this column, but the investigators assessed this outcome only among patients with diabetes within each study arm.

Abbreviations: CI = confidence interval; G = group; HbA1c= hemoglobin A1C or glycosolated hemoglobin, MTM = medication therapy management; NR = not reported; NS = not sufficient; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation.

One medium risk of bias and one high risk of bias (because of self-selection of participants into the intervention arm and control arms) cohort study were conducted primarily by telephone within large, integrated U.S. health care systems.<sup>38,42</sup> The remaining cohort study (medium risk of bias, described in three included publications) involved pharmacists providing MTM services to patients with diabetes within medical clinics that were part of a large, integrated U.S. health care system.<sup>66-68</sup> This study found a larger difference in the percentage of subjects achieving HbA1C less than 7 percent between baseline and the 12-month followup for the intervention group (adjusted difference-in-difference coefficient 2.44; 95% CI, 1.22 to 4.86), but this difference was not maintained 12 months after the end of the study intervention.<sup>66-68</sup> The telephone-based medium risk-of-bias cohort study reported no significant change in mean HbA1c or percentage of subjects achieving a HbA1C less than 7 percent at 6 months for the intervention group compared with the control group.<sup>38</sup> The high risk-of-bias telephone-based cohort study found similar findings.

Based on direct, but inconsistent and imprecise, evidence from two RCTs and two observational studies, all with medium limitations (Table 11), we concluded that the strength of evidence is insufficient to evaluate the effectiveness of MTM interventions to improve mean HbA1c levels or increase the percent of patients achieving a goal HbA1c level.

**Table 11. Hemoglobin A1c: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 154 (102)	Medium	Inconsistent	Direct	Imprecise	One trial: no change in mean HbA1c at 6 months. One trial: significantly greater percentage of patients with HbA1c <7.5 at 12 months.	Insufficient
Observational	2; 2,688 (2,688)	High	Inconsistent	Direct	Imprecise	One study: adjusted findings significant at 12 months for percentage with HbA1c <7%, but findings not maintained at 24 months. One study: no change in mean HbA1c or percentage <7% at 6 months	Insufficient

Abbreviations: HbA1c= hemoglobin A1c; RCT= randomized controlled trial.

## LDL Cholesterol

One RCT and five cohort studies reported on outcomes related to LDL cholesterol (Table 12). The RCT (medium risk of bias), reported the percentage of patients with dyslipidemia who achieved an LDL cholesterol goal based on Adult Treatment Panel III (ATPIII) criteria for lipid management among patients at high risk for medication-related problems in a rural Alabama community.<sup>85</sup> The intervention and control groups did not differ significantly in percentage at goal at baseline (10.5 percent versus 15.8 percent,  $p=0.631$ ) but differed significantly at 12 months (77.8 percent versus 5.9 percent,  $p=0.001$ ; calculated OR, 50.400; 95% CI, 5.271 to

481.915). These findings are quite imprecise, largely because of a sample size of only 19 subjects in each group for this outcome.

**Table 12. LDL cholesterol: Summary of results**

Study Design/Risk of Bias	Study Arms	N of Subjects Analyzed	Outcome Reported by Study and Time Period	Results
Taylor et al., 2003 <sup>85</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	Followup (N inferred from percentage in results) G1: 18 <sup>a</sup> G2: 17 <sup>a</sup>	Percentage of patients at LDL-C goal based on ATPIII criteria at 12 months.	Calculated OR: 56.00, 95% CI: 5.583 to 561.753 p= 0.001
Brummel et al. 2013 <sup>66</sup> ; Soliman et al., 2013 <sup>67</sup> Ramalho de Oliveira et al., 2010 <sup>68</sup>  Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage with LDL-C at goal (defined as less than 100 mg/dl) after 12 months of demonstration  Percentage with LDL-C at goal (defined as less than 100 mg/dl) after 24 months of demonstration (i.e., 12 months after end of demonstration)	Unadjusted calculated OR: 1.794 95% CI 0.936 to 3.438, p=0.078  Adjusted difference in difference coefficient: 1.95, 95% CI 0.81, 4.84, p=0.13  Unadjusted calculated OR: 1.362 95% CI 0.733 to 2.540, p=0.328  Adjusted difference-in-difference coefficient: NR
Jeong et al., 2009 <sup>38</sup>  Cohort/Medium	G1: Participants in Part D Medicare MTM program (opted into program) G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects	G1: 1,515 <sup>a</sup> G2: 1,323 <sup>a</sup>	Mean change (SD) in LDL cholesterol at 6 months  Percentage with LDL cholesterol at goal (<100 mg/dl) at 6 months	Calculated mean difference: -4.1 95% CI -6.019 to -2.181 p< 0.001  Calculated OR: 1.392 95% CI: 1.160 to 1.670 p<0.001
Isetts et al., 2008 <sup>81</sup> Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percentage of patients meeting HEDIS measures related to cholesterol control after cardiovascular event at 12 months	Calculated OR: 2.544, 95% CI: 1.52 to 4.256 p= 0.001
Pindolia et al., 2009 <sup>42</sup> Cohort study/High	G1: Opted in to a telephone-based MTM program G2: Usual medical care (opted out of MTM program)	G1: NR <sup>a</sup> G2: NR <sup>a</sup> (outcome assessed only among patients with coronary artery disease)	Change in percentage of patients with LDL-C less than 100 mg/dl at 6 months	G1: - 5 G2: + 7 p: NR and could not be calculated.

**Table 12. LDL cholesterol: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N of Subjects Analyzed	Outcome Reported by Study and Time Period	Results
Fox et al. 2009 <sup>37</sup> Cohort study/High	G1: MTM program provided through a health plan	G1: 255 G2: 56	Percentage of patients with diabetes with LDL-C less than 100 mg/dl at 12 to 24 months	Calculated OR: 2.228, 95% CI: 1.238 to 4.008; p=0.008
	G2: Usual medical care (eligible but opt-out from MTM program)	G1: 215 G2: 46		
			Mean (SD) LDL-C at 12 to 24 months	Calculated mean difference: -7.4 95% CI: -17.297 to 2.497 p= 0.33 as reported by study authors, p=0.143 as calculated

<sup>a</sup> The investigators assessed this outcome only among patients with hyperlipidemia, diabetes, or coronary artery disease within each study arm but did not report the specific number analyzed.

Abbreviations: ATP III = Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol); CI = confidence interval; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; LDL-C = low density lipoprotein cholesterol; MTM = medication therapy management; N = number; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.

We also evaluated the findings from the five cohort studies. One of the medium risk-of-bias cohort studies involved pharmacists providing MTM services to patients with diabetes within medical clinics that were part of a large, integrated U.S. health care system in Minnesota.<sup>66-68</sup> This study found no significant difference in the percentage of patients achieving an LDL cholesterol goal (defined as less than 100 mg/dl) at 12 months (adjusted difference-in-difference coefficient 1.95; 95% CI, 0.81 to 4.84; p=0.13). The other medium risk-of-bias cohort study involved a telephone-based MTM program delivered within a large, integrated U.S. health care system in California; the analysis presented was limited to patients with a diagnosis of hyperlipidemia, diabetes, or coronary artery disease.<sup>38</sup> This study found a small but significant mean decrease in LDL cholesterol levels in the intervention group compared with controls at 6 months (calculated mean difference, -4.1; 95% CI, -6.019 to -2.181; p< 0.001) and also found a significant increase in the percentage of patients achieving an LDL goal, defined as LDL less than 100 mg/dl (calculated OR, 1.392; 95% CI, 1.160 to 1.670; p<0.001).

Two of the three high risk-of-bias (because of selection bias and baseline characteristics of groups not reported or not adjusted for) cohort studies were telephone-based MTM programs,<sup>37,42</sup> and the remaining high risk-of-bias study was a clinic-based MTM program; all three were conducted in the United States.<sup>81</sup> One study did not provide the information necessary to determine whether the findings reported (change in percentages reaching goal LDL) were evidence of no effect or an effect favoring the control arm.<sup>42</sup> The other two studies reported a direction of effect similar to that reported in the RCT but at a much smaller magnitude.

Overall, we concluded that the strength of evidence is insufficient for the effectiveness of MTM interventions on lowering mean LDL-cholesterol levels or increasing the percentage of patients achieving a LDL-cholesterol goal. This body of evidence included a single RCT with medium study limitations and imprecise findings and an observational body of evidence with high study limitations consisting of two studies. Although we acknowledge the large magnitude of effect in the RCT, these findings were very imprecise, and the magnitude of effect was inconsistent with the observational study findings (Table 13).

**Table 13. LDL cholesterol: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (38)	Medium	Consistency Unknown—single study	Direct	Imprecise	Significantly greater percentage of patients at LDL-C goal in MTM group at 12 months (77.8% vs. 5.9%, $p < 0.001$ , Calculated OR: 56.00, 95% CI: 5.583 to 561.753).	Insufficient
Observational	2; 3,062 (3,062)	High	Consistent	Direct	Imprecise	One study: adjusted difference in difference coefficient: 1.95, 95% CI 0.81, 4.84, $p = 0.13$  Other study: Calculated mean difference in LDL-C levels: -4.1 95% CI -6.019 to -2.181 $p < 0.001$  Calculated OR for achieving LDL goal: 1.392 95% CI: 1.160 to 1.670 $p < 0.001$	Insufficient

Abbreviations: CI = confidence interval; LDL-C = low density lipoprotein cholesterol; MTM = medication therapy management; OR = odds ratio; RCT = randomized controlled trial.

## Blood Pressure

In all, we identified seven, mostly small, studies that measured blood pressure outcomes using various followup periods (Table 14). This evidence base consisted of three RCTs and four cohort studies; the outcomes involved achieving blood pressure goals or becoming normotensive, and changes in systolic or diastolic blood pressure levels (SBP; DBP) or both. Of these studies, we rated one RCT and two cohort studies as medium risk of bias; the remaining RCT and cohort studies were high risk of bias.



**Table 14. Blood pressure: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed <sup>a</sup>	Outcome Reported by Study and Time Period	Results
Taylor et al., 2003 <sup>85</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 24 <sup>a</sup> G2: 29 <sup>a</sup>	Percentage of patients with SBP and DBP at goal at 12 months.	Calculated OR: 28.875, 95% CI: 5.486 to 151.993, p<0.001
Park et al., 1996 <sup>89</sup> RCT/High	G1: Community-pharmacy pharmaceutical care program G2: Usual care	G1:23 G2:26	Percentage of patients who were normotensive (SBP <140 and DBP <90)  Mean SBP (mm Hg) at 4 months.	Calculated OR: 2.455, 95% CI: 0.764 to 7.888, p=0.132  Calculated mean difference: -13.0 95% CI: -23.739 to -2.261, p=0.018
			Mean (SD) DBP (mm Hg) at 4 months	Calculated mean difference: -4.90 95% CI: -10.3 to 0.50, p=0.075
Planas et al., 2009 <sup>90</sup> RCT/High	G1: Community pharmacy hypertension MTM program for patients with diabetes G2: Control group (BP recorded, informed of BP goals at 3 times during study)	G1: 25 G2: 15	OR (95% CI) for intervention group participant achieving BP goal relative to control group.  Mean change in SBP (mm Hg) at 9 months	OR: 12.9 (1.5 to 113.8) p=0.021  Between-group difference: -20.0 (95% CI -32.7 to -7.4) p: 0.003
Brummel et al., 2013, <sup>66</sup> Soliman et al., 2013, <sup>67</sup> Ramalho de Oliveira et al., 2010 <sup>68</sup>  Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage achieving BP goal (defined as less than 130/80) after 12 months of demonstration  Percentage achieving BP goal (defined as less than 130/80) after 24 months of demonstration (i.e., 12 months after end of demonstration)	Unadjusted calculated OR: 0.917 95% CI 0.511 to 1.647, p=0.773  Adjusted difference in difference coefficient: 0.73, 95% CI 0.32 to 1.65, p=0.45  Unadjusted calculated OR: 1.366, 95% CI 0.755 to 2.471, p=0.303  Adjusted difference-in-difference coefficient: NR

**Table 14. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed <sup>a</sup>	Outcome Reported by Study and Time Period	Results
Jeong et al., 2009 <sup>38</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects	G1: 1301 G2: 982 (Study included more subjects but this outcome was assessed among only patients with diabetes and HTN within each study arm)	Percentage with BP control (defined as <130/80 mmHg) at 6 months	Calculated OR: 0.953, 95% CI 0.808 to 1.125, p=0.571
		G1: 1101 G2: 895 (Study included more subjects but this outcome was assessed among only patients with HTN but without DM within each study arm)	Percentage with BP control (defined as <130/80 mmHg) at 6 months	Calculated OR: 0.898, 95% CI 0.733 to 1.099, p=0.296
Carter et al., 1997 <sup>70</sup> Barnette et al. 1996 <sup>71</sup> Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1:25 G2:26	Percentage with BP control	Calculated OR: 1.558, 95% CI: 0.496 to 4.898, p=0.448
			Mean SBP (mm Hg) at 6 months	Calculated mean difference: -9.00 95% CI: -19.451 to 1.451, p=0.0914
			Mean DBP (mm Hg) at 6 months.	Calculated mean difference: -1.00; 95% CI: -5.977 to 3.977, p=0.694
Isetts et al., 2008 <sup>81</sup> Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percentage of patients meeting HEDIS measures related to hypertension management at 12 months.	Calculated OR: 1.728 95% CI: 1.026 to 2.911, p=0.04

<sup>a</sup> The study had more participants but this outcome was measured in only the number of patients specified.

Abbreviations: ATPIII = Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol); BP = blood pressure; CI = confidence interval; DBP=diastolic blood pressure; DM = diabetes mellitus; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HTN = hypertension; mm Hg = millimeters of mercury (a unit of pressure); MTM = medication therapy management; N = number; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; SBP = systolic blood pressure.

## Blood Pressure Goal Attainment

One RCT (medium risk of bias), conducted among of a small number of patients at high risk of medication-related problems receiving pharmaceutical care through family medicine clinics in a rural Alabama community, reported a significant difference in the number of patients at blood pressure goal (SBP  $\leq$  140 mm Hg and DBP  $\leq$  90 mm Hg) at 12 months (91.7 percent versus 27.6 percent, calculated OR 28.875, 95% CI 5.486 to 151.993,  $p < 0.001$ ).<sup>85</sup> The other RCT (high risk of bias due to high attrition, lack of intention to treat analysis, and no adjustment for baseline differences) provided MTM services through community pharmacies to managed care organization enrollees with diabetes and hypertension in Oklahoma.<sup>90</sup> This trial also reported a favorable effect of MTM on the achievement of blood pressure goals (OR 12.9, 95% CI, 1.5 to 113.8;  $p = 0.021$ ). The last trial (high risk of bias for unclear randomization methods, important differences in baseline with no adjustment in analysis, and other factors related to study execution) reported a direction of effect favoring the MTM group, but it was not statistically significant.<sup>89</sup>

The two medium risk-of-bias cohort studies included a telephone-based MTM program within a large, integrated U.S. health care system in California.<sup>38</sup> The other study involved MTM provided by pharmacists in medical clinics within a large, integrated U.S. health care system in Minnesota.<sup>66-68</sup> Both of these studies showed a directional effect favoring the control groups on the percentage of subjects who achieved blood pressure control at 6 and 12 months, but these findings were not statistically significant (calculated OR 0.953, 95% CI, 0.808 to 1.125;  $p = 0.571$ , adjusted difference in difference coefficient, 0.73; 95% CI, 0.32 to 1.65;  $p = 0.45$ ). The two other cohort studies (both high risk of bias) reported findings that were directionally consistent with the trials, but findings were statistically significant in only one of the studies.<sup>70,71,81</sup>

## Systolic and Diastolic Blood Pressure Levels

Three studies reported on systolic blood pressure outcomes, and all were rated as high risk of bias. One RCT provided MTM services through community pharmacies to managed care organization enrollees with diabetes and hypertension in Oklahoma.<sup>90</sup> The MTM group in this trial had a mean decrease of 20.0 mmHg (95% CI, -32.7 to -7.4;  $p = 0.003$ ) in systolic blood pressure compared with the control group. The other RCT provided pharmaceutical care to patients with hypertension through community pharmacies in Illinois and Wisconsin.<sup>89</sup> This study found a mean decrease of 13.0 mmHg (95% CI, -23.739 to -2.261;  $p = 0.018$ ) compared with controls.<sup>89</sup> The cohort study found directionally similar results.<sup>70,71</sup> We found similar results for diastolic blood pressure from the two high risk-of-bias studies that reported this outcome.<sup>70,71,89</sup> Overall, we concluded that the strength of evidence is insufficient for the effectiveness of MTM interventions to increase the percentage of patients achieving a blood pressure goal or decrease systolic blood pressure or diastolic blood pressure levels based on direct but imprecise evidence from one RCT with medium limitations and two observational studies with high limitations (Table 15). In addition, the direction of effect was not consistent between the RCT and observational evidence (Table 15).

**Table 15. Improvement in blood pressure: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (53)	Medium	Consistency unknown—single study	Direct	Imprecise	OR 28.88 (95% CI 5.49 to 151.99, p< 0.001) for percentage of patients with SBP and DBP at goal at 12 months., mean decrease in BP of 20 mm Hg compared with controls	Insufficient
Observational	2; 2,507 (2,507)	High	Consistent	Direct	Imprecise	MTM group less likely to achieve BP goals compared with controls	Insufficient

Abbreviations: BP = blood pressure; mmHg = millimeters of mercury (unit of pressure); MTM = medication therapy management; OR = odds ratio; RCT = randomized controlled trial.

## Drug Therapy Problems Identified

In all, 10 studies addressed the question of the effectiveness of MTM for identifying drug therapy problems. Of these, eight provided information on drug therapy problems only from the intervention arm.<sup>43,49,55,63,72-74,79,89</sup> Thus, these studies cannot inform the question of the comparative effectiveness of MTM.

The two remaining comparative studies (one trial, one cohort study) reported findings about the effectiveness of MTM when compared with usual care (Table 16). The trial results are uninterpretable because the authors report total numbers of drug therapy problems identified in each arm without any measure of variance.<sup>91</sup> We rated the cohort study as risk of bias for uncontrolled selection bias from the comparison of patients who refused services to patients who accepted services.<sup>44</sup> These two studies also did not specify their expected direction of effect. We inferred that the studies expected to find fewer drug therapy problems after the completion of the intervention because the interventions were (apparently) specifically designed to identify and then resolve drug therapy problems. However, studies measuring outcomes during an MTM intervention might, instead, expect to find more drug therapy problems in the intervention arm because the intervention led to greater discovery of various problems. Consequently, we treated the evidence as indirect. Given high study limitations, unknown consistency, indirectness, and lack of precision, evidence was insufficient to draw any conclusions about the effect on MTM interventions on drug therapy problems identified (Table 17).

**Table 16. Drug therapy problems identified: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001 <sup>91</sup> RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Number of drug therapy problems identified for each study arm at 3 months	G1: 1,206 G2: 1,380
Welch et al., 2009 <sup>44</sup> Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No MTM control group (voluntary opt-out)	G1: 459 G2: 123	Percentage with at least 1 potential drug therapy problem during MTM process (timing unclear)	G1: 89.8% G2: 83.7% Risk difference=6.1%, calculated p=0.062

Abbreviations: G = group; MTM = medication therapy management; N = number; RCT = randomized controlled trial.

**Table 17. Drug therapy problems identified: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 904 (582)	High	Consistency unknown—single study	Indirect	Imprecise	Risk difference=6.1%, calculated p=0.062	Insufficient

## Drug Therapy Problems Resolved

In all, we identified nine studies that attempted to report on whether MTM programs resolved drug therapy problems that were identified. Of these, six studies provided information only from the intervention arm.<sup>42,49,51,54,73,74,81,89</sup> Thus, as with drug therapy problems identified, they cannot inform the question of the comparative effectiveness of MTM interventions. Three other studies (two RCTs, one cohort study) provided information on the effectiveness of MTM for resolving drug therapy problems when compared with usual care (Table 18). The cohort study (medium risk of bias) found a significant effect of MTM on the difference in drug therapy problems identified between baseline and a 12-month followup; the investigators interpreted the change in number of drug therapy problems identified over time as drug therapy problems resolved between baseline and followup.<sup>39-41</sup>

One RCT had a high risk of performance bias because of issues concerning site and country-specific variation, coupled with failure to control for differences at baseline and a high overall attrition.<sup>64,65</sup> The other trial shows higher total numbers of all drug therapy problems resolved in the intervention arm, but without measures of variance that account for variation among patients, these results cannot be interpreted with confidence.<sup>91</sup>

**Table 18. Total number of drug therapy problems resolved: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Moczygemba et al., 2011 <sup>39</sup> ; Moczygemba et al., 2011 <sup>40</sup> ; Moczygemba et al., 2008 <sup>41</sup>	G1: Opt-in telephone MTM program G2: No-MTM control group	G1: 60 G2: 60	Medication and health-related problems identified at baseline and 12 months	Parameter estimate for intervention group on predicting change in medication health-related problems from multiple regression: 0.81 Adjusted p: 0.01
Cohort/Medium				NOTE: Regression model adjusted for the following predisposing and need factors: (1) age, (2) sex, (3) race, (4) N of medications, (5) N of chronic diseases, and 6) medication regimen complexity
Krska et al., 2001 <sup>91</sup> RCT/High	G1: Pharmacist-led medication review G2: Usual care, including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems wholly or partially resolved at 3 months	G1: 998 G2: 569
Bernsten et al., 2001 <sup>64,65</sup> RCT/High	G1: Structured pharmaceutical care program in community pharmacy G2: Usual community pharmacy services	Baseline	Number of changes in therapy at baseline	Baseline Calculated mean difference: 0.2, 95% CI: 0.101 to 0.299, p<0.001
		6 months	Number of changes in therapy at 6 months	6 months Calculated mean difference: 0.4, 95% CI: 0.257 to 0.543, p<0.001
		12 months	Number of changes in therapy at 12 months	12 months Calculated mean difference: 0.1, 95% CI: -0.051 to 0.251, p=0.195
		18 months	Number of changes in therapy at 18 months	18 months Calculated mean difference: 0, 95% CI: -0.156 to 0.156, p=1.0
		G1: 1,290 G2: 1,164		
		G1: 1,024 G2: 953		
		G1: 863 G2: 764		
		G1: 704 G2: 636		

Abbreviations: CI = confidence interval; CMR = comprehensive medication review; G = group; MTM = medication therapy management; N = number; RCT = randomized controlled trial.

Two studies reported on specific aspects of drug therapy problems resolved without an overall measure of total number of drug therapy problems resolved (Table 19).<sup>62,79</sup> One medium risk-of-bias cohort study, designed to identify the impact of 2010 Part D MTM programs, compared cohorts (standalone Prescription Drug Plan or Medicare Advantage Prescription Drug Plan) receiving MTM with a comprehensive medication review with cohorts receiving usual care for congestive heart failure, chronic obstructive pulmonary disease, and diabetes, after limiting the sample to those newly eligible or enrolled for MTM and controlling for characteristics such as demographics, medical comorbidities, condition severity, and intensity of provider care.<sup>62</sup> Only one of three measures of drug therapy outcomes showed significant differences in the MTM arm when compared with the usual care arm at 12 months (discontinuation of contraindicated medications for congestive heart failure), but the results were inconsistent, with the

Medicare Part D plan outperforming usual care and Medicare Advantage Part D plan underperforming usual care. The authors note that the timing of measurement (one year after MTM enrollment for intervention arms) may have allowed prescribers to add back problematic drugs over the course of the year.

**Table 19. Specific drug therapy problems resolved: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perlroth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658 G3: 11,260	Remove drug-drug interaction within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Odds (95% CI) Congestive heart failure G1 vs. G13: 0.87 (0.76, 1.00), p>0.05 G3 vs. G14: 1.05 (0.88, 1.26), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 0.92 (0.79, 1.07), p>0.05 G7 vs G16: 1.11 (0.89, 1.38), p>0.05  Discontinue use of high risk medications within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators) Congestive heart failure G1 vs. G13: 1.04 (.97, 1.11), p>0.05 G3 vs. G14: 0.93 (0.86, 1.01), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 1.06 (0.99, 1.13), p>0.05 G7 vs. G16: 1.00 (0.92, 1.09), p>0.05  Comparison – congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care  Comparison - Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care  Comparison - Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care
	G1: enrolled in PDP receiving MTM with CMR	G5: 16,372 G7: 10,575		
	G3: enrolled in MA-PD, receiving MTM with CMR	G9: 16,545 G11: 13,527		
	G5: enrolled in PDP receiving MTM with CMR	G13: 156,441 G14: 51,938		
	G7: enrolled in MA-PD, receiving MTM with CMR	G15: 184,350 G16: 73,623		
	Diabetes	G17: 133,925 G18: 53,912		
	G9: enrolled in PDP receiving MTM with CMR			
	G11: enrolled in MA-PD, receiving MTM with CMR			
	Comparison – congestive heart failure			
	Comparison - Chronic obstructive pulmonary disease			

**Table 19. Specific drug therapy problems resolved: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chrischilles et al., 2004 <sup>79</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Change in prevalence of high-risk medication use 9 months after becoming eligible for PCM	G1: -10.8 percentage points; p<0.05 G2:-1.4 percentage points; no significant change

<sup>a</sup>Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; CMR = comprehensive medication review; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; PCM = pharmaceutical case management; PDP = Medicare Part D Plan; NS = not significant; RCT = randomized controlled trial

The other cohort study (high risk-of-bias) found significantly lower prevalence of high risk medications 9 months after becoming eligible but these result did not control for large differences in baseline prevalence (43.4 percent in the intervention arm and 35.8 percent in the control arm).<sup>79</sup> Because the outcomes reported in these studies are included but not separately analyzed in other studies reported overall numbers of drug therapy problems resolved, we did not separately grade the evidence for these outcomes.

Together (or taking the medium risk-of-bias cohort study alone), these studies offer insufficient evidence, based on study limitations, inconsistency, and imprecision, to judge the effectiveness of MTM on resolving drug therapy problems (Table 20). Evidence from studies reporting on individual measures of drug therapy problems resolved also supports this conclusion.

**Table 20. Drug therapy problems resolved: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 132 (120)	High	Consistency unknown—single study	Indirect	Imprecise	Calculated mean difference: -1.00 (95% CI: -1.967 to -0.033), p=0.04	Insufficient

Abbreviations: CI = confidence intervals;

## Medication Adherence

Fourteen studies reported on the effects of MTM interventions on adherence outcomes.<sup>40,42,44,45,50,56,62,64,66-68,84-86,89,90</sup> One cohort study reported nonadherence determined during MTM (during a mock MTM chart review for the control group);<sup>44</sup> any adherence differences noted between the two groups were unlikely to be attributable to MTM effects. Moreover, the description of nonadherence used in that study (percentage of patients “nonadherent” per chart review) cannot be interpreted because of a lack of a clear definition. For these reasons, we excluded this study from further analysis.

Three remaining studies in the analysis are described in Table 21. Of these 13 studies, eight were RCTs<sup>44,50,56,64,84-86,89,90</sup>; five were cohort studies.<sup>40,42,45,62,66-68</sup> Most studies assessed one of



three different adherence outcomes: (1) the proportion of patients who, based on a threshold of between 75 percent and 80 percent of prescribed doses taken, were deemed to be adherent<sup>42,62,66-68,85</sup>; (2) the percentage of prescribed doses taken<sup>40,45,89,90</sup>; and (3) the scores from an adherence scale score (such as the Morisky Scale).<sup>50,64,86</sup> Two studies assessed miscellaneous aspects of medication-taking behavior<sup>56,84</sup> these included “remembering to take medication,” a medication-taking behavior subscore, and or determining the number of medications (not pills) for which the participant’s reported manner of taking (number of pills and frequency per day) exactly matched the prescribed directions. When studies did not report statistical significance, we calculated the standard difference in means, standard errors, and 95 percent confidence intervals based on raw data.

**Table 21. Medication adherence: Summary of results grouped by type of adherence outcome**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 1: Proportion of patients adherent based on a threshold of percentage of pills taken	Taylor et al., 2003 <sup>85</sup> RCT/Medium	G1:Pharmaceutical care G2: Standard care	G1:33 G2:36	Percentage of patients adherent defined as self-reported taking 80% or more of medications 12 months after baseline	Calculated OR: 9.277 95% CI: 0.480 to 179.263; p= 0.140
	Pindolia et al., 2009 <sup>42</sup> Cohort study/High	G1: Telephone-based MTM program G2: Patients eligible for MTM program who declined enrollment	G1: 292 G2: 1,081 (study year 1)	Percentage of CHF patients who were adherent to at least 75% of ACE/ARB medications based on 2006 claims data: Measured during 6 months post-MTM enrollment	Calculated OR: 1.088 95% CI: 0.834 to 1.417 p=0.533
				Percentage of CHF patients who were adherent to at least 75% of beta blocker medications based on 2006 claims data: Measured during 6 months post-MTM enrollment c	Calculated OR: 1.174 95% CI 0.89 to 1.54 p=0.252
	Brummel et al. 2013 <sup>66</sup> , Soliman, 2013 et al. <sup>67</sup> Ramalho de Oliveira et al., 2010 <sup>68</sup> Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage of patients adherent to aspirin (from pharmacy claims data) at baseline (before MTM), 12-month (during MTM demonstration project), and 24-month (1 year post-demonstration)	Baseline Calculated OR 2.828, 95% CI 0.710 to 11.259, p=0.14) 12 Month Calculated OR 5.981 (95% CI 0.284 to 126.030, p=0.250) 24 Month Calculated OR 1.17 (95% CI 0.072 to 18.903, p=0.912)

**Table 21. Medication adherence: Summary of results grouped by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 1: Proportion of patients adherent based on a threshold of percentage of pills taken (continued)	Perlroth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	Percentage of patients achieving adherence (> 80% of prescribed pills taken) to various specified medications	<b>CHF</b> Adherent to any evidence-based medicine (EBM) for CHF G1 vs. G13: 1.28 <sup>a</sup> (1.19, 1.37) G3 vs. G14: 1.40 <sup>a</sup> (1.29, 1.52) p<0.05
		Chronic obstructive pulmonary disease	G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR	365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	<b>COPD</b> Adherent to long-acting beta agonist (LABA)-only regimen G5 vs. G15: 1.26* (1.14, 1.40) G7 vs. G16: 1.11 (0.95, 1.29) p<0.05
		Diabetes	G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR		Adherent to long-acting anticholinergic (LAAC)-only regimen G5 vs. G15: 1.36* (1.12, 1.65) G7 vs. G16: 1.01 (0.83, 1.24) p<0.05
		Comparison—congestive heart failure	G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care		Adherent to combination regimen G5 vs. G15: 1.43 <sup>a</sup> (1.26, 1.62) G7 vs. G16: 1.20 (1.00, 1.44) p<0.05
		Comparison—Chronic obstructive pulmonary disease	G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care		<b>Diabetes</b> Adherent to diabetes medication G9 vs. G17: 1.33 <sup>a</sup> (1.25, 1.41) G11 vs. G18: 1.35 <sup>a</sup> (1.27, 1.45) p<0.05 Adherent to biguanides medication

**Table 21. Medication adherence: Summary of results grouped by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 1: Proportion of patients adherent based on a threshold of percentage of pills taken (continued)	Perthroth et al., 2013 <sup>62a</sup> Cohort/Medium (continued)	Comparison— Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care			G9: 1.27 <sup>a</sup> (1.19, 1.36) G11: 1.20 <sup>a</sup> (1.12, 1.29) p<0.05  Adherent to DPP-IV inhibitors medication G9 vs. G17: 1.32 <sup>a</sup> (1.12, 1.55) G11 vs. G18: 1.19 (.96, 1.48) p<0.05  Adherent to sulfonylureas medication G9 vs. G17: 1.22 <sup>a</sup> (1.13, 1.31)) G11 vs. G18: 1.28 <sup>a</sup> (1.19, 1.38) p<0.05  Adherent to Thiazolidinediones medication G9 vs. G17: 1.31 <sup>a</sup> (1.19, 1.45) G11 vs. G18: 1.16 <sup>a</sup> (1.04, 1.29) p<0.05  Use of ACE Inhibitor or ARB medication G9 vs. G17: 0.99 (0.90, 1.08) G11 vs. G18: 1.24 <sup>a</sup> (1.12, 1.38) p<0.05  Use of statin medication G9 vs. G17: 1.01 (0.91, 1.13) G11 vs. G18: 1.33 <sup>a</sup> (1.16, 1.52) p<0.05

**Table 21. Medication adherence: Summary of results grouped by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 2: Absolute measure of adherence as percentage of prescribed doses taken	Moczygemba et al., 2011 <sup>39</sup>	G1: Opt-in telephone	G1: 60	Percentage prescribed doses taken: Overall average MPR across all medications measured at 6 months before MTM participation (i.e., baseline) and 12 months after MTM using pharmacy data	Calculated mean difference: -0.040 95% CI: -0.101 to 0.021 p=0.201
	Moczygemba et al., 2011 <sup>40</sup>	Scott & White Health Plan MTM program	G2: 60		
	Moczygemba et al., 2008 <sup>41</sup>	G2: No-MTM control group			
	Retrospective Cohort/Medium				
	Planas et al., 2009 <sup>90</sup>	G1: Collaborative home-based medication review	G1: 25	Percentage mean adherence (percentage of prescribed doses taken) to antihypertensive medication  Measured twice (9 months before and 9 months after baseline visit) and continuously using medication acquisition method, in which days' supply of medication is compared with dates medication was filled using pharmacy refill data.	Calculated mean difference from baseline to 9 months: 0.077 95% CI: -0.127 to 0.281 p=0.46
	RCT/High	G2: No medication review received	G2: 15		
Outcome Type 2: Absolute measure of adherence as percentage of prescribed doses taken (continued)	Park, 1996 <sup>89</sup>	G1: Comprehensive pharmaceutical care	Visit 1 G1: 7 G2: 5	Mean percentage compliance (percentage of prescribed pills taken) from pharmacist report of pill counts  4-month time frame	Calculated mean difference for change from baseline to Visit 4: -0.023 95% CI: -0.175 to 0.129 p=0.767
	RCT/high	G2: Usual care	Visit 2 G1: 21 G2: 23		
			Visit 3 G1: 23 G2: 20		
			Visit 4 G1: 21 G2: 22		

**Table 21. Medication adherence: Summary of results by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 2: Absolute measure of adherence as percentage of prescribed doses taken (continued)	Park, 1996 <sup>89</sup>	G1: Comprehensive pharmaceutical care	Visit 1 G1: 7 G2: 5	Mean percentage compliance (percentage of prescribed pills taken) from pharmacist report of pill counts  4-month time frame	Calculated mean difference for change from baseline to Visit 4: -0.023 95% CI: -0.175 to 0.129 p=0.767
	RCT/High	G2: Usual care	Visit 2 G1: 21 G2: 23		
			Visit 3 G1: 23 G2: 20		
			Visit 4 G1: 21 G2: 22		
	Moore, 2013 <sup>45</sup>	G1: MTM program (opt-in)	G1: 2,250	Medication possession ratio by medication type from pharmacy data and medical claims data from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Asthma MPR (%) Calculated mean difference = 0.62; 95% CI: -2.988 to 4.228; p = 0.736
	Cohort/Medium	G2: control group (refusers)	G2: 2,250		Depression MPR (%) Calculated mean difference = 1.16; 95% CI: -1.667 to 3.987; p = 0.421
					Diabetes MPR (%) Calculated mean difference = 2.37; 95% CI: -0.549 to 5.289; p = 0.112
					Dyslipidemia MPR (%) Calculated mean difference = 4.71; 95% CI: 2.747 to 6.673; p < 0.001
					Hypertension MPR (%) Calculated mean difference = 4.60; 95% CI: 3.211 to 5.989; p < 0.001

**Table 21. Medication adherence: Summary of results by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 3: Self-reported Adherence using Morisky Scale	Bernsten, 2001 <sup>64</sup> ; Sturgess, 2003 <sup>65</sup> RCT/High (pooled data)	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Pooled sample (excluding The Netherlands because no baseline adherence data collected) Baseline G1: 867 G2: 748 18 months G1: 792 G2: 758	Medication adherence: self-reported as assessed by Morisky Scale (Note: Percentage of participants who were adherent defined as patients responded that they “never” experienced any aspects of noncompliance on the 4-item scale with a 4-point response option per item)	Pooled sample (percentage adherent) OR at baseline: 0.82, calculated 95% CI: 0.666 to 1.0, p = 0.050  Calculated OR at 18 months: 1.084, 95% CI: 0.883 to 1.332, p=0.440
	Volume et al. 2001 <sup>86</sup> and Kassam <sup>87</sup> RCT/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Total: 292 G1: NR G2: NR	Self-reported adherence using the Morisky Scale made up of four dichotomous items where summary score is 0–4 with lower scores being better adherence  12 to 13 months after intervention	Calculated mean difference 0.090 95% CI: -0.076 to 0.256 p=0.289
Outcome Type 3: Self-reported Adherence using Morisky Scale (continued)	Jameson et al., 1995 <sup>50</sup> RCT/High (Medium for study overall but high for adherence because of poor outcome measure)	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office	G1: 27 G2: 29	Change in self-reported composite score “understanding and compliance” over 6 months with negative score representing improvement (no further information on measure used)	G1: -1.6 G2: -0.2 95% CI: NR p: NS

**Table 21. Medication adherence: Summary of results by type of adherence outcome (continued)**

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Miscellaneous Adherence Outcomes	Hanlon et al., 1996 <sup>84</sup> RCT/Medium (Low for study overall but medium for adherence because of lack of information about and precision of adherence measure)	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 86 G2: 83	Self-reported medication compliance with 12-month time frame, assessed by determining whether the way patients said they took their medicine (in terms of number of pills and daily frequency) matched how the medication was prescribed. Compliance was defined as the proportion of medications for which the patients' response agreed with the directions.	Calculated OR: 1.076, 95% CI: 0.527 to 2.197, p: 0.84
	Sidel, 1990 <sup>56</sup> RCT/Medium	G1: Received at least 2 pharmacist visits involving medication review, patient-specific education and counseling; followup patient telephone calls and contacting of physicians by pharmacists as needed G2: Contacted only to complete the survey	G1: 92 G2: 104	Change from baseline to 6-month followup in medication-taking behavior Subscore (negative scores indicate improvement, which means decreased risk) Change at 6 months in normative score for remembering to take medicine	G1: -3.47 G2: -4.38 95% CI: NR P < 0.001 for within-group differences p = 0.52 for between-group differences G1: 0.09 G2: -0.19 95% CI: NR p=0.52

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: ACE = angiotension converting enzyme inhibitor; ARB = angiotension receptor blocker; CHF = congestive heart failure; CI = confidence interval; CMR = comprehensive medication review; EBM = evidence-based medicine; G = group; HbA1C = hemoglobin A1C or glycosolated hemoglobin; LAAC = long-acting anticholinergic; LABA = long-acting beta agonist; MA-PD = Medicare Advantage Part D Plan; MPR = medication possession ratio; MTM = medication therapy management; N = number; NR = not reported; OR = odds ratio; PDP = Medicare Part D Plan; RCT= randomized controlled trial; SE = standard error; T = time; vs. = versus.

Of the 4 studies assessing the proportion of patients who achieved threshold adherence levels, one was a small RCT (medium risk of bias);<sup>85</sup> the others were cohort studies: 1 small<sup>66-68</sup> (medium risk of bias) 1 relatively large (high risk of bias),<sup>42</sup> and 1 very large medium risk of bias).<sup>62</sup> Only 1 of these studies found statistically significant positive effects of MTM on adherence<sup>62</sup> and did so for adherence to some but not comparisons for multiple medications. Of the 4 studies that assessed MTM effects on percentage of prescribed doses taken, 2 were small RCTs (both high risk of bias);<sup>89,90</sup> the other 2 were cohort studies, one small, one large (both medium risk of bias).<sup>40,45</sup> Only 1 of these studies found a statistically significant positive effect of MTM on adherence. All 3 studies that assessed adherence using self-reported adherence scales

were small RCTs (1 medium risk of bias<sup>86</sup>; 2 high risk of bias<sup>50,64</sup>). None found a statistically significant effect of MTM on adherence, although 1 high risk-of-bias study<sup>64</sup> did not account for the marked baseline differences and, hence, may have missed a statistically significant difference in change in adherence. This same study (high risk of bias) reported a statistically significant increase in the percentage of individuals who changed from nonadherent to adherent over 18 months (15.25 percent in the intervention group and 12.2 percent in the control group;  $p=0.028$ );<sup>64</sup> however, this assessment did not take into account the percentage in each group that changed from adherent to nonadherent. Finally, the 2 RCTs (both medium risk of bias) that assessed miscellaneous aspects of adherence found no statistically significant differences between groups in adherence outcomes assessed.<sup>56,84</sup> Hence, of the 13 studies that assessed effects of MTM on adherence, 2 large cohort studies that used an objective adherence measure found a statistically significant positive effect on some aspects of adherence to some medications but not others.

Overall, we concluded that evidence is insufficient to draw conclusions about the effectiveness of MTM for improving the proportion of patients who, based on a threshold of 80 percent of prescribed doses taken, were adherent at 6 to 12 months based on direct, imprecise evidence from one small RCT (Table 22) and direct, and precise but inconsistent (regarding effect direction and magnitude) evidence from one small and one large cohort study that together had high study limitations.

Overall, we concluded that there was low strength of evidence about the effectiveness of MTM for improving the proportion of patients who, based on a threshold of 80 percent of prescribed doses taken, were adherent at 6 to 12 months based on direct, imprecise evidence from one small RCT (Table 22) and direct, and precise but inconsistent (regarding effect direction and magnitude) evidence from one small and one large cohort study that had high study limitations. Strength of evidence is also low for improving the absolute percentage of prescribed doses taken at 6 months and 12 months (mean adherence) for hypertension and dyslipidemia treatment, based on inconsistent direct, imprecise evidence from two cohort studies, one small and one large with medium study limitations (Table 23). However, we found insufficient evidence to draw conclusions about the effect of MTM on absolute percentage of prescribed doses taken for other conditions based on these same observational studies. This conclusion is consistent with findings from two small high risk-of-bias RCTs that provided direct, imprecise evidence of these effects at 4 to 9 months. Of note, these two trials had a high level of study limitations and reported opposite directions of effect on absolute percentage of prescribed doses taken, both with nonsignificant differences between groups.



**Table 22. Adherence outcome Type 1—proportion of patients adherent based on a threshold of percentage of pills taken: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (69)	Medium	Unknown (single study)	Direct	Imprecise	100% of intervention patients and 88.9% of controls were adherent (took $\geq$ 80% of medicine); p=0.115	Insufficient
Observational (Cohort)	Cohort: 2; 224 to 200,722; (224 to 200,722)	High	Inconsistent	Direct	Precise	Two studies with findings in opposite direction; larger study showing range of ORs for medication-specific adherence depending on medication  For comparison of PDP versus controls ORs ranged from 0.99 to 1.43 [95% CIs ranged from (0.90,1.08) to (1.26, 1.62)]  For comparison of MA-PD versus controls ORs ranged from 1.10 to 1.40 [95% CIs ranged from (0.83, 1.24) to (1.29, 1.52)]  For clinic-based MTM versus usual care for adherence to aspirin, odds of adherence range from 5.981 (95% CI 0.284 to 126.030, p=0.250) during the intervention to 1.17 one year after the intervention (95% CI 0.072 to 18.903, p=0.912)	Low for benefit

Abbreviations: CI = confidence interval; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; OR = odds ratio; PDP = Medicare Part D Plan; RCT= randomized controlled trial.

**Table 23. Adherence outcome Type 2—absolute measure of adherence as percentage of prescribed doses taken: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Observational	2; 132-4,500 (120-4,500)	High	Inconsistent	Direct	Imprecise	<p>One small study found no difference with small mean difference</p> <p>Calculated mean difference: -0.040 95% CI: -0.101 to 0.021 p=0.201</p> <p>Larger study found a small (difference in adherence ~4.6%) but statistically significant effect of MTM on adherence to medications for some (two of five) conditions but no significant effect for the other conditions.</p>	<p>Low for adherence to treatment for hypertension and dyslipidemia</p> <p>Insufficient for treatment of patients with diabetes, depression and asthma</p>

Abbreviations: CI = confidence interval; MTM = medication therapy management; SE = standard error; SMD = standardized mean difference.

Evidence is also insufficient about improving medication adherence as measured by self-reported scales from one medium risk-of-bias trial (Table 24). Finally (Table 25), regarding miscellaneous medications taking behaviors, such as remembering to take medication, a medication-taking behavior subscore, and the proportion of medications matched with instructions, we concluded that evidence was insufficient for the effect of MTM on these outcomes, based on evidence from two RCTs that was direct but imprecise and inconsistent. Although the significant degree of heterogeneity across adherence measures precluded our ability to assess strength of evidence across all adherence studies, we note that considering the body of evidence for the effect of MTM on adherence, taken together, results from all studies were inconsistently significant with small magnitudes of effect. Across studies, the direction of effect was inconsistent, however, for the two outcomes, “proportion of adherent patients,” and “percentage of prescribed pills taken,” which in all studies were measured objectively using claims and pharmacy data, we found low strength of evidence that MTM had an effect on medication adherence, particularly for certain chronic conditions. Hence, considering the adherence studies as a whole, there appears to be low strength of evidence regarding an effect of MTM on adherence.

**Table 24. Adherence outcome Type 3—self-reported scales: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 363 (292)	Medium	Consistency unknown, single study	Direct	Imprecise	Calculated mean difference: 0.090, 95% CI: -0.076 to 0.256, p=0.289	Insufficient

Abbreviations: MTM = medication therapy management; RCT= randomized controlled trial.

**Table 25. Adherence outcome miscellaneous: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 492 (365)	Medium	Inconsistent	Direct	Imprecise	Two studies with opposite direction of effect, both with non-significant differences between groups	Insufficient

Abbreviations: RCT= randomized controlled trial.

## Medication Appropriateness

Five studies (four RCTs,<sup>59,63,84,85</sup> one cohort study<sup>70</sup>) reported on the effects of MTM interventions on medication appropriateness (Table 26 and Table 27). Of these studies, three assessed medication appropriateness across a broad spectrum of regimens;<sup>70,84,85</sup> the other two trials assessed appropriateness for specific medications.<sup>59,63</sup> In addition, two studies evaluated single aspects of medication appropriateness, across a range of medications.<sup>62,79</sup>

For the three broader studies, two trials used the Medication Appropriateness Index (MAI).<sup>84,85</sup> One of these reported results for the full scale and for each item of the index (each item asks about a different aspect of medication appropriateness) individually;<sup>84</sup> the other trial reported results only for each of the individual items.<sup>85</sup> The cohort study of broad regimens used a panel of three pharmacists to rate the appropriateness of the various antihypertensive regimens on a visual analogue scale.<sup>70</sup>

As shown in Table 26, one RCT (low risk of bias)<sup>84</sup> found a statistically significant improvement in the MAI Scale at 3 and 12 months' followup. The small cohort study (high risk of bias) reported no statistically significant improvement in the three appropriateness scores assessed for blood pressure regimens (appropriateness of regimens, of dosing intervals, and of dosages) although it was very underpowered.<sup>70</sup>

**Table 26. Medication appropriateness scales: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Covariate-adjusted Medication Appropriateness Index assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 17.7 (0.6) G2: 17.6 (0.6)
	G2: Usual care in the General Medicine Clinic			3 months G1: 13.4 (0.6) G2: 16.5 (0.6) 95% CI: NR p<0.0006 for between-group differences, controlling for baseline and other covariates  12 months G1: 12.8 (0.7) G2: 16.7 (0.7) 95% CI: NR p<0.0006 for between- group differences, controlling for baseline and other covariates
Hanlon et al., 1996 <sup>84</sup> RCT/Low (continued)		G1: 105 G2: 103	Change in covariate-adjusted Medication Appropriateness Index assessed at baseline, 3, 12 months by blinded research pharmacist	3 months change in outcome G1: -4.3 G2: -1.1 95% CI: NR  24% improvement in intervention group and 6% improvement in control group p= 0.0006  12 months change in outcome G1: -4.9 G2: -0.9 95% CI: NR 28% improvement in intervention group and 5% improvement in control group p=0.0002

**Table 26. Medication appropriateness scales: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>70</sup> Barnette et al. 1996 <sup>71</sup> Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1: 25 G2: 26	Appropriateness of BP regimen A blinded review panel of three pharmacists evaluated cases in random order on a visual analog scale, using medical records. The investigators averaged and converted scores to a numerical value by measuring the distance from the best option. Score arranged from 0 to 16.2. Higher scores are better.	BP regimen Baseline G1: 8.7 (4.7) G2: 10.3 (4.8) Followup G1: 10.9 (4.5) G2: 10.1 (5.2) p for change scores NR
			Appropriateness of daily dosage	
			Appropriateness of dosing interval	Daily dosage Baseline G1: 11.6 (4.5) G2: 12.6 (4.5) Followup G1: 13.4 (3.7) G2: 13.2 (4.1) p for change scores NR
				Dosing interval Baseline G1: 13.8 (4.3) G2: 13.4 (4.6) Followup G1: 15.1 (2.3) G2: 13.8 (4.1) p for change scores NR

Abbreviations: BP = blood pressure; G = group; N = number; NR = not reported; RCT = randomized controlled trial.

Of note, one<sup>84</sup> (low risk of bias) of the two trials reporting the effect of MTM on general medication appropriateness scales, also provided descriptive data, by intervention group, regarding the proportion of inappropriate prescriptions for each of 10 items on the MAI (which address different aspects of appropriateness). These findings are reported in Appendix E. While one is unable to draw conclusions regarding the findings because they report percentages with prescriptions (rather than “per patient”) as the unit of analysis, they do suggest that some items are likely driving the improvements in MAI in the MTM group more than others. Specifically, six aspects of medication prescription appropriateness: drug indication; dosage; practicality of directions; drug-drug interactions; duplication; duration of therapy seem to show greater improvement in inappropriate prescriptions than do those for four other aspects: effective medication; correctness of directions; drug-disease interactions; expense of medication. Similarly, another study<sup>85</sup> which did not report on the full MAI scale, also reported data regarding the effect of MTM on individual MAI items (Appendix E). The ability to interpret

these descriptive findings is not only, like the other study,<sup>84</sup> hampered by the use of prescriptions rather than patients as the unit of analysis, but also is limited by the marked baseline differences that existed between intervention groups.

Two RCTs (both medium risk of bias) assessed the appropriateness of regimens for specific medications for specific conditions (Table 27). One assessed, among patients at risk for glucocorticoid-induced osteoporosis, the percentages of patients receiving each of three indicated regimens;<sup>63</sup> the investigators found, at 9-month followup, a statistically significant improvement in the percentage appropriately prescribed calcium supplements among MTM recipients compared with controls but not for bisphosphonate or estrogen drug therapy. The other trial assessed the use of angiotensin-conversion enzyme (ACE) inhibitors among heart failure patients.<sup>59</sup> The pharmaceutical care program had a significant effect on the mean percentage of target dose achieved and on the proportion receiving an appropriate alternative medicine among the subsample; such services did not produce a significant effect on the percentage of patients who received an ACE inhibitor.

**Table 27. Medication appropriateness for individual medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
McDonough, 2005 <sup>63</sup> cluster-randomized RCT/Medium	G1: pharmaceutical care provided by pharmacist in a community pharmacy	Baseline G1: 70 G2: 26	9-month followup	Baseline G1: 38.6 G2: 38.5 p for between-group differences at baseline presumed not significant <sup>a</sup>
	G2: usual care Patients at risk for glucocorticoid-induced osteoporosis)	Followup G1:61 G2:19	Percentage of patients taking calcium supplements	Followup G1:55.7 (p<0.05 for within-group difference from baseline) G2: 31.6 p<0.05 for change in outcome between groups from baseline to followup
			Percentage of patients on bisphosphonate drug therapy	Baseline G1: 17.1 G2: 0 p<0.05 for between-group difference at baseline
				Followup G1: 26.2 (p<0.05 for within-group difference from baseline) G2: 10.5 p: NS for between-group difference at followup; change in outcome between baseline and followup was NS between groups

**Table 27. Medication appropriateness for individual medications: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
McDonough, 2005 <sup>63</sup> cluster-randomized RCT/Medium (continued)			Percentage of patients on estrogen drug therapy	Baseline G1: 12.9 G2: 0 P NS for between-group difference at baseline  Followup G1: 16.4 (p<0.05 for within-group difference baseline) G2: 0 p: NS for between-group difference at followup; change in outcome between baseline and followup was NS between groups
Gattis, 1999 <sup>59</sup> RCT/Medium	G1: Clinical pharmacist intervention G2: Usual medical care  Patients with heart failure.	G1: 90 G2: 91	6-month followup  Fraction of target ACEI dose at followup median (25 <sup>th</sup> and 75 <sup>th</sup> percentile values)	Followup: G1: 1 (25 <sup>th</sup> percentile: 0.5, 75 <sup>th</sup> percentile: 1) G2: 0.5 (25 <sup>th</sup> percentile: 0.188, 75 <sup>th</sup> percentile: 1) 95% CI: NR p<0.001
		G1: 12 G2: 19	Of those not on an ACEI at followup, percentage receiving alternative drug therapy	G1: 75 G2: 26 95% CI: NR
		G1: 90 G2: 91	Percentage receiving an ACEI at followup	G1: 87 G2: 79 95% CI: p=0.18

<sup>a</sup>Baseline differences assumed to be nonsignificant because p-value was reported for other outcomes if significantly different between groups.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; G = group; N = number; NR = not reported; NS = nonsignificant; RCT = randomized controlled trial

Overall, we concluded that the strength of evidence is low for the effect of MTM on medication appropriateness (measured by continuous scores on index) at 3 and 12 months based on indirect, precise evidence from one small RCT (Table 28). The findings are consistent with the direction of effect (indirect, imprecise evidence) from a small cohort study with high study limitations and with studies of individual aspects of medication appropriateness.

**Table 28. Medication appropriateness scales: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 208 (208)	Low	Unknown (single study)	Direct	Precise	Improvement in MTM group from score of 17.7 to 13.4 and to 12.8 in 3, 12 months, respectively, p<0.0006 for between-group differences controlling for baseline and other covariates	Low

Abbreviations: MTM = medication therapy management; RCT= randomized controlled trial.

Strength of evidence is insufficient for the efficacy of MTM for improving the appropriateness of medication prescriptions for specific medications (Table 29) based on findings from two small RCTs that provided indirect, imprecise evidence of these effects at 6 or 9 months. This evidence based had medium study limitations, but the trials reported opposite directions of effect based on medication type.

**Table 29. Medication appropriateness for individual medications: Strength of evidence**

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2;277 (261)	Medium	Inconsistent	Direct	Imprecise	Significant improvement in appropriateness in the MTM group for some medications but not others	Insufficient

Abbreviations: MTM = medication therapy management; RCT= randomized controlled trial.

## Medication Dosing

One RCTs (medium risk of bias) assessed the effect of MTM on medication dosing (Table 30).<sup>50</sup> A second study assessed dose adjustment, but we excluded it from this analysis because dosing was assessed only at baseline.<sup>44</sup> The single included trial assessed changes in the number of doses that primary care patients received per day at the end of 6 months; patients in the MTM arm received 1.6 fewer doses than at baseline, whereas control patients received 0.6 more doses per day than at baseline (p=0.007).

Overall, evidence was low for benefit of MTM on medication dosing (Table 30) based on findings from one small RCT with medium study limitations, and indirect, but precise results.



**Table 30. Medication dosing: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 90 (56)	Medium	Unknown	Indirect	Precise	One RCT showing significant decrease in daily doses of medications (Mean difference: -2.2 doses, calculated 95% CI: -3.738 to -0.662)	Low

Abbreviations: RCT= randomized controlled trial.

## Key Points: Patient-Centered Outcomes

- Evidence was insufficient to draw conclusions about the effect of MTM on adverse drug events based on inconsistent and imprecise findings from two RCTs: one with low study limitations and one with medium limitations.
- Evidence was insufficient to draw conclusions about the effect of MTM on cognitive and physical function based on direct but imprecise findings from one RCT with medium study limitations and on affective function based on direct but inconsistent and imprecise findings from two RCTs, both with medium study limitations.
- Evidence was insufficient to draw conclusions about the effect of MTM on gastrointestinal bleeding based on direct but imprecise findings from one observational study with high study limitations.
- Evidence was insufficient to draw conclusions about the effect of MTM on all-cause mortality based on one RCT with medium study limitations and two observational studies, with high study limitations.
- With two exceptions, MTM interventions had no benefit on SF-36 measures (low strength of evidence of no benefit); evidence was insufficient for the SF-36 domain of vitality or emotional role functioning because of imprecision.
- Evidence was insufficient to determine whether MTM interventions improved patient-reported measures for patients with diabetes (one imprecise medium risk-of-bias trial).
- MTM interventions did not improve measures of patient satisfaction (low strength of evidence of no benefit).

## Detailed Synthesis: Patient-Centered Outcomes

### Adverse Drug Events

Four RCTs<sup>50,69,84,85</sup> and one nonrandomized trial<sup>83</sup> reported on prevalence of adverse drug events (ADEs) following MTM or pharmaceutical care interventions (Table 31). The methods for measuring adverse events differed substantially among included studies. Further, although we assumed that the beneficial direction of effect would be for MTM to decrease ADEs, the nonrandomized trial suggested that MTM services may heighten awareness of potential adverse

outcomes by patients and, thus, increase reporting of ADEs by those receiving the intervention.<sup>83</sup> For this outcome, we rated the risk of bias for some studies<sup>50,83,85</sup> as higher than the overall risk of bias because of measurement and detection bias with respect to the measures and methods used to ascertain this outcome.

**Table 31. Adverse events: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcomes Reported by Study and Time Period	Results
Touchette et al., 2012 <sup>69</sup> RCT/Low	G1: Basic MTM services (with medication information from patient interview)	G1: 211	Percentage of patients with an ADE between 0 and 3 months and OR	G1 vs. G3: OR: 1.629 (p = 0.078)
		G2: 218		G2 vs. G3: OR: 0.726 (p = 0.278)
	G2: Enhanced MTM services (pharmacist provided with 2-page clinical summary from patient medical record)	G3: 208	Percentage of patients with an ADE between 3 and 6 months and OR	G1 vs. G3: OR: 1.107 (p = 0.717)
				G2 vs. G3: OR: 0.889 (p = 0.672)
G3: Usual pharmacy care		Mean number (SD) of ADEs per patient between 0 and 3 months	G1 vs. G3: Calculated mean difference, 0.191; 95% CI, -0.031 to 0.413 p=0.091	
			G2 vs. G3: Calculated mean difference, -0.012; 95% CI, -0.239 to 0.215 p=0.917	
			Mean number (SD) of ADEs per patient between 3 and 6 months	G1 vs. G3: Calculated mean difference, 0.284; 95% CI, 0.056 to 0.512 p=0.014
				G2 vs. G3: Calculated mean difference, -0.062; 95% CI, -0.225 to 0.101 p=0.455
Hanlon et al., 1996 <sup>84</sup> RCT/Medium	G1: Clinical pharmacist care within a general medicine clinic	G1:86 G2:83	Percentage with an ADE at 12 months	Calculated OR: 0.649, 95% CI: 0.366 to 1.152, p=0.14
	G2: Usual care			
Taylor et al., 2003 <sup>85</sup> RCT/High <sup>a</sup>	G1: Pharmaceutical care	G1: 33	Percentage of patients with at least one medication misadventure at 12 months	G1: 2.8 <sup>b</sup> (N=4)
	G2: Standard care	G2: 36		G2: 3.0 <sup>b</sup> (N=3)
				Calculated OR based on reported percent: 0.93, 95% CI, 0.056 to 15.603, p=0.0961
				Calculated OR based on reported N: 1.515 (95% CI, 0.312 to 7.344), p= 0.606

**Table 31. Adverse events: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcomes Reported by Study and Time Period	Results
Jameson et al., 1995 <sup>50</sup> RCT/High <sup>a</sup>	G1: Consultation with a clinical pharmacist in a primary care office G2: Standard medical care in a primary care office	G1: 27 G2: 29	Change in mean medication side effect score at 6 months.	G1: -3.7 G2: -1.9 p: NS and unable to calculate.
Fischer et al., 2000 <sup>83</sup> NRCT/High <sup>a</sup>	G1: Comprehensive drug therapy management program G2: Standard community pharmacy practice	G1: 201 G2: 368	OR for likelihood of reporting side effects or problems from prescription medication (95% CI)	1.81 (1.16 to 2.83)

<sup>a</sup> This study was rated medium risk of bias overall, but due to measurement bias with this specific outcome, it was considered high risk of bias for this outcome.

<sup>b</sup> The percentage reported by authors cannot be generated based on the reported N and the reported number of events.

Abbreviations: ADE = adverse drug event; CI = confidence interval; G = group; N = number; NRCT = nonrandomized controlled trial; NS = not significant; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference; vs. = versus.

One RCT (low risk of bias) compared usual care with the provision of basic MTM services designed to mimic conditions similar to a community pharmacy with another study arm that included an enhanced intervention that provided clinical information about the patient to the pharmacist.<sup>69</sup> It reported on outcomes for the period between 0 and 3 months and for the period between 3 and 6 months. The enhanced MTM intervention was superior to the basic MTM intervention at 3 months in the percentage of subjects reporting an ADE; however, the enhanced intervention and usual care at 3 months and three study arms at 6 months did not differ significantly. In addition, the mean number of ADEs per patient was not statistically different between 0 and 3 months across study arms, but both the enhanced MTM and usual care study arms had significantly fewer ADEs per patient than the basic MTM study arm between 3 and 6 months. This RCT found no statistical difference in mean ADEs per patient between the enhanced MTM study arm and usual care between 3 and 6 months. Another RCT (medium risk of bias) compared clinical pharmacy care within a VA general medicine clinic to usual care.<sup>84</sup> This study found that intervention group subjects were less likely to have one or more ADE over 12 months, but this finding spanned the null effect (calculated OR, 0.649; 95% CI, 0.366 to 1.152, p=0.14).

The other two RCTs and the NRCT were considered high risk of bias for the ADE outcome. One RCT provided pharmaceutical care to patients at high risk for medication-related problems seen in family medicine practices in a rural Alabama community;<sup>85</sup> the intervention and control arms did not have significantly different findings with respect to “medication misadventures” at 12 months. We rated this trial as high risk of bias because it used a nonstandard measure (medication misadventure was not defined) and because the control event rates differed by a factor of 10 relative to the low and medium risk-of-bias RCTs. The other RCT compared MTM intervention provided by a pharmacist within a family health center setting in Michigan with usual medical care and reported no significant difference between change in medication side

effect scores using a scale that the study authors had developed for use in the study, but no validity or reliability data for this scale were provided.<sup>50</sup> The nonrandomized trial (high risk of bias for this outcome) compared participants who agreed to participate in a pharmaceutical care program at one of six participating community pharmacies with a group of control patients who received medications at pharmacies that did not provide pharmaceutical care services;<sup>83</sup> study participants were significantly more likely (OR, 1.81; 95% CI, 1.16 to 2.83) to report experiencing symptoms or problems related to prescription medication than control participants, an effect the authors attributed to increased awareness of medication side effects in the intervention group. Without a clear understanding of the hypothesized mechanism of action in each study for influencing ADEs and the lack of study methods for minimized detection bias, we cannot interpret the conflicting results presented by the nonrandomized trial relative to the findings from the RCTs.

Overall, we concluded that evidence is insufficient to draw conclusions about the efficacy of MTM for reducing adverse drug events based on direct, but inconsistent and imprecise, evidence from one low and one medium risk of bias RCT (Table 32).

**Table 32. Adverse drug events: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 845 (806)	Medium	Inconsistent	Direct	Imprecise	Direction and magnitude of effect differs between the two trials	Insufficient

Abbreviation: RCT = randomized controlled trial.

### Cognitive, Affective, and Physical Function

Two RCTs (both medium risk of bias) reported on changes in cognitive, affective, or physical function at 6 weeks and at 3 months.<sup>75,92</sup> In one RCT, the intervention was provided in a general medicine outpatient clinic in North Carolina to simplify medication regimens among cognitively intact patients ages 65 or older at high risk for medication-related adverse events (Table 33). The investigators measured cognitive function using three different tests. They measured affective function using the Center for Epidemiological Studies Depression Scale and the Self-Rating Anxiety Scale and physical functioning using three different tests. Patients in the intervention arm experienced no significant changes in any of these measures when compared with patients in the control arm.

The other RCT evaluated the use of the Dader method for pharmaceutical care among women receiving treatment for anxiety or depression in specialty clinics at a university hospital in Brazil. This study found significant mean changes in both the Beck Depression Inventory and the Beck Anxiety Inventory compared with the control arm. In addition, the percentage of patients achieving a depression remission was higher in the intervention arm, but these findings were not significant (calculated OR, 2.406; 95% CI, 0.601 to 9.632; p=0.215). Overall, we conclude that the strength of evidence is insufficient for the effect of MTM on cognitive or physical function based on a single, imprecise RCT with medium study limitations (Table 34). We also conclude that the strength of evidence is insufficient for the effect of MTM on affective

function based on inconsistent and imprecise findings from two RCTs with medium study limitations (Table 35).

**Table 33. Cognitive, affective, and physical function: Summary of findings**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcomes Reported by Study and Time Period	Results	
Williams, 2004 <sup>92</sup> RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	At 6 weeks:	Calculated mean differences (unadjusted for baseline differences):	
			Timed manual performance	0.300 95% CI, -1.093 to 1.693; p=0.673	
			Physical performance test	-3.300 95% CI, -13.370 to 6.770, p=0.52	
			Functional reach	0.00 95% CI, -1.076 to 1.076; p=1.0	
			Digit Span (WAIS)	0.200 95% CI, -1.277 to 1.677; p=0.791	
			Digit Symbol (WAIS)	0.00 95% CI, -5.134 to 5.134; p=1.0	
			Randt Memory Test	0.00 95% CI, -1.182 to 1.182; p=1.00	
			CES-D score	-1.10 95% CI, -3.813 to 1.613; p=0.427	
			Self-rating Anxiety Scale score	-0.100 95% CI, -2.392 to 2.192; p=0.932	
			Marques et al. 2013 <sup>75</sup> RCT/Medium	G1: Dader method pharmacotherapy intervention G2: Usual care	G1: 22 G2: 26
Mean change (SD) in Beck Depression Inventory	G1: -13.5 (NR) G2: -2.5 (NR) 95% CI: NR p: 0.0275				
Mean change (SD) in Beck Anxiety Inventory	G1: -13.0 (NR) G2: -3.5 (NR) 95% CI: NR p: 0.0194				
Percentage with Depression remission (defined as BDI < 11)	Calculated OR, 2.406; 95% CI, 0.601 to 9.632; p=0.215				
G1: 5 G2: 5	Percentage with severe depression improvement	Calculated OR 2.667 95% CI, 0.158 to 45.141. p=0.497			
G1:13 G2:13	Percentage with moderate depression improvement	Calculated OR 14.00 95% CI, 1.385 to 141.485. p=0.025			

Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies-Depression Scale; CI = confidence interval; G = group; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale.

**Table 34. Cognitive and physical function: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 140 (133)	Medium	Consistency unknown-single study	Direct	Imprecise	One study with no significant differences between arms	Insufficient

Abbreviation: RCT= randomized controlled trial.

**Table 35. Affective function: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 198 (181)	Medium	Inconsistent	Direct	Imprecise	One study with no significant calculated mean differences in depression or anxiety scores, the other study with significant differences in mean depression and anxiety scores, but no significant difference in percentage achieving a depression remission	Insufficient

Abbreviation: RCT= randomized controlled trial.

## Mortality

One RCT<sup>59</sup> and two cohort studies<sup>44,48</sup> reported all-cause mortality outcomes following MTM interventions at 6 months to 4 years (Table 36). The RCT (medium risk of bias) conducted in a university general cardiology clinic compared a study arm that included a clinical pharmacist intervention for heart failure patients with usual medical care<sup>59</sup> and found decreased mortality within 6 months, but this finding spanned the null effect (OR, 0.59; 95% CI, 0.12 to 2.49, p=0.48).

Both cohort studies (Table 34) (both medium risk of bias) measured mortality outcomes for beneficiaries who met MTM program eligibility and opted in to a telephone-based MTM program provided through an integrated health care system compared with eligible beneficiaries who opted out of the MTM program.<sup>44,48</sup> One study reported a statistically significant reduction in all-cause mortality at 6 months in the intervention arm, when adjusted for age, sex, and baseline disease, and health care utilization levels (adjusted OR, 0.5; 95% CI, 0.3 to 0.9; p=0.044). The other study reported a similar direction of effect (adjusted HR, 0.92; 95% CI, 0.87 to 0.96; p< 0.001). The RCT reporting mortality outcome also reported a composite measure that combined all-cause mortality with nonfatal heart failure events and found the intervention arm experienced a significant benefit from the program (OR, 0.221; 95% CI, 0.07 to 0.65; p=0.005).<sup>59</sup>

**Table 36. All-cause mortality: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome Reported by Study and Time Period	Results
RCT/Medium	G1: Clinical pharmacist intervention in addition to usual medical care G2: Usual medical care	G1: 90 G2: 91	OR for all-cause mortality within 6 months	OR: 0.59 95% CI, 0.12 to 2.49 p=0.48
Welch et al., 2009 <sup>44</sup> Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR for all-cause mortality, within 6 months (adjusted for age, sex, chronic disease score, specific baseline utilization)	Adjusted OR: 0.5 95% CI, 0.3 to 0.9 p=0.044
Yamada et al., 2012 <sup>48</sup> Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Adjusted HR for all-cause mortality within 1 to 4 years (adjusted for age, sex, Charlson comorbidity index, CHF, ESRD)	Adjusted HR: 0.92 95% CI 0.87 to 0.96 p< 0.001

Abbreviations: CHF = congestive heart failure; CI = confidence interval; DCG = diagnostic cost group (a measure of health care use and comorbidity); ESRD = end-stage renal disease; G = group; HR = hazard ratio; MTM = medication therapy management; OR = odds ratio; RCT = randomized controlled trial.

Overall, we concluded that evidence is insufficient for the efficacy of MTM for reducing all-cause mortality at 6 months to 4 years based on direct evidence from a single, imprecise RCT with medium study limitations and two inconsistent observational studies with high study limitations (Table 37). We relied more heavily on the RCT evidence for our overall SOE rating because of the inability of observational study designs to adequately mitigate for selection bias relative to a mortality outcome compared with RCT designs.

**Table 37. All-cause mortality: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 181 (181)	Medium	Consistency unknown, single body of evidence	Direct	Imprecise	OR: 0.59 95% CI: 0.12 to 2.49 p=0.48	Insufficient
Observational	2; 173,329 (173,329)	High	Inconsistent	Direct	Precise	One study OR 0.5 95% CI, 0.3 to 0.9; Second study: adjusted HR: 0.92 95% CI 0.87 to 0.96 p<0.001	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio; RCT= randomized controlled trial.

## Gastrointestinal Bleeding Events

One cohort study (high risk of bias because of selection bias) reported the relative risk reduction in gastrointestinal bleeding events among patients with a diagnosis of arthritis enrolled in a telephone-based MTM program within a large U.S. integrated health care system.<sup>42</sup> The investigators compared the number of gastrointestinal bleeds after 6 months between patients with arthritis who did and did not enroll in the MTM program. The specific N analyzed was not included. Enrolled patients had a 60 percent relative reduction in gastrointestinal bleeds; the

nonenrolled patients had no change in gastrointestinal bleeds (p=0.001 for between-group difference in change in gastrointestinal bleeds).

Overall, we concluded that evidence is insufficient for the efficacy of MTM for reducing gastrointestinal bleeding events based on direct but imprecise evidence from one cohort study with high study limitations (Table 38).

**Table 38. Gastrointestinal bleeding events: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Observational	1; 1,388 (unclear)	High	Consistency unknown—single study	Direct	Imprecise	RRR 60% (p=0.001)	Insufficient

Abbreviation: RRR = relative risk reduction.

## Self-Reported Health Status: SF-36 Measures

### SF-36 Measures: Overview

Eight RCTs<sup>54,55,64,84-86,89,91</sup> and one cohort study<sup>70</sup> reported health status outcomes using the Medical Outcomes Study Short-Form questionnaire (SF-36) (Table 39). The eight SF-36 domains, which combine into two components, are as follows—*physical health*: physical functioning, physical role functioning, bodily pain, and general health perceptions; and *mental health*: vitality, emotional role functioning, social role functioning, and mental health. Seven trials<sup>54,55,64,84,85,89,91</sup> and the cohort study<sup>70</sup> reported scores for all eight domains. One trial reported only its two component scores (i.e., physical health; mental health).<sup>86</sup> Finally, one trial reported both component and domain scores.<sup>55</sup> The trials differed by overall risk of bias (one, low; four, medium, and three, high); the cohort study was high risk of bias.

**Table 39. Scores on SF-36 measures: Summary of effects from meta-analyses**

SF-36 Components and Domains	Time Periods and Risk of Bias for Included Trials	Number of Studies	Total Number With/Without MTM	Mean Difference 95% CI Lower Limit to Upper Limit p-value	Q-value (df for Q) p-value	I-squared
Physical functioning domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	1.171 CI: -3.871 to 6.214 p=0.649	3.873 (2) p=0.144	48.363
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	-0.438 CI: -2.641 to 1.765 p=0.697	4.478 (4) p=0.345	10.669
Physical role functioning domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	3.392 CI: -1.223 to 8.007 p=0.150	0.988 (2) p=0.610	0
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	0.733 CI: -3.429 to 4.895 p=0.730	7.238 (4) p=0.124	44.733
Bodily pain domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	3.320 CI: -0.792 to 7.433 p=0.114	2.765 (2) p=0.251	27.658
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	1.459 CI: -2.793 to 5.711 p=0.501	21.061 (4) p<0.001	81.007



**Table 39. Scores on SF-36 measures: Summary of effects from meta-analyses (continued)**

SF-36 Components and Domains	Time Periods and Risk of Bias for Included Trials	Number of Studies	Total Number With/Without MTM	Mean Difference 95% CI Lower Limit to Upper Limit p-value	Q-value (df for Q) p-value	I-squared
General health perceptions domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	1.916 CI: -0.007 to 3.839 p=0.051	0.856 (2) p=0.652	0
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,308	2.476 CI: 2.123 to 2.829 p<0.001	1.624 (4) p=0.804	0
Vitality domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	2.797 CI: 0.655 to 4.939 p=0.010	0.965 (2) p=0.617	0
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	1.299 CI: -0.305 to 2.904 p=0.112	4.750 (4) p=0.314	15.793
Social functioning domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	2.932 CI: -0.085 to 5.949 p=0.057	1.078 (2) p=0.583	0.000
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	0.631 CI: 0.290 to 0.973 p<0.001	3.407 (4) p=0.492	0
Emotional role functioning domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	5.386 CI: -7.244 to 18.016 p=0.403	7.794 (2) p=0.20	74.341
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	3.441 CI: -4.000 to 10.882 p=0.365	18.742 (4) p=0.001	78.657
Mental health domain	All time periods, low or medium risk of bias	3 <sup>54,84,85</sup>	566/603	1.615 CI: -0.362 to 3.593 p=0.109	0.968 (2) p=0.616	0
	All time periods, all risk of bias	5 <sup>54,55,84,85,89</sup>	968/1,038	1.109 CI: 0.280 to 1.928 p=0.009	1.274 (4) p=0.866	0

Abbreviations: CI = confidence interval; df = degrees of freedom; MTM = medication therapy management; SF-36 = 36-Item Short Form Health Survey; Q = Cochran's Q test.

One trial (medium risk of bias) focused on patients at high risk of experiencing a drug-related problem.<sup>54</sup> This trial compared an intervention arm that included a clinical pharmacist intervention delivered in an ambulatory care clinic with usual medical care. It reported between-group differences with p-values less than 0.05 for four of the eight SF-36 domains (namely, bodily pain, general health perceptions, vitality, and mental health) and for a question that assessed change in health status. All these differences favored the intervention group. However, to control for multiple comparisons, the investigators set alpha at 0.01 when evaluating statistical significance. Using this more conservative alpha level, they investigators reported that only the bodily pain domain and the item assessing change in health status were statistically significant.

Of the eight remaining studies reporting results for SF-36 domains), four trials (one low risk of bias;<sup>84</sup> three medium risk of bias<sup>55,85,91</sup>) reported no statistically significant between-group differences on any SF-36 score. Two trials<sup>64,89</sup> and the cohort study<sup>70</sup> (all high risk of bias) reported one statistically significant (p<0.05) between-group difference, favoring the intervention group—specifically for vitality<sup>89</sup>—among the total of 24 comparisons examined across the three studies. Finally, for one trial (medium risk of bias overall), we rated risk of bias for the SF-36 outcomes as high because of numerous errors in the table reporting these findings

(e.g., group mean not contained within 95% CI, group mean not centered within 95% CI);<sup>55</sup> it reported no statistically significant between-group differences on any SF-36 elements.

## SF-36 Measures: Meta-Analyses

Our analysis focuses on the three trials rated either low or medium risk of bias that provided sufficient data to calculate mean differences for the eight SF-36 domain scores.<sup>1-3</sup> We also conducted sensitivity analyses that included the two high risk-of-bias trials in addition.<sup>55,89</sup> We omitted one trial from the meta-analyses altogether because it reported only that none of the SF-36 domains differed significantly but did not give any precise values.<sup>91</sup> Similarly, we excluded one trial<sup>64</sup> and the cohort study<sup>70</sup> in the meta-analyses because they did not report standard deviations, standard errors, or exact p-values for any of the between-group comparisons; both studies reported that MTM did not produce any significant differences in any SF-36 domain. Finally, we omitted one trial from the domain-specific meta-analyses because it reported only component scores.<sup>86</sup> To correct for the potential inflation of Type I error attributable to multiple comparisons, we used a threshold of  $\alpha/\text{number of tests}$  (i.e., domains;  $0.05/8=0.006$ ) when evaluating statistical significance. Below, we describe our findings for each SF-36 domain, focusing on the meta-analyses of just the low to medium risk-of-bias trials (i.e., the smaller meta-analysis). We did not conduct a meta-analysis for the SF-36 component scores because only one trial was rated as low to medium risk of bias for these outcomes.

## SF-36 Domain Scores

**Physical functioning.** Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 1.17; 95% CI, -3.87 to 6.21;  $p=0.65$ ;  $I^2=48.36$ ). Adding the two high risk-of-bias studies did not alter this conclusion (mean difference: -0.44; 95% CI, -2.64 to 1.77;  $p=0.70$ ;  $I^2=10.67$ ) (Appendix F-1).

**Physical role functioning.** Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 3.39; 95% CI, -0.79 to 7.43;  $p=0.11$ ;  $I^2=27.66$ ). Adding the two other studies did not alter this conclusion (mean difference: 0.73; 95% CI, -3.43 to 4.90;  $p=0.73$ ;  $I^2=44.73$ ) (Appendix F-2).

**Bodily pain.** Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 3.32; 95% CI, -1.22 to 8.01,  $p=0.15$ ;  $I^2=0$ ). Adding the two other studies did not alter this conclusion (mean difference: 1.46; 95% CI, -2.79 to 5.71;  $p=0.50$ ;  $I^2=81.01$ ) (Appendix F-3).

**General health perceptions.** Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 1.92; 95% CI, -0.02 to 3.84,  $p=0.051$ ;  $I^2=0$ ). With the additional studies, however, results suggested a beneficial effect of MTM interventions on general health perceptions (mean difference: 2.48; 95% CI, 2.12 to 2.83,  $p<0.001$ ;  $I^2=0$ ) (Appendix F-4).

**Vitality.** Results of the smaller meta-analysis showed no benefit for the MTM interventions, after correcting for multiple comparisons (mean difference: 2.80; 95% CI, 0.65 to 4.94;  $p=0.01$ ;  $I^2=0$ ). If we had set alpha at the conventional 0.05 level, our findings would demonstrate a beneficial effect of MTM interventions. Adding the two other studies to the analysis did not change the no-benefit results for the MTM interventions, even at the more conventional alpha level (mean difference: 1.30; 95% CI, -0.31 to 2.90;  $p=0.11$ ;  $I^2=15.79$ ) (Appendix F-5).

**Emotional role functioning.** Results from the smaller meta-analysis showed no benefit for the MTM interventions (mean difference: 5.39; 95% CI, -7.24 to 18.02;  $p=0.40$ ;  $I^2=74.34$ ).

Adding the other two studies did not alter this conclusion (mean difference: 3.44; 95% CI, -4.00 to 10.88;  $p=0.37$ ;  $I^2=78.66$ ). However, the high  $I^2$  statistic for both these meta-analyses suggested considerable heterogeneity among the studies for this particular domain (Appendix F-6).

**Social role functioning.** Results from the low and medium risk-of-bias analysis showed no benefits from MTM interventions (mean difference: 2.93; 95% CI, -0.09 to 5.95;  $p=0.057$ ;  $I^2=0$ ). With the additional studies, however, results suggested a beneficial effect of MTM interventions (mean difference: 0.63; 95% CI, 0.29 to 0.97;  $p<0.001$ ;  $I^2=0$ ) (Appendix F-7).

**Mental health.** Results from the smaller meta-analysis showed no benefit for the MTM interventions (mean difference: 1.62; 95% CI, -0.36 to 3.59;  $p=0.11$ ;  $I^2=0$ ). Adding the two other studies did not alter this conclusion, after correcting for multiple comparisons (mean difference: 1.11; 95% CI, 0.28 to 1.94,  $p=0.009$ ;  $I^2=0$ ) (Appendix F-8).

Two RCTs provided data for the SF-36 physical and mental component scores.<sup>55,86</sup> Although we rated both trials as medium risk of bias overall, we rated one of them<sup>55</sup> as high risk of bias for the SF-36 outcomes because of errors in the table presenting these findings. None of the between-group differences examined in either study were statistically significant with alpha set at 0.05.

### SF-36 Strength of Evidence Grades

Based on the evidence from low- and medium risk-of-bias trials (3 trials; 1,343 randomized, 1,169 analyzed) with medium study limitations, precise, and direct evidence, we graded the strength of evidence for the effect of MTM interventions on six of the eight SF-36 domains and the overall physical and mental component scores as low for no benefit. For the remaining two domains—vitality and emotional role functioning, we judged the evidence as imprecise and rated the evidence as insufficient (Table 40).

**Table 40. SF-36: Strength of evidence**

SF-36 Domain	Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Physical functioning domain	RCTs	3; 1,343 (1.169)	Medium	Inconsistent	Direct	Precise	Mean difference: 1.171 CI: -3.871 to 6.214 $p=0.649$	Low for no benefit
Physical role functioning domain	RCTs	3; 1,343 (1.169)	Medium	Consistent	Direct	Precise	Mean difference: 3.392 CI: -1.223 to 8.007 $p=0.150$	Low for no benefit
Bodily pain domain	RCTs	3; 1,343 (1.169)	Medium	Inconsistent	Direct	Precise	Mean difference: 3.320 CI: -0.792 to 7.433 $p=0.114$	Low for no benefit

**Table 40. SF-36: Strength of evidence (continued)**

SF-36 Domain	Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
General health perceptions domain	RCTs	3; 1,343 (1.169)	Medium	Consistent	Direct	Precise	Mean difference: 1.916 CI: -0.007 to 3.839 p=0.051	Low for no benefit
Vitality domain	RCTs	3; 1,343 (1.169)	Medium	Consistent	Direct	Imprecise (results not corrected or multiple comparison)	Mean difference: 2.797 CI: 0.655 to 4.939 p=0.010	Insufficient
Social functioning domain	RCTs	3; 1,343 (1.169)	Medium	Consistent	Direct	Precise	Mean difference: 2.932 CI: -0.085 to 5.949 p=0.057	Low for no benefit
Emotional role functioning domain	RCTs	3; 1,343 (1.169)	Medium	Inconsistent	Direct	Imprecise (wide confidence intervals)	5.386 CI: -7.244 to 18.016 p=0.403	Insufficient
Mental health domain	RCTs	3; 1,343 (1.169)	Medium	Inconsistent	Direct	Precise	Mean difference: 1.615 CI: -0.362 to 3.593 p=0.109	Low for no benefit

Abbreviations: CI = confidence interval; RCT= randomized controlled trial; SF-36 = 36-Item Short Form Health Survey.

### Condition-Specific Quality of Life

Two small RCTs<sup>72,74</sup> reported condition-specific quality-of-life outcomes (Table 41). One RCT (medium risk of bias) of just patients with diabetes compared patients in a study arm that included a clinical pharmacist intervention delivered in an ambulatory care clinic with those receiving usual medical care.<sup>72</sup> The investigators reported no significant difference in diabetes-specific quality-of-life between the intervention and control arms at the end of 6 months. The other RCT<sup>73,74</sup> (high risk of bias) of patients with renal disease reported a significant difference at 1 year favoring the pharmaceutical care program We graded the strength of evidence, using only the medium risk-of-bias trial, as insufficient (single study, direct, but imprecise) (Table 42).

**Table 41. Condition-specific quality of life: Summary of results**

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
Clifford et al., 2002 <sup>72</sup> RCT/Medium	G1: Collaborative pharmaceutical care program G2: Standard outpatient care for diabetes	G1: 48 G2: 25	Diabetes Quality of Life instrument Scale of 1 to 5 Higher scores indicate greater dissatisfaction, worry, or impact of diabetes	Baseline G1: 2.0 (0.6) G2: 1.9 (0.5) p: NS 6-month followup G1: 1.9 (0.5) G2: 1.9 (0.4) p>0.15
Pai et al., 2009 <sup>73</sup> ; Pai et al., 2009 <sup>74</sup> RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44 Year 1: G1: 44 G2: 36 Year 2: G1: 24 G2: 32	Renal Quality of Life Profile Maximum score = 172 Higher scores indicate worsening of HRQOL	Total Score Baseline G1: 71.9 (40) G2: 74.5 (33.5) Year 1 G1: 71.4 (33.6) G2: 87.5 (30.4) p<0.05 for G1 vs. G2 for Y1 Year 2 G1: 56.5 (32.6) G2: 68.8 (35.8)

Abbreviations: G =group; HRQOL = health-related quality of life; NS = not significant; RCT= randomized controlled trial.

**Table 42. Condition-specific quality of life: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 73 (73)	Medium	Consistency unknown—single study	Direct	Imprecise	Nonsignificant improvement of 0.1 point on a 5-point scale in the intervention group compared with no change in the control group	Insufficient

Abbreviation: RCT= randomized controlled trial.

## Patient Satisfaction

Five studies reported on various patient satisfaction measures and outcomes; four were trials (including two cluster randomized trials)<sup>51,64,84,86</sup> and one was a cohort study.<sup>70</sup> All compared patient satisfaction outcomes for patients receiving some form of MTM intervention and patients receiving some type of usual care (Table 43). Of these studies, we rated two RCTs low or medium risk of bias, two cluster randomized trials as medium or high risk of bias; and the cohort study as high risk of bias.

One RCT (low risk of bias) focused on patients age 65 and older who were taking five or more regularly scheduled medications.<sup>84</sup> This study compared patients who receiving clinical pharmacist intervention delivered in an ambulatory care clinic with those receiving usual outpatient care. The study reported non-significant between-group differences for two

satisfaction measures (i.e., satisfaction with general health care and satisfaction with pharmacy-related care).

**Table 43. Patient satisfaction: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	General health care satisfaction at 12-month followup (Higher scores indicate greater dissatisfaction)	G1: 1.5 (0.7) G2: 1.6 (0.8) p=0.70
			Pharmacy-related health care satisfaction at 12-month followup (Higher scores indicate greater dissatisfaction)	G1: 5.2 (1.5) G2: 5.4 (1.7) p=0.52
Malone et al., 2000 <sup>51</sup> ; Ellis et al., 2000 <sup>52</sup> ; Malone et al., 2001 <sup>54</sup> ; Ellis et al., 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e. no pharmaceutical care)	G1: 447 G2: 484	Patient satisfaction with primary health care provider (Higher scores indicate greater satisfaction)	Time 1 G1: 51.9 (7.5) G2: 51.9 (7.5)
				Time 2 G1: 51.7 (7.3) G2: 51.9 (7.5) p=NS
Bernsten et al., 2001 <sup>64</sup> ; Sturgess et al., 2003 <sup>65</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1,290 G2: 1,164  6 months G1: 1,024 G2: 953  12 months G1: 863 G2: 764  18 months G1: 704 G2: 636	Percentage rating pharmacy services provided as "excellent"	Baseline G1: 66.2 G2: 68.2 p NR
				6 months G1: 72.8 G2: 63.7 p <0.05
				12 months G1: 73.4 G2: 71.2 p NR
				18 months G1: 73.8 G2: 64.6 p <0.05

**Table 43. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
			Percentage agreeing with statement "I am satisfied with the services provided by the pharmacy that I regularly visit."	Baseline G1: 92.0 G2: NR  6 months G1: 95.1 G2: NR  12 months G1: 93.9 G2: NR  18 months G1: NR G2: NR  p=NS for all between-group differences
Carter et al., 1997 <sup>70</sup> , Barnette et al., 1996 <sup>71</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	All results are percentage of patients agreeing or strongly agreeing with a specific statement, as measured at 6-month followup	
			"I am very satisfied with the pharmacy services I receive,"	G1: 100 G2: 96 p=0.065
			"Overall, the program provided a valuable service to me"	G1: 100 G2: 80 p=0.0018
			"The quality of information provided to me by the pharmacist was excellent"	G1: 100 G2: 88 p=0.012
			"My participation in this program helped me to understand high blood pressure better"	G1: 100 G2: 83 p= 0.011
			"The area was private enough for me to feel comfortable talking about my high blood pressure"	G1: 96 G2: 96 p=0.036
			"I felt comfortable talking with the pharmacist about my health problems"	G1: 100 G2: 96 p=0.052
			"I am confident the pharmacist is able to help me control my high blood pressure"	G1: 100 G2: 92 p=0.340
			"I am confident the information provided by the pharmacist to the physician improved my health care."	G1: 87 G2: 83 p=0.325
			"There are things about the high blood pressure program that could be better."	G1: 9 G2: 0 p=0.157

**Table 43. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>70</sup> , Barnette et al., 1996 <sup>71</sup> Cohort/High	(continued)	(continued_	"I am very willing to continue to see the pharmacist for help with my high blood pressure control."	G1: 95 G2: 88 p=0.459
			"I think the pharmacist should provide this type of service for everyone."	G1: 77 G2: 75 p=0.890
			"I think the pharmacist should be paid for this type of service."	G1: 91 G2: 82 p=0.379
Volume et al., 2001 <sup>86</sup> , Kassam et al., 2001 <sup>87</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care G2: Traditional pharmacy care	Baseline N=363 G1: 159 G2: 204  Time 2: N=317 G1: NR G2: NR  Time 3: N=292 G1: NR G2: NR	General satisfaction (Higher numbers reflect greater dissatisfaction)	Baseline G1: 1.59 (0.77) G2: 1.56 (0.73)
				6-Month G1: 1.51 (0.84) G2: 1.57 (0.72)
				12-Month G1: 1.53 (0.77) G2: 1.62 (0.88)
				p=NS for all between-group differences
			Interpersonal skills (Higher numbers reflect greater dissatisfaction)	Baseline G1: 1.36 (0.48) G2: 1.37 (0.53)
				6-Month G1: 1.37 (0.59) G2: 1.35 (0.57)
				12-Month G1: 1.31 (0.50) G2: 1.45 (0.72)
				p=NS for all between-group differences
			Evaluation and goal setting (Higher numbers reflect greater dissatisfaction)	Baseline G1: 2.58 (1.12) G2: 2.74 (1.09)
				6-Month G1: 2.46 (0.98) G2: 2.98 (1.24)
	12-Month G1: 2.49 (1.10) G2: 2.90 (1.08)			
	p<0.05 for between-group differences in score changes from Time 1 to Time 2 and Time 1 to Time 3			



**Table 43. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>86</sup> ; Kassam et al., 2001 <sup>87</sup> RCT-Cluster Randomized/Medium (continued)			Trust (Higher numbers reflect greater dissatisfaction)	Baseline
				G1: 1.62 (0.66)
				G2: 1.46 (0.57)
				6-Month
				G1: 1.40 (0.54)
				G2: 1.39 (0.58)
				12-Month
				G1: 1.43 (0.58)
				G2: 1.51 (0.75)
				p<0.05 for between-group differences in score changes from Time 1 to Time 2
p<0.05 for group x measure interaction over all three time periods				
Helping patients (Higher numbers reflect greater dissatisfaction)				Baseline
				G1: 2.25 (1.31)
				G2: 2.22 (1.14)
				6-Month
				G1: 1.98 (1.17)
				G2: 2.23 (1.15)
				12-Month
				G1: 2.07 (1.22)
				G2: 2.37 (1.21)
				p= S for all between-group differences
Explanation (Higher numbers reflect greater dissatisfaction)				Baseline
				G1: 1.34 (0.55)
				G2: 1.34 (0.63)
				6-Month
				G1: 1.39 (0.67)
				G2: 1.30 (0.56)
				12-Month
				G1: 1.38 (0.73)
				G2: 1.35 (0.61)
				p= NS for all between-group differences

**Table 43. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results			
Volume et al., 2001 <sup>86</sup> ; Kassam et al., 2001 <sup>87</sup> RCT-Cluster Randomized/Medium (continued)			Pharmacy finances (Higher numbers reflect greater dissatisfaction)	Baseline			
				G1: 3.08 (1.82)			
				G2: 2.85 (1.80)			
				6-Month			
				G1: 2.89 (1.89)			
				G2: 2.86 (1.75)			
			12-Month				
			G1: 3.08 (1.80)				
			G2: 3.16 (1.88)				
							p=NS for all between-group differences
			Drug plan finances (Higher numbers reflect greater dissatisfaction)	Baseline			
				G1: 3.31 (1.70)			
G2: 3.41 (1.75)							
6-Month							
G1: 3.45 (1.96)							
G2: 3.39 (1.83)							
12-Month							
G1: 3.65 (1.67)							
G2: 3.56 (1.83)							
				p=NS for all between-group differences			
Communicates with doctor (Higher numbers reflect greater dissatisfaction)	Baseline						
	G1: 1.50 (0.77)						
	G2: 1.60 (0.89)						
	6-Month						
	G1: 1.36 (0.63)						
	G2: 1.72 (1.00)						
12-Month							
G1: 1.36 (0.65)							
G2: 1.74 (0.97)							
				p<0.05 for between-group differences in score changes from Time 1 to Time 3			

Abbreviations: G = group; N = number; NR = not reported; NS = not significant; RCT= randomized controlled trial.

The other RCT (medium risk of bias) focused on patients at high risk of experiencing a drug-related problem.<sup>54</sup> This study compared patients receiving a clinical pharmacist intervention delivered in an ambulatory care clinic with those in usual medical care. The study reported a nonsignificant between-group difference on a measure assessing patient satisfaction with the primary care provider.

One cluster trial (medium risk of bias) focused on patients ages 65 or older who were taking three or more medications concurrently.<sup>86</sup> This study evaluated a community pharmacy-based intervention and assessed nine different measures of satisfaction at baseline, at 6-7 months

following baseline, and at 12 to 13 months following baseline. This study reported statistically significant between-group change in a measure labeled, *Evaluation and Goal Setting*. This measure included six items assessing the extent to which the pharmacist involved the patient in setting therapeutic goals. However, none of the items asked directly about patient satisfaction with the goal setting process. This study also reported a statistically significant between-group change from baseline to the 12- 13-month followup on a measure labeled, *Communicates with Doctor*. This measure included two items asking about whether the patient’s pharmacist and doctor work together to determine the most appropriate therapy for the patient. Neither item asked directly about patient satisfaction with the level of pharmacist-doctor communication. Finally, this study reported a statistically significant between-group change in a measure labeled, *Trust*. At baseline, patients in the intervention group reported lower trust in their pharmacist. Over the course of the study, their level of trust improved to the level reported by patients in the control group at baseline, accounting for the between group differences reported. The study reported no statistically significant between-group changes on the remaining six satisfaction measures, including a measure that directly assessed overall satisfaction with pharmacy services.

When grading strength of evidence, we did not consider the results from the remaining cluster trial RCT<sup>64</sup> and the cohort study<sup>70</sup> because they were rated as high risk of bias. We also did not consider findings from three other studies (one RCT,<sup>72</sup> one nonrandomized clinical trial,<sup>49</sup> and one cohort study<sup>42</sup>) because they assessed only changes in satisfaction over time in the intervention arm and did not make any between-group comparisons. Overall, we concluded that the strength of evidence for MTM interventions with respect to patient satisfaction was low for no benefit (Table 44).

**Table 44. Patient satisfaction: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 1,625 (1,463)	Medium	Consistent	Direct	Precise	17 of 21 between-group differences small and not statistically significant; 4 statistically significant differences ranged in magnitude from -0.15 to -0.36, favoring MTM	Low for no benefit

Abbreviations: MTM = medication therapy management; RCT = randomized controlled trial.

## Resource Utilization

### Key Points: Resource Utilization

- Effective MTM interventions might plausibly lead to either an increase or a decrease in resource utilization, depending on the baseline status of the patient and intended goals of the intervention. When studies did not present a clear hypothesis or expected direction of effect, we were unable to interpret changes in resource utilization outcomes as either a benefit or a harm of MTM interventions.
- Evidence was insufficient to assess the effectiveness of MTM in changing numerous measures of use of health care resources. These included use of generic medications; several measures of medication costs (costs of patient copays for medication, overall outlays on medications, medications and other medical costs); outpatient visits and costs;

laboratory tests and costs; emergency department visits and costs; and and length of hospital stay.

- MTM intervention reduced medication costs for health plans (3 trials, medium study limitations, consistent, indirect, imprecise).
- MTM interventions among patients with a variety of clinical conditions from trials did not demonstrate a consistent change in the number of hospitalizations when compared with usual care, but one cohort study that partially addressed confounding found evidence of reduced hospitalization in the intervention arm (high study limitations, unknown consistency, direct, precise). Together, the lack of consistency across studies suggests insufficient evidence on the number of hospitalizations.
- In one large cohort, MTM interventions appeared to reduce the risk and costs of hospitalization for patients with diabetes (high study limitations, unknown consistency, direct, precise), but results for patients with unspecified or other clinical conditions did not support these results.
- MTM interventions in the home reduce the rate of hospitalizations for patients with heart failure (one cohort, high study limitations, direct, precise, low strength of evidence of benefit).

## Detailed Synthesis: Resource Utilization

### Use of Generic Medications

Understanding whether a change in the number of medications taken following an MTM intervention is a measure of appropriate resource utilization requires knowledge of the goal of drug therapy. A decrease in the number of medications can represent regimen simplification and resolution of therapeutic duplication; thus, it can be interpreted as a measure of appropriate resource utilization. The converse—that is, an increase in number of medications—cannot, however, be interpreted as a measure of inappropriate resource use. An increase in number of medications can, in fact, represent appropriate use of resources when it resulted from identifying and resolving an inadequate drug regimen.

Numerous studies provided information on the number of medications at followup in intervention and control arms or on the change in number of medications between baseline and followup.<sup>37,49-51,55,57,61,62,64,73,74,82,84-86,93,94</sup> The use of generic medications, by contrast, can be interpreted as cost-saving.

Three cohort studies examined the use of generic medications (Table 45). One cohort study, designed to identify the impact of 2010 Part D MTM programs, compared cohorts (standalone Prescription Drug Plan or Medicare Advantage Prescription Drug Plan) receiving MTM with a comprehensive medication review with cohorts receiving usual care for congestive heart failure, chronic obstructive pulmonary disease, and diabetes, after limiting the sample to those newly eligible or enrolled for MTM and controlling for characteristics such as demographics, medical comorbidities, condition severity, and intensity of provider care.<sup>62</sup> The study found very low generic substitution ratios, likely because many patients were already on generic medications. In a small number of instances, intervention arms were statistically significant from control arms, but the direction of change was inconsistent and the total magnitude of change was small. Two studies evaluated telephone-based MTM<sup>42,57</sup> and one also compared community pharmacy-based MTM with educational mailings.<sup>57</sup> We assessed both studies as high risk of bias owing to lack of

adjustment for potential confounding from study design (intervention refusers versus acceptors)<sup>42</sup> or lack of capacity of pharmacists or inability to reach patients.<sup>57</sup>

**Table 45. Use of generic medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>62a</sup>	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR  Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR  Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR  Comparison—congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care  Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care  Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	Generic substitution ratio within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Odds (95% CI) For CHF/COPD/diabetes drugs Congestive heart failure G1 vs. G13: 0.001 (-0.000, 0.002), p>0.05 G3 vs. G14: 0.005 (0.003, 0.006), p<0.05  Chronic obstructive pulmonary disease G5 vs. G15: -0.001 (-0.003, 0.000), p>0.05 G7 vs. G16: 0.000 (-0.002, 0.002), p>0.05  Diabetes G9 vs. G17: -0.000 (-0.000, 0.000), p>0.05 G11 vs. G18: 0.000 (-0.000, 0.000), p>0.05  For non-CHF/COPD/diabetes drugs Congestive heart failure G1 vs., G13: 0.000 (-0.002, 0.002), p>0.05 G3 vs., G14: -0.010 (-0.013, -0.008), p<0.05  Chronic obstructive pulmonary disease G5 vs., G15: 0.000 (-0.001, 0.003), p>0.05 G7 vs., G16: 0.006 (0.003, 0.009), p<0.05  Diabetes G9 vs., G17: -0.001 (-0.002, 0.000), p>0.05 G11 vs., G18: -0.002 (-0.003, -0.001), p<0.05
Pindolia et al., 2009 <sup>42</sup>	G1: Telephone based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1081	Increase in the overall use of generic drugs	G1: 6% G2: 3%  p not calculated because baseline percentages not provided

**Table 45. Use of generic medications: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Winston et al., 2009 <sup>57</sup> Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Weighted generic substitution ratio: 30-day equivalent claims divided by total number of claims	Calculated mean differences for G1 vs. G3: 1.2 (95% CI: 0.724 to 1.676; p<0.001)  Calculated mean difference for G2 vs. G3: 0.80 (95% CI: -0.246 to 1.846; p=0.134)

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; G = group; CMR = comprehensive medication review; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; N = number; PDP = Medicare Part D Plan.

Together (or taking the medium risk-of-bias cohort study alone), these studies offer insufficient evidence, based on study limitations, inconsistency, and imprecision, to judge the effectiveness of MTM on use of generic medications (Table 46).

**Table 46. Use of generics for MTM versus usual care: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 63,198–200,722 (63,198–200,722)	High	Consistency unknown (single study)	Direct	Imprecise	Odds range from -0.01 to 0.006	Insufficient

Abbreviation: MTM = medication therapy management.

## Medication Costs: Overview

Eighteen studies reported data on costs of prescription medications (Table 47). We use the same language as the authors in describing their measures; they varied in study design and risk of bias and used a wide range of measures that cannot all be meaningfully combined. We categorized these outcomes in four groups; patient out-of-pocket costs (copayments), health plan costs or claims, combined outlays by patients and insurers, and combinations of medications and other costs. Table 47 lists studies in order by outcome category (or outcomes in some cases) and then alphabetically by author name. Later sections offer a detailed synthesis by these four categories of costs and describe the relevant studies in more detail. We were unable to categorize one high-risk-of-bias cohort study<sup>70,71</sup> because it did not offer sufficient information on how “charges” were calculated. We note that several studies use the term “costs” although the specific measure used may not reflect true costs if they do not account for profits or subsidies.

**Table 47. Measures used in studies of costs of medications**

<b>Study</b>	<b>Prescription Costs to Patients</b>	<b>Total Expenditures on Medications by Health Plan</b>	<b>Total Outlays on Medication</b>	<b>Medication and Other Costs Combined</b>
Christensen et al., 2007 <sup>49</sup>	Difference in patient copayment for prescriptions over 6 months	Difference in insurer payment for prescriptions over 6 months		
Fox et al., 2009 <sup>37</sup>	Mean Medicare Part D copayment costs per patient per month  Mean Medicare Part D and non- Part D copayments	NA	Mean Medicare Part D drug costs (total Medicare Part D drug costs (patient copays + insurance plan medication costs + dispensing fees)	NA
Pindolia et al., 2009 <sup>42</sup>	Out-of-pocket prescription costs per health plan member	NA	Total prescription drug costs per health plan member (2006)	NA
Shimp et al., 2012 <sup>60</sup>	Annualized prescription drug costs for patient-paid amount	Annualized prescription drug costs for University of Michigan-paid amount	NA	NA
Chrischilles et al., 2004 <sup>79</sup>	NA	Mean amount billed per patient for active drugs (based on Medicaid claims)	NA	NA
Hirsch et al, 2011 <sup>76</sup> ; Hirsch et al, 2009 <sup>77</sup>	NA	Paid claims amount for all prescription medications, ART medications, and non-ART medications (total cost-cost of ART medications)	NA	Paid claims amounts for inpatient, hospital outpatient (includes emergency department), outpatient, mental health, laboratory/X-ray, and AIDS Waiver Program
Jameson et al., 1995 <sup>50</sup>	NA	Cost of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	NA	NA
Moore et al., 2013 <sup>45</sup>	NA	Total plan-paid costs for all dispensed medications in pre- and post-periods	NA	Total plan-paid costs for all dispensed medications in pre- and post-periods+total plan-paid costs for all covered medical services in pre- and post-periods
Moczygemba et al., 2012 <sup>39</sup> Moczygemba et al., 2011 <sup>40</sup> Moczygemba et al., 2008 <sup>41</sup>	NA	Total Part D drug costs (based on prescription claim records, excludes non-Part D drug costs	NA	NA

**Table 47. Measures used in studies of costs of medications (continued)**

Study	Prescription Costs to Patients	Total Expenditures on Medications by Health Plan	Total Outlays on Medication	Medication and Other Costs Combined
Perlroth et al., 2013 <sup>62</sup>	NA	Total payments recorded on Part D claims for all prescription medications not used for treatment of condition specific to MTM eligibility (CHF, COPD, or diabetes)	NA	NA
Sellors et al., 2003 <sup>55</sup>	NA	Mean daily medication costs to the Ontario Drug Benefit Program	Mean daily medication costs	Mean cost of health care resources per senior (total costs, including all hospital stays)
Sellors et al., 2001 <sup>61</sup>	NA	Mean daily medication costs to the Ontario Drug Benefit Program	Mean daily medication costs	NA
Wittayanukorn et al., 2013 <sup>80</sup>	NA	Mean pharmacy expenditures	NA	Mean pharmacy expenditures+mean medical expenditures
Hanlon et al., 1996 <sup>84</sup> Cowper et al., 1998 <sup>94</sup>	NA	NA	Price to the VA for the agent, plus the average cost of filling prescriptions	Drug outlays + average per diem cost of inpatient care based on annual output and expenditure data for bed sections in the cost distribution report + costs of surgery based on relative value weights, and VA costs per relative value weight + health services valued using 1991 estimates of VAMC unit costs; costs for non-VA hospital care were imputed using logic underlying VA cost methodology
Jeong et al., 2009 <sup>38</sup>	NA	NA	Total prescription costs (full retail cost of medication had the patient not had insurance coverage)	NA
Krska et al., 2001 <sup>91</sup>	NA	NA	Average monthly costs of prescribed medication per patient (excluding costs of prescribed medicines not taken)	NA
Malone et al., 2000 <sup>51</sup> , Ellis et al., 2000 <sup>52</sup> , Malone et al., 2001 <sup>54</sup> , Ellis et al., 2000 <sup>53</sup>	NA	NA	Mean drug costs (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	NA



**Table 47. Measures used in studies of costs of medications (continued)**

Study	Prescription Costs to Patients	Total Expenditures on Medications by Health Plan	Total Outlays on Medication	Medication and Other Costs Combined
Pai et al., 2009 <sup>73</sup> , Pai, 2009 <sup>74</sup>	NA	NA	Mean drug costs (calculated from average wholesale price)	NA
Staresinic et al., 2007 <sup>43</sup>	NA	NA	Total prescription cost per MTM program beneficiary per month ([gross drug cost=ingredient cost paid + dispensing fee + sales tax]/member months in Part D contract)	NA
Welch et al., 2009 <sup>44</sup>	NA	NA	Mean medication costs per day (from data on study beneficiaries' purchases of ambulatory prescription medications)	NA
Williams, 2004 <sup>92</sup>	NA	NA	Average monthly wholesale price of prescription and non-prescription drugs	NA
Winston et al., 2009 <sup>57</sup>	NA	NA	Mean drug cost per patient per month (based drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, before subtracting any patient cost-sharing amounts)	NA
Yamada, 2012 <sup>48</sup>	NA	NA	Change in annual prescription cost (details not specified)	NA
Bernsten et al., 2001 <sup>64</sup> , Sturgess et al., 2003 <sup>65</sup>	NA	NA	NA	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs
Fischer et al., 2002 <sup>82</sup>	NA	NA	NA	Change in total charges for inpatient care, outpatient care, and pharmacy charges

Abbreviations: ART = antiretroviral therapy; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; GPs = general practitioners; MTM = medication therapy management; NA = not applicable; VA = Veterans' Administration; VAMC = Veterans' Administration Medical Center

### Medication Costs: Patient Copayments

Four studies (one medium risk-of-bias RCT,<sup>60</sup> one nonrandomized controlled trial [NRCT] of medium risk of bias<sup>49</sup> and two cohort studies of high risk of bias<sup>37,42</sup>) compared the copayments for patients who refused MTM with patients who accepted MTM enrollment. These studies provided inconsistent evidence that patient medication co-payments increased following MTM. Table 48 documents the main findings. We calculated mean differences between groups when

the original authors did not provide those data; all currencies are rounded to two decimals (i.e., for U.S. currency, cents). The trial showed a decrease in costs of \$234 in the intervention arm and \$170 in the control arm, but without information on numbers in each arm, we cannot calculate variance.

**Table 48. Patient copayments: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Shimp et al., 2012 <sup>60</sup> RCT/Medium	G1: MTM program for University of Michigan beneficiaries, entitled Focus on Medicines G2: Usual care (not described)	G1: NR G2: NR	Annualized prescription drug costs for patient-paid amount	12 months before first visit G1: 1,334 ± 593 G2: 1,293 ± 680 95% CI: NR p: NR at baseline  12 months after second visit G1: 1,100 ± 645 G2: 1,123 ± 643 95% CI: NR p: NR at followup  Mean difference with variance between arms not calculable without N, reported P for G1 from baseline to followup: 0.004 p for G2 from baseline to followup: 0.062
Christensen et al., 2007 <sup>49</sup> NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in patient copayment for prescriptions over 6 months in USD (SD)	Calculated mean difference for G1 vs. G2: 80.40 USD; 95% CI, 10.43 to 150.37 p=0.024  Calculated mean difference for G1 vs. G3= 88.60 USD; 95% CI, 24.61 to 152.59 p=0.007
Fox et al., 2009 <sup>37</sup> Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (refusers)	G1: 247 G2: 50	Mean difference in Medicare Part D medication copayment costs per patient per month  Mean difference in all medication copayments (Medicare Part D and not Part D) per patient per month	Calculated mean difference: -3.92 USD, 95% CI, -25.71 to 17.87 p=0.724  Calculated mean difference: -1.71 USD 95% CI, -24.53 to 21.11 p=0.883
Pindolia et al., 2009 <sup>42</sup> Cohort/High	G1: Telephone-based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1,081	Mean out-of-pocket prescription costs per health plan member in USD (assumed per year, as NR in study) (SD)	Calculated mean difference: 77.00 USD; 95% CI, -71.82 to 225.82 p=0.311

Abbreviations: CI = confidence interval; G = group; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SD = standard deviation; USD = United States dollars.

The NRCT compared patients in the MTM arm with controls within and outside the intervention county; the control arms had declines in copayments and the MTM had increases in copayments. The two cohort studies had inconsistent and imprecise estimates of effect; one study showed an increase in copayments for the MTM arm and a decline for the control arm,<sup>42</sup> and the other reported a smaller increase in the MTM arm than in the control arm.<sup>37</sup> None of these studies explained whether the increase in copayment was a result of an appropriate change in medication therapy or the desired effect of the intervention. Although the results were precise in the NRCT and suggested an increase in medication copayments following MTM, the lack of directness in interpreting this outcome as a measure of appropriate resource utilization and the absence of other low and medium risk-of-bias studies with sufficient information to assess consistency of findings suggests insufficient evidence to judge the effect of MTM interventions on patient medication co-payment (Table 49).

**Table 49. Patient copayments: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1, NR (NR)	Medium	Consistency unknown, single study	Indirect	Not reported	Calculated mean difference= -64 USD, variance not calculable	Insufficient
NRCT	1; 1,639 (1,606)	High	Consistency unknown, single study	Indirect	Precise	Calculated mean difference for MTM vs. same country control: 80.40 USD; 95% CI, 10.43 to 150.37 p=0.024  Calculated mean difference for MTM vs. different county control: 88.60 USD; 95% CI, 24.61 to 152.59 p=0.007	Insufficient

Abbreviations: CI = confidence interval; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; USD = United States dollars.

### Medication Costs: Expenditures by Insurers

Three RCTs (all medium risk of bias),<sup>50,55,61</sup> the NRCT reported on above,<sup>49</sup> and six cohort studies (four medium<sup>39-41,45,62,80</sup> and two high risk of bias<sup>76,77,79</sup>) measured the net effect of MTM on expenditures incurred by insurers on medications (Table 50). Changes in health plan drug expenditures attributable to MTM depend on the net effect of MTM activities, which can entail adding clinically needed drugs, increasing doses or frequency, substituting therapeutically equivalent lower cost drugs, and simplifying regimens (singly or in combination). For individual patients, a net increase in expenditures may be the outcome of a more appropriate drug regimen. Included studies provided only the net effect on expenditures at the study arm level. All trials demonstrated that MTM either reduced health plan expenditures or limited the increase in expenditures over time for patients receiving the MTM intervention when compared with patients in the control or comparison arm. These results were not precise, however; confidence intervals included the null effect for all but one trial. Results from the nonrandomized studies came from very disparate studies: the smallest included 120 patients and the largest as many as 200,722 patients. The inherent heterogeneity within and across these studies likely explains the lack of consistency in direction, magnitude, and precision of effects.

**Table 50. Total expenditures on medications by insurers: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Insurers	Results
Jameson et al., 1995 <sup>50</sup> RCT/Medium	G1: Pharmacotherapy consultation G2: Usual care	G1: 27 G2: 29	Change in cost of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	Calculated mean difference: USD -293.00 95% CI: -501.50 to -84.50 p<0.01
Sellers et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient to the Ontario Drug Benefit Program (assumed CAD) at 5 months	Calculated mean difference: -0.19 95% CI: -1.52 to 1.14 p = 0.78  Calculated mean difference over 6 months=-0.19*30*6=-34 CAD
Sellers et al., 2001 <sup>61</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 61 G2: 60	Mean daily medication costs to the Ontario Drug Benefit Program (assumed CAD) at 6 months	Calculated mean difference in CAD (95% CI) = -0.48 (-1.44 to 0.48) P=0.33  Calculated mean difference over 6 months=-0.48*30*6=-86.4
Christensen et al., 2007 <sup>49</sup> NRCT/Medium	G1: Patients receiving pharmacist-provided MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in amount insurer paid for prescriptions over 6 months	Calculated mean difference for G1 vs. G2 in USD: -54.70 95% CI: -287.59 to 178.19 p=0.645  Calculated mean difference for G1 vs. G3: - 7.20 USD; 95% CI: -230.80 to 216.40 p=0.950
Moczygemba et al., 2011 <sup>39</sup> ; Moczygemba et al., 2011 <sup>40</sup> ; Moczygemba et al., 2008 <sup>41</sup>  Cohort/Medium	G1: MTM-eligible patients who opted into a telephone MTM program G2: MTM-eligible patients who did not opt-in to the MTM program.	G1: 60 G2: 60	Mean Part D drug costs (based on prescription claim records, excludes non-Part D drug costs) (SD) at baseline and 12 months	Reported mean difference: - 800 USD 95% CI NR, p=0.03 for t-test, but no significant predictors when sociodemographic, health-related, and use variables were controlled for in the multiple regression analysis
Moore et al., 2013 <sup>45</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Total plan-paid costs for all dispensed medications in pre- and post-periods 1 year before invitation to MTM program and 1 year after	Calculated mean difference in USD (95% CI): 425 (109.79 to 12,054.24) p: < 0.001

**Table 50. Total expenditures on medications by insurers: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Insurers	Results
Perlroth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658 G3: 11,260	Total payments recorded on Part D claims for all prescription medications not used for treatment of condition specific to MTM eligibility (CHF, COPD, or diabetes)	Adjusted costs in USD (95% CI) Congestive heart failure cohort G1 vs. G13: 87.05 (7.33, 166.78), p<0.05 G3 vs. 14: 140.52 (55.79, 225.25), p<0.05
	G1: enrolled in PDP receiving MTM with CMR	G5: 16,372 G7: 10,575 G9: 16,545		
	G3: enrolled in MA-PD, receiving MTM with CMR	G11: 13,527 G13: 156,441 G14: 51,938		Chronic obstructive pulmonary disease cohort G5 vs. 15: 42.55 (-28.12, 113.22), p>0.05 G7 vs. G16: 95.45 (18.88, 172.02), p<0.05
	Chronic obstructive pulmonary disease	G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	
	G5: enrolled in PDP receiving MTM with CMR			Diabetes G9 vs. G17: 109.70 (50.16, 169.25), p<0.05 G11 vs. G18: 173.79 (118.35, 229.22), p<0.05
	G7: enrolled in MA-PD, receiving MTM with CMR			
	Diabetes	G9: enrolled in PDP receiving MTM with CMR		
	G11: enrolled in MA-PD, receiving MTM with CMR			
	Comparison— congestive heart failure	G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care		
	Comparison— Chronic obstructive pulmonary disease	G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care		
Comparison— Diabetes	G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care			

**Table 50. Total expenditures on medications by insurers: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Insurers	Results
Wittayanukorn et al., 2013 <sup>80</sup> Cohort/Medium	G1: Pharmacist provided face-to-face MTM services for 30–60 minutes per encounter, not always including a followup visit G2: Patients who did not receive MTM services	G1: 63 G2: 62	Mean pharmacy expenditures, during the 6 months prior to the initial MTM visit and costs during the 6 months after the initial MTM visit, in USD	Mean between-group cost difference in USD (SD): -31.9 (25.1) p<0.001
Chrischilles et al., 2004 <sup>79</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Mean amount billed per patient for active drugs (based on Medicaid claims) (SD) at baseline and at 9 months	Calculated mean difference: USD -0.95 95% CI: -58.67 to 56.77 p=0.974
Hirsch et al., 2011 <sup>76</sup> Hirsch et al., 2009 <sup>77</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606	Paid claims amount for all prescription medications, ART medications, and non-ART medications (total cost-cost of ART medications)	Mean USD (SE) 2005 G1: 26,797 (703) G2: 22,544 (290) p<0.001  2006 G1: 27,671 (613) G2: 23,190 (315) p<0.001  2007 G1: 29,955 (679) G2: 25,690 (362) p<0.001

<sup>a</sup> Perlroth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: ART = antiretroviral therapy; CAD = Canadian dollars; CI = confidence interval; G = group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; N = number; PCM = pharmaceutical case management; PDP = Medicare Part D Plan; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SMD = standardized mean difference; USD = United States dollars.

We did not pool estimates of effect for the trials or the observational studies because of heterogeneity in outcomes, timing, and setting.

Based on the lack of precision and directness, we rated the evidence from medium risk-of-bias trials as low for benefit to evaluate the effect of MTM on expenditures by insurers; results from cohort and nonrandomized studies do not support a similar judgment, but the discrepancy in the strength of evidence from trials and nonrandomized studies is likely explained by the huge variability within and across observational studies (Table 51).

**Table 51. Health plan expenditures: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 1,085 (965)	Medium	Consistent	Indirect	Imprecise	Mean difference varies from -34 CAD to -293 USD over 6 months	Low for benefit
NRCT and Cohort	5; 125–200,722 (120–200,722)	High	Inconsistent	Indirect	Imprecise	Mean difference varies from -800 USD over 1 year to 425 USD over 2 years	Insufficient

Abbreviations: CAD = Canadian dollars; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; USD = United States dollars.

### Medication Costs: Total Outlays on Medications

Seven RCTs (one low risk of bias,<sup>84,94</sup> five medium risk of bias<sup>51-55,84,91,92,94</sup> and one high risk of bias<sup>73,74</sup>) and seven cohort studies, two medium<sup>38,48</sup> and five high risk of bias,<sup>37,42-44,57</sup> measured the effect of MTM on total outlays on medications. As with other data on resource utilization, we found it challenging to interpret inconsistent results when studies did not specify the expected mechanism of action and predicted direction of effect. An additional challenge relates to the wide variation in data sources and degree of clarity on how investigators calculated outlays. In some studies, the specific measure used includes the combination of expenditures incurred by insurers and patients for prescription medications (Table 52). In other studies, the measure is based on wholesale costs or full retail costs in the absence of insurance, but whether and how the cost is split between the insurer and the patient is unclear, nor is it clear how these wholesale or retail costs relate to actual incurred costs. Calculated differences in Table 52 are rounded to two decimals.

**Table 52. Total outlays on medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual price to the VA for the agent, plus the average cost of filling prescriptions (time period NR) (25th-75th percentile)	Mean cost in USD G1: 1,006 (574–1,285) G2: 1,096 (566–1,456) 95% CI: NR p: NS at 0.05 level, specifics NR  Calculated mean difference per month: $-90/12 = -7.5$ USD
Krska et al., 2001 <sup>91</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Average monthly costs of prescribed medication per patient in British pounds (£) (SD) at 3 months (calculated using information from patients on actual use)	Calculated mean difference: $-\pounds 0.19$ , 95% CI: -6.69 to 6.49 p=0.956.

**Table 52. Total outlays on medications: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Malone et al., 2000 <sup>51</sup> ; Ellis et al., 2000 <sup>52</sup> ; Malone et al., 2001 <sup>54</sup> ; Ellis et al., 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual drug costs in (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	Calculated mean difference: USD 63.00 95% CI: -5.08 to 131.08; p=0.07 Calculated mean difference per month: USD 63/12=USD 5.25
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient at 5 months (assumed CAD)	Calculated mean difference: 0.19 (assumed CAD) 95% CI: -0.85 to 1.23 p=0.72
Sellors et al., 2001 <sup>61</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 61 G2: 60	Mean daily medication costs (assumed CAD) at 6 months	Calculated mean difference: -0.41 CAD (-1.40 to 0.58) p: 0.42
Williams, 2004 <sup>92</sup> RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	Average monthly wholesale price of prescription and nonprescription drugs	Reported mean difference: -20.16 USD 95% CI: -5.78 to -34.54 p: 0.006
Jeong et al., 2009 <sup>38</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program (opted in to MTM program) G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects.	G1: 2,780 G2: 2,251	Full retail cost of medication had the patient not had insurance coverage at 6 months before and 6 months after enrollment in USD	Calculated mean difference in USD (95% CI): -563 (-735.33 to -390.67) p<0.001
Yamada et al., 2012 <sup>48</sup> Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Change in annual prescription costs	Mean change adjusted for age, sex, Charlson, CHF, ESRD: +\$310 (271 to 350) p<0.001  2010 subgroup only (different unspecified criterion for MTM): -\$46 (-\$107 to \$15) p NS adjusted for age, sex, Charlson, CHF, ESRD
Pai, 2009 <sup>73</sup> ; Pai, 2009 <sup>74</sup> RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean drug costs (calculated from average wholesale price) over 2 years	Pharmaceutical care reduced mean drug costs by USD 6.21 compared with the usual care group, p=NS, no absolute costs or other details reported
Fox et al., 2009 <sup>37</sup> Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (refusers)	G1: 247 G2: 50	Mean difference in annual Medicare Part D drug costs (patient copayment + insurance plan medication costs + dispensing fee)	Calculated mean difference: USD -27.78, 95% CI -125.82 to 26.60 p=0.57



**Table 52. Total outlays on medications: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Pindolia et al., 2009 <sup>42</sup> Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1,081	Total annual prescription drug cost per health plan member in USD	Calculated mean difference: -62.22, 95% CI -112.469 to -11.971; p=0.015
Staresinic et al., 2007 <sup>43</sup> Cohort/High	G1: MTP program (acceptors) G2: Usual care (refusers)	G1: 282 G2: 1,544	Total prescription cost per MTM program beneficiary per month (gross drug cost=ingredient cost paid + dispensing fee + sales tax per member-months in Part D contract)	Participants spent less on prescription medications on average (described as per member per month drug spending) than nonparticipants. Figure provided suggested a decrease in spending of between USD 100 and USD 150 in the intervention group, but exact numbers not reported.
Welch et al., 2009 <sup>44</sup> Cohort/High	G1: MTM program provided to home-based beneficiaries G2: Opt-out among home-based patients eligible for MTM	G1: 459 G2: 336	Mean change in medication costs per day at 6 months. (Estimates come from data on study beneficiaries' purchases of ambulatory prescription medications)	Difference in difference: USD 3.62, SD NR, adjusted p=0.203  NOTE: Age, sex, chronic disease score, and preperiod drug cost included in multivariate regression modeling for adjusted P
			Mean percentage increase in medication costs per day at 6 months (no SD reported)	Adjusted OR : 1.4 95% CI: 1.1 to 1.9  NOTE: Model adjusted for age, sex, chronic disease score, and baseline medication cost
Winston et al., 2009 <sup>57</sup> Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed, call-center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Mean (SD) drug cost per patient per month after 8 months of services (based on drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, before subtracting any patient cost-sharing amounts)	Calculated mean difference for G1 vs. G3: USD -35.00, 95% CI -43.390 to -26.610; p<0.001  Calculated mean difference for G2 vs. G3: USD -15.0, 95% CI, -33.411 to 3.411; p=0.11

Abbreviations: CAD = Canadian dollars; CHF = congestive heart failure; CI = confidence interval; ESRD = end-stage renal disease; G = group; MTM = medication therapy management; NR = not reported; NS = not significant; RCT= randomized controlled trial; USD = United States dollars; VAMC = Veterans Affairs Medical Center.

We did not pool the five medium risk-of-bias studies because of the heterogeneity of measures.<sup>51-55,92</sup> Two suggested an increase in outlays in the intervention arm<sup>51-55</sup> (although estimates were imprecise and confidence intervals contained the null effect), two suggested a reduction,<sup>61,92</sup> and one suggested no effect.<sup>91</sup> The medium risk-of-bias cohort studies similarly

demonstrated inconsistent results;<sup>38,48</sup> in fact, the same study demonstrated a difference in outcomes based on the specific criteria for MTM enrolment by year within the program.<sup>48</sup> The high risk-of-bias studies similar reported inconsistent results: some reported reduced outlays<sup>42,43,57</sup> and others showed increased outlays<sup>37,44</sup> or no effect<sup>73,74</sup> following MTM.

Based on the lack of consistency, directness, and precision, we rated the evidence from five medium risk-of-bias trials and two cohort studies as insufficient to evaluate the effect of MTM on total outlays on medications (Table 53).

**Table 53. Total outlays on medications: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	6; 2,804 (2,636)	Medium	Inconsistent	Indirect	Imprecise	Mean difference varies from -20.16 USD to +5.25 USD per month	Insufficient
Cohort	2, 177,565 (177,565)	High	Inconsistent	Indirect	Imprecise	Mean difference varies from -563 USD to +310 USD annually	Insufficient

Abbreviations: RCT=randomized controlled trial; USD= United States dollars.

### Medication Costs: Combined Medication and Other Costs

Three trials (one low,<sup>84,94</sup> one medium,<sup>55</sup> and one high risk of bias<sup>64,65</sup>), one NRCT (medium risk of bias<sup>82</sup>), and three cohort studies (two medium<sup>45,80</sup> and one high risk of bias<sup>76,77</sup>) provided inconsistent evidence of change in combined medication and other costs (variably defined in each study) (Table 54). Studies did not report their results in sufficient detail to allow pooling. Based on available information, we judged the evidence to be insufficient to evaluate the effect of MTM on combined medication and other costs (Table 55).

**Table 54. Medication and other costs: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Medication and Other Costs	Results
Hanlon et al., 1996 <sup>84,94</sup>	G1: Usual care, plus clinical pharmacist care.  G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Total cost = drug outlays + average per diem cost of inpatient care based on annual output and expenditure data for bed sections in the cost distribution report + costs of surgery based on relative value weights, and VA costs per relative value weight + health services valued using 1991 estimates of VAMC unit costs; costs for non-VA hospital care were imputed using logic underlying VA cost methodology (time period NR) (25th-75th percentile)	Mean cost in USD G1: 7,873 (1,622–6,649) G2: 5,926 (1,608–7,036) 95% CI: NR p: NS at 0.05 level, specifics NR
RCT/Low				

**Table 54. Medication and other costs: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Medication and other costs	Results
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379	Mean cost of health care resources per patient, including all hospital stays at 5 months (CAD assumed)	Calculated mean difference: 249.41 (assumed CAD), 95% CI: -338.39 to 837.21; p=0.406
		G2: 409		Calculated mean difference: -8.10 (assumed CAD), 95% CI: -386.72 to 4,350.52; p=0.923
Bernsten et al., 2001 <sup>64,65</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs	Cost data not pooled and analyzed for costs because health care systems differed between 7 countries included in the study. However, authors reported no significant between-group differences in any country (p=NS)
		G1: 867 G2: 748		
		6 months G1: NR G2: NR		
		12 months G1: NR G2: NR		
		18 months G1: NR G2: NR		
Fischer et al., 2002 <sup>82</sup> NRCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Change in total charges for inpatient care, outpatient care, and pharmacy charges	G1: -900 G2: -2,000 95% CI: NR P: NS, no details reported Calculated mean difference: USD 1,100.
Moore et al., 2013 <sup>45</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2250 G2: 2250	Total plan-paid costs for all dispensed medications + total plan-paid costs for all covered medical services 1 year before invitation to MTM program and 1 year after	Calculated mean difference in USD (95% CI): -1,039 (-2,084.85 to 6.849) p=0.052
Wittayanukorn et al., 2013 <sup>80</sup> Cohort/Medium	G1: Pharmacist provided face-to-face MTM services for 30-60 minutes per encounter, not always including a followup visit G2: Patients who did not receive MTM services	G1: 63 G2: 62	Mean total expenditures (pharmacy+medical), during the 6 months prior to the initial MTM visit and costs during the 6 months after the initial MTM visit, in USD	Mean between-group cost difference in USD (SD): -359.3 (219.2) p<0.001

**Table 54. Medication and other costs: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Medication and other costs	Results
Hirsch et al., 2011 <sup>76</sup> Hirsch et al., 2009 <sup>77</sup> Cohort/High	G1: Patients served at pilot pharmacies	2005 G1: 439	Paid claims amounts for inpatient, hospital outpatient (includes emergency department), outpatient, mental health, laboratory/X-ray, and AIDS Waiver Programc	Mean USD (SE) 2005 G1: 35,546 (1,093) G2: 33,501 (505) p=0.079  2006 G1: 36,806 (980) G2: 35,230 (575) p= 0.157  2007 G1: 38,983 (1,023) G2: 38,856 (633) p= 0.915
	G2: Patients served at nonpilot pharmacies	2006 G1: 617 G2: 1,617		
		2007 G1: 628 G2: 1,606		

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; GP = general practitioner; MTM = medication therapy management; NR = not reported; NS = not significant; RCT = randomized controlled trial; SE = standard error; USD = United States dollars.

**Table 55. Medication and other costs: Strength of evidence**

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1097, N (996)	Medium	Inconsistent	Indirect	Imprecise	Differences in mean costs ranging from -8.1 CAD to 1,947 USD	Insufficient
NRCT and Cohort	3; 5,300 (5,300)	High	Inconsistent	Indirect	Imprecise	Differences in mean costs ranging from to -1,039 to 1,100 USD	Insufficient

Abbreviations: CAD = Canadian dollars; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; USD = United States dollars.

## Number of Outpatient Visits

Eleven studies examined the effect of MTM interventions, when compared with usual care, on outpatient visits. These studies varied in geographic setting (seven Western European countries,<sup>64,65</sup> the United States,<sup>45,51-54,56,69-71,79,82,84,94</sup> the United Kingdom,<sup>91</sup> Canada<sup>55</sup>), period of evaluation (3 months to 36 months), specific outcome measure (ranging from a focus on visits with physicians to total ambulatory care visits or contacts with physicians and nurses), and risk of bias. They are described in Table 56. No study indicated whether the intervention was specifically designed to increase or to decrease outpatient visits; as a result, the directionality of the results cannot be interpreted as a benefit or a harm.

**Table 56. Number of outpatient visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Mean general medicine clinic visits (time period NR) (25th–75th percentile)	G1: 5.5 (3–6) G2: 5.8 (3–7) 95% CI: NR p: NS at 0.05 level, specifics NR
			Mean other clinic visits (time period NR) (25th–75th percentile)	G1: 7.7 (3–10) G2: 10.9 (2–15) 95% CI: NR p: NS at 0.05 level, specifics NR
Krska et al., 2001 <sup>91</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: NR G2: NR	Hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist review	No differences; details NR
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> ; Malone, 2001 <sup>54</sup> ; Ellis, 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of clinic visits (including visits with the pharmacists in the intervention arm) over 12 months	Calculated mean difference: 2.0, 95% CI: -0.415 to 4.415, p= 0.104
Sellers et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Number of clinic visits over 5 months	Calculated mean difference: -0.02, 95% CI: -1.274 to 1.234, p=0.975
Sidel, 1990 <sup>56</sup> RCT/Medium	G1: Patients received at least 2 pharmacist visits involving medication review, patient-specific education and counseling; followup patient telephone calls and contact of physicians as needed G2: Patients contacted only to complete the survey.	G1: 92 G2: 104	Change in number of ambulatory visits over past 3 months, measured at baseline and again at 36 months	Calculated mean difference: -1.41, 95% CI: -2.98 to 0.160, p=0.078
Touchette et al., 2012 <sup>69</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	3-6 months	G1 vs. G3 Calculated mean difference: 0.50, 95% CI: -0.388 to 0.488, p=0.823
			G1: 183 G2: 190 G3: 183	G2 vs. G3 Calculated mean difference: -0.50, 95% CI: -0.383 to 0.483, p=0.821
Bernsten et al., 2001 <sup>64,65</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	G1: 1,024 G2: 953	Mean number of contacts with primary care providers, including home visits and office appointments at 6 months	Calculated mean difference: 0.120 95% CI: -0.461 to 0.701, p=0.686

**Table 56. Number of outpatient visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Moore et al., 2013 <sup>45</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of physician visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Calculated mean difference (95% CI): 2.48 (1.674 to 3.286, p<0.001)
Fischer et al., 2002 <sup>82</sup> NRCT/High	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Changes in number of clinic visits over 1 year	Intention-to-treat analysis Adjusted between-group difference not significant, details NR
Carter et al., 1997 <sup>70,71</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Number of distinct dates of service over 6 months	G1: 2.2 (2.4) G2: 1.0 (1.0) 95% CI: NR, p=0.07
Chrischilles et al., 2004 <sup>79</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Number of outpatient facility claims at 12 months	Results NR, p=0.121

Abbreviations: CI = confidence interval; DRP, drug-related problems; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; PCM = pharmaceutical care management; RCT = randomized controlled trial.

Three RCTs (all low or medium risk of bias) provided sufficient data on outpatient visits within the first year to pool results.<sup>51-55,69</sup> A meta-analysis of these studies, including results for the basic MTM arm for Touchette et al. (rather than the “enhanced MTM” arm),<sup>69</sup> across outcomes from 5 to 12 months yielded an estimated standardized mean difference of 0.049 (95% CI, -0.034 to 0.133, p=0.247; I<sup>2</sup>=0) (Appendix F-9). Including the results of the “enhanced MTM” arm instead of the basic MTM arm did not change the direction or precision or results (standardized mean difference: 0.041; 95% CI -0.042 to 0.125, p=0.331, I<sup>2</sup>=0). Likewise, adding one trial with high risk of bias (stemming primarily from attrition bias<sup>64,65</sup>) to the meta-analysis did not alter the direction or precision of the estimate of effect (standardized difference in means: 0.032; 95% CI, -0.032 to 0.095, p=0.326, I<sup>2</sup>=0). Two studies (one low and one medium risk of bias) found fewer outpatient visits in the intervention arm, but confidence intervals spanned the null<sup>56</sup> or the authors reported that the results were not statistically significant at the p=0.05 level.<sup>84,94</sup> A seventh medium risk-of-bias RCT noted “no differences in hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist review” but did not indicate whether this observation extended to the control arm and offered no statistics.<sup>91</sup> The single nonrandomized controlled study found no differences between study arms in an intention-to-treat analysis.<sup>82</sup>

One medium risk-of-bias cohort study reported a greater increase in physician visits in the intervention arm compared with the control arm.<sup>45</sup> Two high risk-of-bias cohort studies,<sup>70,71,79</sup> reported no statistically significant differences between study arms in the number of outpatient facility claims but offered no additional information.

Based on the lack of consistency, we graded the body of evidence of medium risk-of-bias trials and cohort study as insufficient to evaluate the effect of MTM interventions on outpatient resource utilization (Table 57).

**Table 57. Number of outpatient visits: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,362 (2,208)	Medium	Inconsistent	Indirect	Precise	Standardized mean difference: 0.049; 95% CI, -0.034 to 0.133, p=0.247; I <sup>2</sup> =0	Insufficient
Cohort	1; 2250 (2250)	High	Consistency unknown-single study	Indirect	Imprecise	Calculated mean difference (95% CI): 2.48 (1.674 to 3.286, p<0.001	Insufficient

Abbreviations: CI = confidence interval; RCT= randomized controlled trial.

## Cost of Outpatient Visits

Five studies examined the effect of MTM interventions, when compared with usual care, on the costs of outpatient visits (Table 58). These studies included four set in the United States<sup>51-54,70,71,76,77,79</sup> and one set in Canada.<sup>55</sup> The period of evaluation ranged from 5 months to 3 years.

As with studies on the number of outpatient visits, no study indicated that the intervention was designed specifically to raise or lower the costs of outpatient visits; as a result, the directionality of the results cannot be interpreted as a benefit or a harm. As with other costs analyses, the data are in U.S. dollars unless otherwise specified and rounded to nearest two decimals.

**Table 58. Costs of outpatient visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Annual health care costs in USD for general medicine clinic care at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients(time period NR) (25th–75th percentile)	G1: 334 USD (200–366) G2: 356 USD (183–427) 95% CI: NR p: NS at 0.05 level, specifics NR Monthly cost: -22/12= - 1.83 USD
	G2: Usual care in the General Medicine Clinic		Annual health care costs for other clinic care in USD at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients(time period NR) (25th–75th percentile)	G1: 422 (67–500) G2: 565 (23–923) 95% CI: NR p: NS at 0.05 level, specifics NR Monthly cost: -143/12= - 11.92 USD
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> ; Malone, 2001 <sup>54</sup> ; Ellis, 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual cost of clinic visits	Calculated mean difference: USD -102.00 95% CI: -187.81 to -16.20 p=0.02 Monthly cost difference: - 102/12= - 8.50 USD

**Table 58. Costs of outpatient visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of physician visits (assumed CAD) at 5 months	Calculated mean difference: 5.66, 95% CI: -24.22 to 35.54, p=0.71
				Monthly cost difference: 5.66/5= 1.132 CAD
				Mean cost of clinic visits (assumed CAD) at 5 months
				Calculated mean difference: -2.13, 95% CI: -20.46 to 16.20, p=0.82
				Monthly cost difference: -2.13/5= -0.43 CAD
			Mean cost of other health care services and visits to health care professionals (assumed CAD) at 5 months	Calculated mean difference: -4.70 95% CI: -140.22 to 130.82; p=0.95
				Monthly cost difference: -4.70/5= -0.94 CAD
Carter et al., 1997 <sup>70,71</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Hypertension-related charges (SD) at 6 months	Calculated mean difference: USD 70.00, 95% CI: 15.97 to 124.03, p=0.011
				Monthly cost difference: 70/6= 11.67 USD
				Mean visit charges at 6 months
				Calculated mean difference: USD 487.00, 95% CI: 44.87 to 929.14, p=0.031
				Monthly cost difference: 487/6= 81.17 USD
Chrischilles et al., 2004 <sup>79</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Outpatient facility claims at 12 months	Results NR, p=0.107
Hirsch et al., 2011 <sup>76</sup> Hirsch et al., 2009 <sup>77</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005	Outpatient costs (not defined)	Mean USD (SE)
		G1: 439		
		G2: 1,795		
		2006		
		G1: 617		
		G2: 1,617		
		2007		
		G1: 628		
		G2: 1,606		
				2005 G1: 112 (11) G2: 44 (2) p<0.001
				2006 G1: 82 (7) G2: 43 (2) p<0.001
				2007 G1: 83 (7) G2: 40 (2) p<0.001

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; NR = not reported; PCM = pharmaceutical care management; RCT = randomized controlled trial; SD = standard deviation; USD = United States dollars.



One low risk-of-bias and two medium risk-of-bias trials offered inconsistent evidence on the effect of MTM interventions on outpatient costs. Two U.S.-based VA studies<sup>51-54,84,94</sup> found results favoring the intervention group, but the results were not statistically significant in one study.<sup>84,94</sup> The Canadian study found no significant differences by study arm.<sup>55</sup> Two cohort studies (high risk of bias) found significantly higher costs for the intervention arm than the usual care arm.<sup>70,71,76,77</sup> Another U.S.-based cohort study of the Medicaid program in Iowa (high risk of bias) found no statistically significant differences in cost of outpatient visits by intervention arm but did not report details to determine direction of effect.<sup>79</sup>

Based on the lack of consistency and precision, we graded the body of evidence from the two trials as being insufficient to evaluate the effect of MTM interventions on the costs of outpatient visits (Table 59).

**Table 59. Costs of outpatient resource utilization: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,151 (2,050)	Medium	Inconsistent	Indirect	Imprecise	Variable estimates <sup>a</sup>	Insufficient

<sup>a</sup> Dissimilar time periods and measures, ranges are not meaningful.

Abbreviation: CAD = , Canadian dollar; RCT= randomized controlled trial; USD = , U.S. dollars.

## Number of Laboratory and Diagnostic Tests

Understanding whether a change in the number and costs of laboratory tests as a result of an MTM intervention measures appropriate resource use requires knowledge of the goals of drug therapy. MTM could raise numbers and costs of laboratory and diagnostic tests by identifying patients who should be receiving more frequent laboratory monitoring or by starting patients on new drugs that require laboratory monitoring based on their clinical situation. However, MTM could also lower numbers and costs of laboratory and diagnostic tests if it produces better coordination of care and prevents duplicative testing. Included studies did not specify the expected direction of effect from MTM on the number and costs of laboratory and diagnostic tests.

Two trials (both medium risk of bias; one set in the United States<sup>51-54</sup> the other in Canada<sup>55</sup>) reported on the number of laboratory tests following MTM interventions (Table 60). The Canadian study included the number and costs of imaging procedures over a 5-month period;<sup>55</sup> the U.S.-based study did not specify the inclusion of imaging procedures and evaluated tests and costs over a 12-month period. The U.S.-based found statistically significant differences; the Canadian study failed to find any significant differences.

**Table 60. Number of laboratory and diagnostic tests: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> (interventions); Malone, 2001 <sup>54</sup> (detailed QOL outcomes); Ellis, 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual number of laboratory tests	Calculated mean difference: -1.6, 95% CI: -2.550 to -0.650, p=0.001
Sellers et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of laboratory tests and imaging procedures at 5 months	Calculated mean difference: 0.15, 95% CI: -0.959 to 1.259, p=0.791

Abbreviations: CI = confidence interval; G =group; N = number; QOL = quality of life; RCT= randomized controlled trial.

The small number of studies limits our ability to explore causes for the observed heterogeneity. Factors such as differences in health systems, period of evaluation, and definition of the outcome could explain differences in results. Based on lack of consistency, we graded the body of evidence from these two medium risk-of-bias trials as insufficient to evaluate either the effect of MTM interventions on the number of laboratory and diagnostic and diagnostic tests (Table 61).

**Table 61. Number of laboratory and diagnostic tests: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1,943 (1,842)	Medium	Inconsistent	Indirect	Imprecise	Differences range from +0.15 to -1.6 tests	Insufficient

Abbreviations: RCT = randomized controlled trial.

## Costs of Laboratory and Diagnostic Tests

The two medium risk-of-bias studies reporting data on number of laboratory and diagnostic tests also provided information on costs.<sup>51-55</sup> Two other studies, one low risk of bias<sup>84,94</sup> and one high risk of bias,<sup>76,77</sup> provided information on costs. The challenges associated with interpreting evidence on number of laboratory and diagnostic tests apply to costs as well (Table 62). The three U.S.-based studies showed a trend of reduced costs of laboratory and diagnostic tests in the intervention arm, but these results were not consistent in magnitude of effect or precision.<sup>51-54,76,77,84,94</sup> The Canadian study showed an increase in laboratory and imaging costs in the intervention arm.<sup>55</sup>

**Table 62. Costs of laboratory tests: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for diagnostic tests at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients, (25th–75th percentile)	G1: 214 (52–318) G2: 354 (55–473) 95% CI: NR p: NS at 0.05 level, specifics NR
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> ; Malone, 2001; <sup>54</sup> Ellis, 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual costs for laboratory tests	Calculated mean difference: USD -33.00 95% CI: -65.96 to -0.04, p=0.05
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all lab and imaging procedures at 5 months (assumed CAD)	Calculated mean difference: 6.24 (assumed CAD) over 5 months, 14.98 over 12 months 95% CI: -46.34 to 58.88 p=0.816
Hirsch et al., 2011 <sup>76</sup> Hirsch et al., 2009 <sup>77</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606	Costs of laboratory/x-ray services	Mean USD (SE) 2005 G1: 389 (34) G2: 402 (17) p=0.736  2006 G1: 387 (28) G2: 407 (18) p=0.530  2007 G1: 401 (29) G2: 402 (18) p=0.974

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; N = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; SE = standard error; USD = United States dollars.

Based on lack of consistency, we graded the body of evidence from these three medium risk-of-bias trials as insufficient to evaluate either the effect of MTM interventions on the costs of laboratory tests (Table 63).

**Table 63. Costs of laboratory tests: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2051 (2,050)	Medium	Inconsistent	Indirect	Imprecise	Differences range from +15 CAD to -140 USD	Insufficient

Abbreviations: CAD= Canadian dollars; RCT = randomized controlled trial; USD = United States dollars.

## Emergency Department Visits

Nine studies reported changes in emergency department (ED) visits following MTM interventions: four trials (one low risk of bias,<sup>84,94</sup> two medium risk of bias,<sup>55,69</sup> and one high risk

of bias<sup>85</sup>) and five cohort studies (four medium risk of bias<sup>44,45,62,80</sup> and one high risk of bias<sup>46,47</sup>) (Table 64). We excluded data from one study in the analysis below because it reported total number of events by each intervention arm rather than by patients within intervention arm.<sup>80</sup> We could not pool results from the eight studies with complete data because we did not have sufficient numbers of studies with similar designs. Across all low and medium risk-of-bias studies, the confidence intervals for the effects from the medium risk-of-bias studies spanned the null effect for the entire study<sup>44,55,84,94</sup> or a subset of analyses.<sup>62,69</sup> Studies with multiple comparisons found some signals of benefit. For example, the low risk-of-bias trial found a lower mean number of ED visits in the intervention arm when compared with the usual care, but this effect was statistically significant only for the basic MTM arm.<sup>69</sup> Likewise, a medium risk-of-bias cohort study of 2010 Medicare Part D found consistently lower odds of all-cause ED visits across all clinical conditions but did not find the same consistency of direction, magnitude, or precision for condition-specific ED visits.<sup>62</sup> One trial, rated high risk of bias for this outcome, reported a decline in ED visits in the intervention arm and no change in the control arm;<sup>85</sup> it did not, however, provide patient-level means. As a result, we are unable to judge the variance within the sample. Another high risk-of-bias cohort study found lower odds of ED visits among patients accepting MTM when compared with patients refusing or disenrolling from MTM, but the study did not account for confounders that may have influenced MTM participation and outcomes.<sup>46,47</sup>

**Table 64. Emergency department visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Mean emergency room visits (time period NR) (25th-75th percentile)	G1: 1.6 (0–2) G2: 2.3 (0–3) 95% CI: NR p: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of ED or urgent care visits and ambulance use at 5 months	Calculated mean difference: -0.03 95% CI: -0.113 to 0.053 p=0.48
Touchette et al., 2012 <sup>69</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	Mean number of ED visits per participant between 3–6 months after intervention	G1 vs. G3 calculated mean difference: -0.138 95% CI: -0.258 to -0.018 p=0.025  G2 vs. G3 calculated mean difference: -0.118, 95% CI: -0.242 to 0.006 p=0.062
Taylor et al., 2003 <sup>85</sup> RCT/High	G1: Pharmaceutical care group G2: Standard care	G1: 33 G2: 36	Change in number of ED visits from 12 months before baseline through 12 months after	G1: -12 G2: 0 p=0.044
Moore et al., 2013 <sup>45</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of ED visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Calculated mean difference (95% CI): 0.04 (-0.043 to 0.123, p=0.346)

**Table 64. Emergency department visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Perloth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658	Odds of any all-cause emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators) (95% CI)	For PDP	
	G1: enrolled in PDP receiving MTM with CMR	G3: 11,260		Congestive heart failure	
	G5: 16,372	G7: 10,575		G1 vs. G13: 0.94 (0.90, 0.98), p<0.05	
	G3: enrolled in MA-PD, receiving MTM with CMR	G9: 16,545		Chronic obstructive pulmonary disease	
	G11: 13,527	G13: 156,441		G5 vs. G15: 0.89 (0.86, 0.93), p<0.05	
	G14: 51,938	G15: 184,350		Diabetes	
	G16: 73,623	G17: 133,925		G9 vs. G17: 0.96 (0.92, 1.00), p>0.05	
	G18: 53,912				
	G7: enrolled in MA-PD, receiving MTM with CMR			Odds of condition-specific emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators) (95% CI)	For PDP
	Diabetes				Congestive heart failure
G9: enrolled in PDP receiving MTM with CMR			G1 vs. G13: 1.01 (0.95, 1.07), p>0.05		
G11: enrolled in MA-PD, receiving MTM with CMR			Chronic obstructive pulmonary disease		
Comparison—congestive heart failure			G5 vs. G15: 1.09 (1.04, 1.15), p<0.05		
G13: enrolled in PDP, usual care			Diabetes		
G14: enrolled in MA-PD, usual care			G9 vs. G17: 1.00 (0.96, 1.05), p>0.05		
Comparison—Chronic obstructive pulmonary disease					
G15: enrolled in PDP, usual care					
G16: enrolled in MA-PD, usual care					
Comparison—Diabetes					
G17: enrolled in PDP, usual care					
G18: enrolled in MA-PD, usual care					
Welch et al., 2009 <sup>44</sup> Cohort/medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of ED visit from 6 month before MTM through 6 months after MTM (adjusted for age, sex, chronic disease score, specific baseline utilization)	Reported adjusted OR: 0.9 95% CI: 0.6 to 1.3, p NR	

**Table 64. Emergency department visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong, <sup>46</sup> ; Jeong, 2012 <sup>47</sup> Cohort/High	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	G1: 23,638 G2: 14,232 G3: 1,810	Percentage with ED visits within 12 months of CMR	Calculated OR G1 vs. G2: 0.867 (0.832–0.904, p<0.001); calculated OR for G1 vs. G3: 0.845 (0.768–0.930, p=0.001)

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; CMR = comprehensive medication review; DRP = drug related problems; ED = emergency department; G = group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; OR = odds ratio; PCP = primary care physician; RCT = randomized controlled trial.

Given the lack of consistency and precision, evidence is insufficient to draw conclusions about the effectiveness of MTM in reducing ED visits (Table 65).

**Table 65. Emergency department visits: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 1,734 (1,552)	Medium	Inconsistent	Direct	Imprecise	Mean difference ranges from -0.7 (p not significant) to -0.03 to -0.138 (95% CI -0.113 to 0.053)	Insufficient
Observational	3; Ranges from 904–200,722 (795–200,722)	High	Inconsistent	Direct	Imprecise	Adjusted OR ranges from 0.89 to 1.09; mean difference (1 study): 0.04 (95% CI: -0.043 to 0.123, p=0.346)	Insufficient

Abbreviations: OR = odds ratio; RCT= randomized controlled trial.

## Emergency Department Costs

Two trials (one low risk of bias<sup>84,94</sup> and one medium risk of bias<sup>55</sup>) and two cohort studies (one medium risk of bias<sup>62</sup> and one high risk of bias<sup>79</sup>) reported on costs of ED visits following MTM interventions (Table 66). Despite differences in geographic setting and health care delivery systems (Canada<sup>55</sup> and the United States<sup>62,79,84,94</sup>), period of evaluation (5 months,<sup>55</sup> and 12 months<sup>62,79</sup>), and risk of bias, no study demonstrated an effect of any MTM-type intervention (Table 66).<sup>55,62,79,84,94</sup> Variations within the large cohort study and across studies suggest that MTM may be associated with additional costs or costs saving. Because the evidence does not

offer consistency or precision of results, we graded it as insufficient to evaluate the effect of MTM on ED costs (Table 67).

**Table 66. Costs of emergency department visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for emergency room visits (25th-75th percentile) in USD (95% CI)	G1: 119 (0–146) G2: 171 (0–219) 95% CI: NR p = NS at 0.05 level, specifics NR
Sellers et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of ED or urgent care visits and ambulance use at 5 months in \$ (assumed CAD) (SE)	Calculated mean difference: -\$5.60 (assumed CAD) 95% CI: -\$23.06 to \$11.86 p=0.53
Chrischilles et al., 2004 <sup>79</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges for ED claims at 12 months	Results NR p=0.513
Perlroth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR  Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR  Comparison—congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care  Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care  Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	Change in costs of any all-cause emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) in USD (95% CI)  Change in costs of condition-specific emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	For PDP Congestive heart failure G1 vs. G13: -12.66 (-33.61, 8.30), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: -16.21 (-35.37, 2.96), p>0.05  Diabetes G9 vs. G17: -8.76 (-23.65, 6.12), p>0.05 For PDP Congestive heart failure G1 vs. G13: -3.17 (-14.59, 8.25), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 12.81 USD (-.14, 25.76), p>0.05 Diabetes G9 vs. G17: -3.27 (-15.37, 8.84), p>0.05

<sup>a</sup> Perlroth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CAD = Canadian dollars, CI = confidence interval; CMR = comprehensive medication review; ED = Emergency department; G = group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; PCM = pharmaceutical care management; PDP = Medicare Part D Plan; SE = standard error; USD = United States dollars.

**Table 67. Cost of emergency department visits: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1097 (996)	Medium	Consistent	Direct	Imprecise	Mean difference ranges from -52 USD to -5.6 CAD	Insufficient
Cohort	1: 150,470–200,722 (150,470–200,722)	High	Consistency unknown-single study	Direct	Imprecise	Difference ranges from -16 USD to +12.8 USD	Insufficient

Abbreviations: CAD = Canadian dollars; RCT = randomized controlled trial; USD = United States dollars.

## Hospitalizations

Twelve studies measured hospitalizations as an outcome following MTM interventions.<sup>44,47,48,51–55,62,64,65,69,73,74,78,80,84,91,94</sup> Of these, we have excluded data from two studies in the analysis below because they reported total number of events by each intervention arm rather than by patients within intervention arm. As a result, we are unable to assess variance.<sup>80,91</sup> We report on the mean number of hospitalizations, the risk of hospitalization, and the rates of hospitalization (Table 68).

**Table 68. Hospitalizations: Mean number, risk and rates**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Mean hospital admission (time period NR) (25th–75th percentile)	G1: 0.7 (0–1) G2: 0.8 (0–1) 95% CI: NR p= NS at 0.05 level, specifics NR
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> (interventions); Malone, 2001 <sup>54</sup> (detailed QOL outcomes); Ellis, 2000 <sup>53</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of hospitalizations	Calculated mean difference: 0.06, 95% CI: -0.051 to 0.171, p=0.29
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of all-cause hospitalizations  Mean drug-(medications) related hospitalizations	Calculated mean difference: 0.03 95% CI: -0.085 to 0.025, p=0.289  Calculated mean difference: 0 95% CI: -0.28 to 0.28 p=1.0



**Table 68. Hospitalizations: Mean number, risk and rates (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>69</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment)	Time One G1: 180 G2: 190 G3: 193	Percentage of participants with at least one hospital visit at 3 to 6 months	G1 vs. G3: Calculated OR: 2.069, 95% CI: 1.104 to 3.878 p=0.02
	G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care	Time Two G1: 183 G2: 190 G3: 183		G2 vs. G3: Calculated OR: 1.345, 95% CI: 0.693 to 2.609 p=0.381
			Mean number of hospital visits per participant	G1 vs. G3: Calculated mean difference: 0.039, 95% CI: -0.047 to 0.125, p=0.37  G2 vs. G3: Calculated mean difference: 0.045, 95% CI: -0.037 to 0.127, p=0.28
Bernsten et al., 2001 <sup>64,65</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748	Percentage with ≥1 hospitalization in the prior 18 months	Pooled sample Baseline (during 18 months before study) Overall: NR G1: 41.7 G2: 41.3 p=NS 18 months Overall: NR G1: 35.6 G2: 40.4 p=NS, cannot be calculated without N
		6 months G1: NR G2: NR		
		12 months G1: NR G2: NR		
		18 months G1: NR G2: NR		
Pai, 2009 <sup>73</sup> ; Pai, 2009 <sup>74</sup> RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean number of all-cause hospitalizations over 2 years	G1: 1.8 (2.4) G2: 3.1 (3) 95% CI: NR, cannot be calculated without N p: 0.02
			Cumulative hospitalized time in days (SD)	Cumulative hospital time G1: 9.7 days (14.7) G2: 15.5 days (16.3) 95% CI: NR, cannot be calculated without N p=0.06
Moore et al., 2013 <sup>45</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of inpatient visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Calculated mean difference (95% CI): -0.21(-0.265 to -0.155, p<0.001

**Table 68. Hospitalizations: Mean number, risk and rates (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Perlroth et al., 2013 <sup>62a</sup>  Cohort/Medium	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350	Odds of any all-cause hospitalization within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	Congestive heart failure G1 vs. G13: 0.90 (0.86, 0.94), p<0.05 G3 vs. G14: 0.96 (0.91, 1.02), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 0.90 (0.87, 0.94), p<0.05 G7 vs. G16: 0.96 (0.91, 1.01), p>0.05  Diabetes G9 vs. G17: 0.91 (0.87, 0.95), p<0.05 G11 vs. G18: 0.93 (0.88, 0.98), p<0.05	
	Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR	G16: 73,623 G17: 133,925 G18: 53,912			
	Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR			Odds of any CHF/COPD/diabetes-related hospitalization within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	Congestive heart failure G1 vs. G13: 0.95 (0.90, 1.0), p<0.05 G3 vs. G14: 1.03, (0.97, 1.09), p>0.05 Chronic obstructive pulmonary disease G5 vs. G15: 1.04 (0.99, 1.08), p>0.05 G7 vs. G16: 0.91 (0.86, 0.97), p<0.05  Diabetes G9 vs. G17: 0.91 (0.87, 0.96), p<0.05 G11 vs. G18: 0.92 (0.87, 0.97), p<0.05
	Comparison—congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care				
	Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care				
	Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care				
Yamada et al., 2012 <sup>48</sup>  Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Odds of hospital admission between 1 to 4 years depending on when patient was enrolled	0.91 (0.88 to 0.93) p< 0.001  Note: adjusted for age, sex, Charlson, CHF, and ESRD (95% CI)	

**Table 68. Hospitalizations: Mean number, risk and rates (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong, <sup>46</sup> ; Jeong, 2012 <sup>47</sup> Cohort/High	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	G1: 23,638 G2: 14,232 G3: 1,810	Percentage hospitalized within 12 months of CMR	Calculated OR G1 vs. G2: 0.794 (0.760–0.830); calculated OR for G1 vs. G3: 0.606 (0.550–0.668)
Roughead, 2009 <sup>78</sup> Cohort/Medium	G1: Collaborative home-based medication review G2: No medication review received	G1: 273 G2: 5,444	Rate of hospitalization for heart failure at any time during study	Adjusted HR (95% CI): 0.55, : 0.39 to 0.77 p: NR  NOTE: Model adjusted for age, sex, comorbidity, SES, season, region of residence, and numbers of prescriptions, prescribers, pharmacies, changes in medications, hospitalizations, occupational therapy visits, and speech therapy visits
Welch et al., 2009 <sup>44</sup> Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of hospitalization from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization)	Reported adjusted OR: 1.4 95% CI: 1.1 to 2.0; p values NR  NOTE: Model adjusted for age, sex, chronic disease score, specific baseline utilization

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CHF = congestive heart failure; CI = confidence interval; CMR = comprehensive medication review; DCG = diagnostic cost group (a measure of health care use and comorbidity); DRP = drug-related problems; ESRD = end-stage renal disease; G = group; HR = hazard ratio; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management, N = number; NR = not reported; NS = not significant; OR = odds ratio; PCP = primary care physician; PDP = Medicare Part D Plan; QOL = quality of life; RCT = randomized controlled trials; RR = relative risk; SES = socioeconomic status.

Five trials (one low risk-of-bias study,<sup>84,94</sup> three medium risk-of-bias study,<sup>51-55,69</sup> and one high risk-of-bias study<sup>74</sup>) and one medium risk-of-bias cohort study<sup>45</sup> reported on the change in number of hospitalizations or mean number of hospitalizations following MTM interventions (Table 68). The low risk-of-bias study did not provide sufficient information on variance to allow pooling.<sup>84,94</sup> Using a random-effects model, we pooled results for three medium risk-of-bias trials<sup>51-55,69</sup> for all-cause hospitalizations and obtained a mean difference of 0.037, 95% CI, -0.006 to 0.080; p=0.094; I<sup>2</sup>=0 (Appendix F-10). We obtained similarly small effect sizes and

wide confidence intervals spanning the null when including the enhanced arm of the Touchette et al. study (0.038, 95% CI -0.004 to 0.081;  $p=0.076$ ;  $I^2=0$ )<sup>69</sup> or including the single high risk-of-bias trial (0.033, 95% CI -0.046 to 0.112;  $p=0.412$ ;  $I^2=54.484$ ).<sup>74</sup> One study also provided data to calculate an effect size and confidence intervals for drug-related hospitalizations that also overlapped the null effect.<sup>55</sup> These results are consistent with the findings of the low risk-of-bias study, which reported no statistically significant differences in number of hospitalizations. The medium risk-of-bias cohort study was not consistent with the trial evidence: it found significantly lower inpatient visits among MTM acceptors compared with MTM refusers.<sup>45</sup>

Six studies (one medium-risk-of-bias RCT,<sup>69</sup> three medium risk-of-bias cohort studies,<sup>44,48,62</sup> one high risk-of-bias RCT,<sup>64,65</sup> and one high risk-of-bias cohort study<sup>46,47</sup>) reported on the percentage hospitalized following MTM (Table 68) and odds or hazard ratios of hospitalization. Not all studies provided sufficient data to allow the generation of a summary estimate of effect with confidence intervals, nor we did find sufficient numbers of studies of similar design to permit pooling. The results are inconsistent; two studies (one low risk-of-bias trial and one medium risk-of-bias cohort) suggested higher hospitalizations with MTM rather than usual care,<sup>44,69</sup> and three studies (one medium risk-of-bias cohort study,<sup>48</sup> one high risk-of-bias trial,<sup>64,65</sup> and one high risk-of-bias cohort study)<sup>46,47</sup> suggested lower hospitalizations for the MTM arm (but with confidence intervals overlapping the null in one instance).<sup>64,65</sup> The sixth study, a large medium risk-of-bias study of Medicare Part D in 2010, conducted separate analyses for cohorts by plan type (standalone Prescription Drug Plan or Medicare Advantage Prescription Drug Plan) and clinical condition (congestive heart failure, chronic obstructive pulmonary disease, and diabetes) for the odds of all-cause hospitalization and condition-specific hospitalization.<sup>62</sup> The diabetes cohort had lower risks of hospitalization (all-cause or condition-specific) regardless of plan type. For the other cohorts in this study, the magnitude, direction, and precision of the effect varied by specific analysis. The inconsistency in results may be a consequence of the wide range of included populations and interventions.

One cohort study (medium risk of bias) reported a decreased rate of hospitalization for heart failure at any time during study. This study of home medications review was designed specifically to delay the next hospitalization among patients with heart failure in Australia.<sup>78</sup>

Based on inconsistent results from trials with medium study limitations, we rated MTM as having insufficient on the mean number of hospitalizations. One cohort study offers low strength of evidence of reduced number of inpatient visits (Table 69). The lack of consistency between the trial and cohort results and the higher risk of bias from cohort studies of acceptors and refusers suggest that the overall strength of evidence from all designs is insufficient for lack of consistency. We rated the evidence on the risk of hospitalization as insufficient based on inconsistent (or unknown consistency) and imprecise evidence (Table 70) for unspecified clinical conditions, COPD, or CHF alone. We rated the evidence as low for benefit for diabetes cohort. We draw attention to the risk of selective analysis reporting in the evidence on diabetes. Only one study elected to provide condition-specific outcomes<sup>62</sup>; further analysis on diabetes cohorts from existing studies or new studies with fewer limitations may well change the direction, magnitude, and precision of effect from available evidence. By contrast, we rated the evidence on the rate of hospitalization as low based on a precise estimate from a large cohort study (Table 71); we note that the findings from a single study of a very specific intervention (home medicines review) of heart failure patients limits its applicability to patients with other morbidities and settings. Together, the lack of consistency across these measures of hospitalization likely reflects heterogeneity in numerous factors in this evidence base.

**Table 69. Mean number of hospitalizations: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,580 (2,208)	Medium	Consistent	Direct	Imprecise	Mean difference of 0.037 (95% CI -0.006 to 0.080)	Insufficient
Cohort	1, 4,500 (4,500)	High	Consistency unknown- single study	Direct	Precise	Calculated mean difference (95% CI): -0.21(-0.265 to -0.155, p<0.001	Low for benefit

Abbreviations: CI = confidence interval; RCT = randomized controlled trial.

**Table 70. Risk of hospitalization: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 637 (556)	Low	Consistency unknown, single study	Direct	Imprecise	OR for MTM basic vs. usual care: 2.069, 95 % CI: 1.104 to 3.878 p=0.02  OR for MTM enhanced vs. usual care: 1.345 95 % CI: -0.693 to 2.609 p=0.381	Insufficient
Cohort	Cohort CHF or COPD or unspecified: 3; 904-200,722 (795 - 200,722)  Diabetes: 1; 150,470 (150,470)	High	CHF or COPD or unspecified: Inconsistent  Diabetes: Consistency unknown, single study	Direct	CHF or COPD or unspecified: imprecise  Diabetes: precise	Adjusted OR CHF or COPD or unspecified: ranges from 0.90 to 1.4  Diabetes: ranges from 0.91 to 0.93	CHF or COPD or unspecified  Insufficient  Diabetes: Low for benefit

Abbreviations: CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; MTM = medication therapy management; OR = odds ratio; RCT= randomized controlled trial.

**Table 71. Rate of hospitalization: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 5,717 (5,717)	High	Consistency unknown, single study	Direct	Precise	Adjusted HR (95% CI): 0.55 (0.39 to 0.77)	Low for benefit

Abbreviations: CI = confidence interval; HR = hazard ratio.

## Hospitalization Costs

Two trials (medium risk of bias)<sup>51-55</sup> and two cohort studies (one medium risk of bias<sup>62</sup> and one high risk of bias<sup>79</sup>) reported changes in costs of hospitalization following MTM interventions (Table 72). Although two studies were set in the United States, one evaluated outcomes from Veteran Affairs Medical Centers<sup>51-54</sup> and the other evaluated claims from the Iowa Medicaid program.<sup>79</sup> The third study was set in Canada.<sup>55</sup> The period of evaluation of outcomes ranged from 5 months<sup>55</sup> to 12 months.<sup>51-54,79</sup> The other cohort study, designed to identify the impact of 2010 Part D MTM programs, compared cohorts (standalone Prescription Drug Plan or Medicare Advantage Prescription Drug Plan) receiving MTM with a comprehensive medication review with cohorts receiving usual care for congestive heart failure, chronic obstructive pulmonary disease, and diabetes, after limiting the sample to those newly eligible or enrolled for MTM and controlling for characteristics such as demographics, medical comorbidities, condition severity, and intensity of provider care.<sup>62</sup> Three were consistent in demonstrating no effect of MTM interventions on the costs of hospitalization; the large Part D evaluation demonstrated inconsistent results by clinical condition. MTM appeared to consistently reduce costs of all-cause and condition-specific hospitalization costs for the diabetes cohort only. Based on lack of consistency in direction of effect and lack of precision, we graded the body of evidence as being insufficient to evaluate the effect of MTM interventions on the cost of hospitalization overall and low for diabetes (Table 73).

**Table 72. Costs of hospitalization: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for inpatients 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients	Mean USD (25th–75th percentile) G1: 5751 (0–3780) G2: 3349 (0–4824) 95% CI: NR p: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>55</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all admissions to hospital (assumed CAD) over what time period	Calculated mean difference: \$159.74 (assumed CAD) 95% CI: -\$281.99 to \$601.47 p=0.478
Malone, 2000 <sup>51</sup> ; Ellis, 2000 <sup>52</sup> Malone, 2001 <sup>54</sup> (Ellis, 2000 <sup>53</sup> ) RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual hospitalization costs	Calculated mean difference: -\$221.00 95% CI: -\$566.33 to \$124.33 p=-0.21

**Table 72. Costs of hospitalization: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perlroth et al., 2013 <sup>62 a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658	All hospitalization costs: Generic substitution ratio within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators)	Risk adjusted costs in USD for PDP (95% CI) G1 vs. G13: -526.19 (-.919.71, -132.66), p<0.05 G5 vs. G15: -249.70 (-574.03, 74.62), p>0.05 G9 vs. G17: -398.98 (-651.21, -146.75), p<0.05
	G1: enrolled in PDP receiving MTM with CMR	G3: 11,260		
	G5: enrolled in PDP receiving MTM with CMR	G7: 10,575		
	G3: enrolled in MA-PD, receiving MTM with CMR	G9: 16,545		
	G11: enrolled in MA-PD, receiving MTM with CMR	G11: 13,527		
	G13: enrolled in PDP receiving MTM with CMR	G13: 156,441		
	G5: enrolled in PDP receiving MTM with CMR	G14: 51,938		
	G7: enrolled in MA-PD, receiving MTM with CMR	G15: 184,350		
	Diabetes	G16: 73,623		
	G9: enrolled in PDP receiving MTM with CMR	G17: 133,925		
	G11: enrolled in MA-PD, receiving MTM with CMR	G18: 53,912		
	Comparison— Congestive heart failure			
	G13: enrolled in PDP, usual care			
G14: enrolled in MA-PD, usual care				
Comparison—Chronic obstructive pulmonary disease				
G15: enrolled in PDP, usual care				
G16: enrolled in MA-PD, usual care				
Comparison—Diabetes				
G17: enrolled in PDP, usual care				
G18: enrolled in MA-PD, usual care				
Chrischilles et al., 2004 <sup>79</sup>  Cohort/High	G1: PCM-eligible patients who received PCM services	G1: 524	Inpatient claims within 9 months of becoming eligible for PCM	Results NR, p= 0.937
G2: PCM-eligible patients who did not receive PCM services	G2: 1,687			

<sup>a</sup> Perlroth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CAD = Canadian dollars; CHF = congestive heart failure; CMR = comprehensive medication review; COPD = chronic obstructive pulmonary disease; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; PCM = pharmaceutical care management; PDP = Medicare Part D Plan; RCT = randomized controlled trial; USD = United States dollars.

**Table 73. Cost of hospitalization: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,151 (2,050)	Medium	Inconsistent	Direct	Imprecise	Inconsistent direction of effect but consistent in lack of significant effect	Insufficient
Cohort	CHF or COPD: 1; 169,099-200,722 (169,099 - 200,722)  Diabetes: 1; 150,470 (150,470)	High	Consistency unknown (single study)	Direct	Imprecise for CHF or COPD, precise for diabetes	Differences range from -526 USD to 200 USD for CHF and COPD  Differences range from -363 USD to -399 USD for diabetes	Insufficient for CHF or COPD  Low for benefit for diabetes

Abbreviations: CAD = Canadian dollars; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; RCT= randomized controlled trial; USD = United States dollars.

## Hospital Length of Stay

Two trials (one low<sup>84,94</sup> and one high risk of bias<sup>73,74</sup>) reported inconsistent results on the effects of MTM interventions on length of hospital stay. Neither study reported statistically significant results, but the low risk-of-bias study found longer stays in the intervention arm and the high risk-of-bias study found shorter stays in the intervention arm (Table 74). Based on lack of precision of the results, we graded this outcome as having insufficient evidence to evaluate the effect of MTM interventions on the length of hospital visits (Table 75).

**Table 74. Length of hospitalization: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>84,94</sup>  RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Hospitalized days (time period NR)	Mean (25th–75th percentile) G1: 6.7 (0–5) G2: 4.9 (0–6) 95% CI: NR p: NS at 0.05 level, specifics NR
Pai et al., 2009 <sup>73</sup> ; Pai et al., 2009 <sup>74</sup>  RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44  Year 1: G1: 44 G2: 36  Year 2: G1: 24 G2: 32	Cumulative hospital time (days) over 2 years	Cumulative hospital time G1: 9.7 days (14.7) G2: 15.5 days (16.3) p: 0.06  Pharmaceutical care reduced length of stay by 21% compared with the standard of care group. p=NS

Abbreviations: G = group; NR = not reported; NS = not significant; RCT= randomized controlled trial.



**Table 75. Length of hospital stay: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 208 (208)	Low	Consistency unknown—single study	Direct	Imprecise	MTM reduced length of stay 1.8 days	Insufficient

Abbreviations: MTM = medication therapy management; RCT= randomized controlled trial.

## Key Question 3: Outcomes of Medication Therapy Management by Intervention Features

### Key Points

- Studies do not routinely report outcomes of MTM by intervention features.
- We found evidence on five intervention features informed by a single study for each feature: access to patient data,<sup>69</sup> intensity of care coordination and followup after comprehensive medication review,<sup>88</sup> pharmacy intensity of adoption of the intervention,<sup>79</sup> community pharmacy versus call-center pharmacy,<sup>57</sup> and private versus Medicaid coverage of pharmaceutical care.<sup>58</sup> With the exception of the investigation reporting on access to patient data, these studies had a high risk of bias.
- Evidence was insufficient on access to patient data, intensity of care coordination and followup after comprehensive medication review, pharmacy intensity of adoption of the intervention, community pharmacy versus call-center pharmacy, and private versus Medicaid coverage of pharmaceutical care for most outcomes.
- MTM programs with pharmacist access to patient records reduces the number of adverse drug events (low strength of evidence) when compared basic MTM programs.
- Community pharmacists increase the generic dispensing ratio more than call-center-based pharmacists (low strength of evidence).

### Detailed Synthesis: Intervention Features

#### Access to Patient Records

A single trial (medium risk of bias) of 556 patients overall (373 in the two MTM arms) evaluated differences between two MTM intervention arms; one without access to patient records (denoted “basic” MTM) and one specifically with such access in the form of a two-page clinical synopsis containing basic data on a patient’s medical history, laboratory values, and current medications, including over-the-counter and herbal medications (denoted “enhanced MTM”).<sup>69</sup> Table 76 provides the effect size and strength of evidence for the seven outcomes assessed in this trial. In all instances, we rated the trial as medium for study limitations and unknown for consistency; we do not repeat these ratings in the table. With the exception of mean number of adverse drug events, which suggested benefit for enhanced MTM when compared with basic MTM (low strength of evidence), we found insufficient evidence to evaluate the comparative effectiveness of the two arms.

**Table 76. Access to patient records (basic MTM versus enhanced MTM): Strength of evidence**

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Percentage with ≥ 1 ADE	Direct	Imprecise	Calculated OR: 1.294, 95% CI: 0.768 to 2.180, p=0.333	Insufficient
Percentage with ≥ 1 emergency department visit	Direct	Imprecise	Calculated OR: 1.222, 95% CI: 0.795 to 1.878, p=0.360	Insufficient
Percentage with ≥ 1 hospitalization	Direct	Imprecise	Calculated OR: 1.539, 95% CI: 0.862 to 2.746, p=0.145	Insufficient
Mean number of ADEs	Direct	Imprecise	Calculated mean difference: 0.346, 95% CI: 0.112 to 0.580, p=0.004	Low for benefit
Mean number of emergency department visits	Direct	Imprecise	Calculated mean difference: -0.001, 95% CI: -0.119 to 0.117, p=0.987	Insufficient
Mean number of hospitalizations	Direct	Imprecise	Calculated mean difference: 0.055, 95% CI: -0.038 to 0.148, p=0.244	Insufficient
Mean number of physician visits	Indirect	Imprecise	Calculated mean difference: 0.100, 95% CI: -0.322 to 0.522, p=0.643	Insufficient

Abbreviations: ADE = adverse drug event; CI = confidence interval; OR = odds ratio.

## Intensity of Care Coordination and Followup Following Comprehensive Medication Review

One RCT (high risk of bias) of 131 patients aged 65 or older compared comprehensive drug therapy review and subsequent coordination and followup with the patient and physician with comprehensive review and subsequent referral to the usual pharmacist only (Table 77).<sup>88</sup> For all outcomes, we rated this study as high for study limitations and unknown for consistency (not repeated in table). We found insufficient evidence to judge the effectiveness of MTM by intensity of adoption on all reported outcomes.

**Table 77. Intensity of care coordination and followup following comprehensive medication review: Strength of evidence**

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Hoarding drugs	Indirect	Imprecise	Calculated OR: 1.08, 95% CI (0.52–2.27); p=0.830	Insufficient
Non-prescribed drugs discontinued	Indirect	Imprecise	Calculated OR: 1.00, 95% CI (0.07–13.77); p=1.000	Insufficient
Taking home remedies	Indirect	Imprecise	Calculated OR: 1.48, 95% CI (0.65–3.34); p=0.348	Insufficient
Mean symptoms reported	Direct	Imprecise	Calculated mean: 0.70, 95% CI (-0.73–2.13); p=0.34	Insufficient
Mean medication adherence	Indirect	Imprecise	Calculated mean: 1.60, 95% CI (-14.40–17.60); p=0.84	Insufficient
Estimated annual prescription costs in USD per client	Direct	Imprecise	Calculated mean: -65.00, 95% CI (-305.67–175.67); p=0.60	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio; USD = United States dollars.

## Pharmacy Intensity of Adoption

One cohort study (high risk of bias) of 2,211 patients evaluated eight outcomes based on pharmacy intensity of adoption of the MTM intervention (Table 78).<sup>79</sup> Specifically, the authors categorized pharmacies that completed recommendations in at least one quarter into four groups: (1) for at least 50 percent of patients, high-intensity pharmacy (2) 25 to 49 percent as moderate

intensity; (3) 1 to 24 percent as low intensity; and (4) no recommendations study as no intensity. For all outcomes, we rated this study as high for study limitations and unknown for consistency (not repeated in table). Outcomes for which we can infer a benefit or a harm from the effect are rated as direct outcomes. We found insufficient evidence to judge the effectiveness of MTM by intensity of adoption on all reported outcomes.

**Table 78. Pharmacy intensity of adoption: Strength of evidence**

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Number of emergency department claims	Direct	Imprecise	Findings NR, p=0.330	Insufficient
Number of inpatient institutional claims	Direct	Imprecise	Findings NR, p=0.839	Insufficient
Number of outpatient facility claims	Indirect	Imprecise	Findings NR, p=0.112	Insufficient
Number of pharmacy, institutional, and medical services	Indirect	Imprecise	Findings NR, p=0.616	Insufficient
Emergency department claims	Direct	Imprecise	Findings NR, p=0.652	Insufficient
Inpatient institutional claims	Direct	Imprecise	Findings NR, p=0.862	Insufficient
Outpatient facility claims	Indirect	Imprecise	Findings NR, p=0.212	Insufficient
Pharmacy, institutional, and medical services	Indirect	Imprecise	Findings NR, p=0.166	Insufficient

Abbreviation: NR = not reported.

## Community Pharmacy Versus Call Center

One large cohort study (high risk of bias) of the MirixiaPro platform (95,736 patients enrolled, 73,793 analyzed) compared patients using a community pharmacy, which included both face-to-face and telephone interactions, with patients using a call center pharmacy (Table 79).<sup>57</sup> The investigators measured three diverse outcomes. In all instances, we rated the study as high for study limitations and unknown for consistency (not repeated in table). Outcomes for which we can infer a benefit or a harm from the effect are rated as direct outcomes. We found insufficient evidence for drug cost and drug use outcomes, which we rated as indirect evidence with high study limitations. MTM delivered by community pharmacists increases the weighted generic dispensing ratio (GDR) when compared with MTM delivered by call-center pharmacists (low strength of evidence). The study defines the weighted GDR as the number of generic 30-day equivalent claims divided by the total number of claims, and then weighted for each patient by a factor equal to the individual's total prescription volume multiplied by a constant to hold sample size unchanged.

**Table 79. Community pharmacy versus call center: Strength of evidence**

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Drug cost per patient per month (USD)	Indirect	Precise	Calculated mean difference: -20.0, 95% CI: -32.826 to -7.174, p=0.002	Insufficient
Drug use per patient per month	Indirect	Precise	Calculated mean difference: -0.370, 95% CI: -0.477 to -0.263, p<0.001	Insufficient
Weighted generic dispensing ratio	Direct	Precise	Calculated mean difference: 9.710, 95% CI: 9.583 to 9.837, p<0.001	Low

Abbreviations: CI = confidence interval; USD = United States dollars.

## Type of Payer

One cohort study (high risk of bias, N=615) compared outcomes for patients with Medicaid and patients with private insurance (Table 80).<sup>58</sup> The investigators reported on three diverse

outcomes. In all instances, we rated the study as high for study limitations and unknown for consistency (not repeated for each outcome in the table). We found insufficient evidence to judge the effectiveness of MTM by type of payer on all reported outcomes.

**Table 80. Type of payer: Strength of evidence**

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Per-patient Medication Appropriateness Index at followup	Direct	Precise	Calculated mean difference: 0.81, 95% CI: -1.303 to 2.923, p=0.452	Insufficient
Proportion of patients for whom cost was a problem at followup	Direct	Precise	Calculated OR: 1.498, 95% CI: 0.807 to 2.778, p=0.20	Insufficient
Drug therapy problems identified	Direct	Precise	2.6 in both arms, p=1.0	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio.

## Key Question 4. Outcomes of MTM by Patient Characteristics

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

## Key Question 5. Harms of Medication Therapy Management Interventions

### Key Points

- Studies do not routinely report harms that result from MTM interventions. One study reported on inconvenience from information received through an MTM intervention. Study limitations and lack of precision of these results suggested that evidence was insufficient to evaluate the effect of MTM interventions on harms.

### Detailed Synthesis: Inconvenience

A single cohort study (high risk of bias) compared pharmaceutical care with usual care (Table 81).<sup>70,71</sup> The investigators reported that patients in the intervention arm were less likely to agree or strongly agree with the statement that they were inconvenienced by monthly appointments with the pharmacists than patients in the control arm (40 percent versus 69 percent; calculated OR, 0.278; 95% CI, 0.088 to 0.875; p=0.029). The sample size does not meet optimal information size criteria, suggesting lack of precision of the results.

**Table 81. Inconvenience: Strength of evidence**

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 55 (51)	High	Consistency unknown-single study	Direct	Imprecise	Calculated OR: 0.278, 95% CI: 0.088 to 0.875; p=0.029	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio.

## Discussion

We conducted a systematic review of benefits and harms of medication therapy management (MTM) programs. Because of the wide variation in types of interventions classified as MTM, we first catalogued intervention components and implementation features of MTM interventions (Key Question [KQ] 1). We then evaluated the effect of MTM on intermediate, patient-centered, and resource utilization outcomes (KQ 2). We also reviewed the evidence to identify how these effects might vary by specific intervention components and features (KQ 3) and patient characteristics (KQ 4). Finally, we reviewed the evidence on harms associated with MTM (KQ 5).

Below, we summarize the main findings and strength of evidence, where applicable. We then discuss the findings in relationship to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions.

This evidence base consisted of 44 studies (21 randomized controlled trials [RCTs], 4 controlled clinical trials, and 19 cohort studies) reported in 61 articles. Most RCTs compared an MTM intervention with usual care rather than with a different active intervention; most observational studies were cohort studies. Numerous studies had methods problems that led us to rate them as having a medium or high risk of bias; only a few studies were of low risk of bias. When possible (enough studies similar in intervention, populations, and outcomes measured), we conducted meta-analyses of data from RCTs; in some cases, we did two sets, one with and one without the high risk-of-bias trials.

### Key Findings and Strength of Evidence

#### **KQ 1: Intervention Components and Implementation Features**

Of the 44 included studies, over three-quarters were broadly focused MTM interventions with patients that had a wide-ranging collection of conditions; the remaining studies were narrowly focused MTM interventions with patients that had a specific condition. All studies used a pharmacist as the interventionist. Services were provided face-to-face in half of included studies. Included studies provided interventions in a variety of clinical settings, including community pharmacies, centralized pharmacies or pharmacy call centers, and outpatient medical clinics, and some used home visits; half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.

Whether termed “pharmaceutical care” or “MTM,” studies did not describe intervention components and features in a consistent manner or in sufficient detail. These drawbacks were especially prevalent for intervention intensity and frequency of followup, method of patient enrollment for services, level of integration with usual care, and reimbursement characteristics for rendered MTM services. KQ 1 was descriptive in nature, so we did not grade strength of evidence.

#### **KQ 2: Overall Effectiveness**

Of the 44 studies included in this review, we rated 16 as high risk of bias overall; that is, concerns about randomization failure, confounding, or overall attrition increased the risk of bias for all outcomes. In addition, we rated some studies that were otherwise of low or medium risk of bias as high for individual outcomes, chiefly because of measurement or detection bias related to the specific outcome. These instances are specified in the relevant section the Results chapter

We rated the strength of evidence for each outcome from low- or medium risk-of-bias studies when available. MTM significantly improved some measures of medication adherence, medication appropriateness assessed in general and medication dosing (Table 82). However, we did not find evidence of benefit for any other intermediate outcomes on which we had data. No studies addressed either goals of therapy or patient engagement.

**Table 82. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions**

<b>Intermediate Outcome</b>	<b>Study Design: No. Studies (N Patients Analyzed)</b>	<b>Strength of Evidence</b>	<b>Supporting Judgment</b>	<b>Findings and Direction of Effect</b>
Anticoagulation	RCT: 1 (10)	Insufficient	Medium study limitations, consistency unknown-single study, direct, imprecise	Therapeutic INR achieved, 100% vs. 16.7%; p = 0.048.
HbA1c	RCT: 2 (102)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One trial with significantly greater percentage of patients with HbA1c <7.5% at 12 months.
	Cohort: 2 (2,688)	Insufficient	High study limitations, inconsistent, direct, imprecise	One study: adjusted findings significant at 12 months for percentage with HbA1c <7%, but findings not maintained at 24 months. Other study: no change in mean HbA1c or percentage <7% at 6 months.
Low-density lipoprotein cholesterol	RCT: 1 (38)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Calculated OR, 56.00; 95% CI, 5.583 to 561.753.
	Cohort: 2 (3,062)	Insufficient	High study limitations, inconsistent, direct, imprecise	One study: adjusted difference in difference coefficient, 1.95; 95% CI, 0.81 to 4.84; p = 0.13. Other study: calculated OR for achieving LDL goal, 1.392; 95% CI, 1.160 to 1.670; p <0.001.
BP	RCT: 1 (53)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	MTM group 28 times more likely to achieve BP goals than controls.
	Cohort: 2 (2,507)	Insufficient	High study limitations, consistent within design but inconsistent with RCT, direct, imprecise	MTM group less likely to achieve BP goals than controls.
Drug therapy problems identified	Cohort: 1 (582)	Insufficient	High study limitations consistency unknown, indirect, imprecise	Risk difference, 6.1%; calculated p = 0.062.
Drug therapy problems resolved	Cohort: 1 (120)	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Calculated mean difference, -1.00; 95% CI, -1.967 to -0.033; p = 0.04.

**Table 82. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions (continued)**

Intermediate Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication adherence measured as proportion adherent to a threshold	RCT: 1 (69)	Insufficient	Medium study limitations, consistency unknown, direct, precise	100% of intervention patients and 88.9% of controls were adherent; $p = 0.115$ .
	Cohort: 2 (224 to 200,722)	Low for benefit	High study limitations, inconsistent, direct, precise	Two studies with findings in opposite direction; larger study showing range of ORs for medication-specific adherence depending on medication.  For comparison of PDP vs. controls, ORs ranged from 0.99 to 1.43; 95% CIs ranged from (0.90, 1.08) to (1.26, 1.62).  For comparison of MA-PD vs. controls ORs ranged from 1.10 to 1.40; 95% CIs ranged from (0.83, 1.24) to (1.29, 1.52).  For clinic-based MTM vs. usual care for adherence to aspirin, odds of adherence ranged from 5.981 (95% CI, 0.284 to 126.030; $p = 0.250$ ) during the intervention to 1.17 1 year after the intervention (95% CI, 0.072 to 18.903; $p = 0.912$ ).
Medication adherence measured as percentage of prescribed doses taken	Cohort: 2 (120 - 4,500)	Low for benefit for adherence to treatment for hypertension and dyslipidemia  Insufficient for treatment of patients with diabetes, depression and asthma	High study limitations, inconsistent, direct, imprecise	Calculated mean difference from small study, -0.040; 95% CI, -0.101 to 0.021; $p = 0.201$ .  Larger study found a small (difference in adherence ~4.6%) but statistically significant effect of MTM on adherence to medications for some (2 of 5) conditions but no significant effect for the other conditions.
Medication adherence using self-report measures	RCT: 1 (292)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Calculated mean difference, 0.090; 95% CI, -0.076 to 0.256; $p = 0.289$ .
Medication adherence, miscellaneous measures	RCT: 2 (365)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Two studies with opposite direction of effect, both with non-significant differences between groups
Medication Appropriateness General Index Scores	RCT: 1 (208)	Low for benefit	Low study limitations, consistency unknown, direct, precise	Improvement in MTM group from score of 17.7 to 13.4 at 3 months and 12.8 at 12 months.
Medication-specific appropriateness	RCT: 2 (261)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Significant improvement in appropriateness in the MTM group for some medications but not others

**Table 82. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions (continued)**

Intermediate Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication dosing	RCT: 1 (56)	Low for benefit	Medium study limitations, consistency unknown, indirect, precise	Mean difference, -2.2 doses; calculated 95% CI, -3.738 to -0.662
Goals of therapy	0	NA	NA	NA
Patient engagement	0	NA	NA	NA

Abbreviations: BP = blood pressure; CI = confidence interval, HbA1c = Hemoglobin A1c; INR = International Normalized Ratio; LDL = low density lipoprotein; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NA = not applicable; OR = odds ratio; PDP = Medicare Part D Plan; RCT = randomized controlled trial.

Similarly, we did not have evidence of benefit for most patient-centered outcomes, including adverse drug events or mortality (Table 83). MTM did not improve most measures of health-related quality of life (low strength of evidence for no benefit). We graded the “vitality” and “emotional role functioning” domains of the Medical Outcomes Study Short-Form (SF36) questionnaire as insufficient for this domain. For the SF-36, neither the other six domains nor the two component scores (physical health, mental health) showed significant benefit from MTM interventions. The various patient satisfaction items also showed no impact from MTM programs (low strength of evidence for no benefit). We found no evidence on activities of daily living, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking.

**Table 83. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions**

Patient-Centered Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Adverse drug events	RCT: 2 (806)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Direction and magnitude of effect differs between the 2 trials
Cognitive and physical function	RCT: 1 (133)	Insufficient	Imprecise Medium study limitations, consistency unknown, direct, imprecise	No significant differences between arms
Affective function	RCT: 2 (181)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	One study with no significant calculated mean differences in depression or anxiety scores; the other study with significant differences in mean depression and anxiety scores, but no significant difference in percentage achieving a depression remission.



**Table 83. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions (continued)**

Patient-Centered Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Mortality	RCT: 1 (181)	Insufficient	Medium study limitations consistency unknown, direct, imprecise	OR, 0.59; 95% CI, 0.12 to 2.49; p = 0.48.
	Cohort: 2 (173,329)	Insufficient	High study limitations, inconsistent (magnitude), direct, imprecise	One study: OR, 0.5; 95% CI, 0.3 to 0.9. Second study: adjusted HR, 0.92; 95% CI, 0.87 to 0.96; p < 0.001.
Gastrointestinal bleeding events	Cohort: 1 (unclear)	Insufficient	High study limitations, consistency unknown, direct, imprecise	RRR, 60%; p = 0.001.
General health-related quality of life domains other than vitality and emotional role functioning	RCT: 3 (1,169)	Low for no benefit	Medium study limitations, consistent for physical role functioning, general health perceptions, and social functioning domains, inconsistent for physical functioning, bodily pain, and mental health domains, direct, precise	Variable mean difference with CIs consistently spanning the null effect.
General health-related quality of life for vitality and emotional role functioning domain	RCT: 3 (1,169)	Insufficient	Medium study limitations, consistent, direct, imprecise (not corrected for multiple comparisons or wide CIs)	Vitality: Mean difference of 2.797; 95% CI, 0.655 to 4.939; p = 0.010. Emotional role functioning: Mean difference of 5.386, 95% CI, -7.244 to 18.013)
Condition-specific health-related quality of life (diabetes)	RCT: 1 (73)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Nonsignificant improvement of 0.1 point on a 5-point scale in the intervention group compared with no change in the control group.
Patient satisfaction	RCT: 3. (1,463)	Low for no benefit	No difference Medium study limitations, consistent, direct, precise	No differences on 17 of 21 items of patient satisfaction; 4 statistically significant differences ranged in magnitude from -0.15 to -0.36, favoring MTM.
Activities of daily living	0	NA	NA	NA
Work or school absenteeism	0	NA	NA	NA
Patient and caregiver participation in medical care and decisionmaking	0	NA	NA	NA

Abbreviations: CI = confidence interval, HR = hazard ratio; MTM = medication therapy management; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial.

Outcomes related to using health resources were similarly not much influenced by MTM interventions (Table 84). Two exceptions may merit attention: (1) health plan expenditures on medication costs and (2) the proportion and costs of hospitalization for patient with diabetes. In both instances, MTM interventions improved outcomes. MTM trials implemented in settings with a broad range of patients did not show a consistent signal of reduction in the number of hospitalizations but a single cohort study that partially addressed confounding inherent in studies of refusers and acceptors found a lower mean number of inpatient visits for patients accepting MTM when compared with patients refusing MTM. Overall, we judge the strength of evidence for this outcome to be insufficient owing to lack of consistency.

**Table 84. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions**

Resource-Utilization Outcomes	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Use of generics	Cohort: 1 (63,198 to 200,722)	Insufficient	High study limitations, consistency unknown, direct, imprecise	Odds range from -0.01 to 0.006.
Medication costs: patient copayments	RCT: 1 (NR)	Insufficient	Medium study limitations, consistency unknown, indirect, precision cannot be determined	Calculated mean difference, -64 USD; variance not calculable.
	Cohort: 1 (1,606)	Insufficient	High study limitations, consistency unknown, indirect, precise	Calculated mean difference for MTM vs. same-country control, 80.40 USD; 95% CI, 10.43 to 150.37; p = 0.024.  Calculated mean difference for MTM vs. different country control, 88.60 USD; 95% CI, 24.61 to 152.59; p = 0.007.
Medication costs: health plan expenditures	RCT: 3; (965)	Low for benefit	Medium study limitations, consistent, indirect, imprecise	Mean difference varies from -34 CAD to -293 USD over 6 months.
	NRCT and cohort: 5; (120 to 200,722)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varies from -800 USD over 1 year to 425 USD over 2 years.
Medication costs: total outlays	RCT 6 (2,636)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Mean difference varies from -20.16 USD to +5.25 USD per month.
	Cohort: 2 (177,565)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Mean difference varies from -563 USD to +310 USD annually.
Medication costs: medication costs plus other expenditures	RCT: 2 (996)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences in mean costs range from -8.1 CAD to 1,947 USD.
	NRCT and cohort: 3 (5,300)	Insufficient	High study limitations, inconsistent, indirect, imprecise	Differences in mean costs range from -1,039 to 1,100 USD.

**Table 84. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions (continued)**

Resource-Utilization Outcome	Study Design: No. Studies (N Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Number of outpatient visits	RCT: 3; (2,208)	Insufficient	Medium study limitations, inconsistent, indirect, precise	Standardized mean difference, 0.049; 95% CI, -0.034 to 0.133; p = 0.247; I <sup>2</sup> = 0.
	Cohort: 1 (4,500)	Insufficient	High study limitations, consistency unknown, indirect, imprecise	Calculated mean difference, 2.48; 95% CI, 1.674 to 3.286; p <0.001.
Outpatient costs	RCT: 3 (2,050)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Variable estimates.
Number of laboratory tests	RCT: 2 (1,842)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences range from +0.15 to -1.6 tests.
Costs of laboratory tests	RCT: 3 (2,050)	Insufficient	Medium study limitations, inconsistent, indirect, imprecise	Differences range from +15 CAD to -140 USD.
Number of emergency department visits	RCT: 3 (1,552)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Mean difference ranges from -0.7 (p not significant) to -0.03 (95% CI, -0.113 to 0.053).
	Observational: 3 (795 to 200,722)	Insufficient	High study limitations, inconsistent, direct, imprecise	Adjusted OR ranges from 0.89 (95% CI, 0.6 to 1.3) to 1.09; mean difference (1 study), 0.04; 95% CI, -0.043 to 0.123; p = 0.346.
Costs of emergency department visits	RCT: 2 (996)	Insufficient	Medium study limitations, consistency unknown, direct, imprecise	Mean difference ranges from -52 USD to -5.6 CAD.
	Cohort: 1 (150,470 to 200,722)	Insufficient	High study limitations, consistency unknown, direct, imprecise	Difference ranges from -16 USD to +12.8 USD.
Hospitalization: number	RCT: 3 (2, 208)	Low for no benefit	Medium study limitations, consistent, direct, precise	Mean difference, 0.037; 95% CI, -0.004 to 0.080.
	Cohort: 1 (4,500)	Low for benefit	High study limitations, consistency unknown, direct, precise	Mean difference, -0.21; 95% CI, -0.265 to -0.155; p <0.001.

**Table 84. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions (continued)**

Use of Resources Outcomes	Study Design: No. Studies (N of Patients Analyzed)	Strength of Evidence	Supporting Judgment	Study Findings and Direction of Effect
Hospitalization: risk	RCT: 1 (556)	Insufficient	Low study limitations, consistency unknown, direct, imprecise	OR for basic MTM vs. usual care, 2.069; 95% CI, 1.104 to 3.878; p = 0.02.  OR for enhanced MTM vs. usual care, 1.345; 95% CI, -0.693 to 2.609; p = 0.381.
	Cohort—CHF, COPD, or unspecified: 3 (795 to 200,722)	CHF, COPD, or unspecified: insufficient	High study limitations, inconsistent, direct, imprecise	Adjusted OR ranges from 0.90 to 1.4.
	Diabetes: 1 (150,470)	Diabetes: low for benefit	High study limitations, consistency unknown, direct, precise	OR ranges from 0.91 to 0.93.
Hospitalization: rate (patients with heart failure and home medicine review)	Cohort: 1 (5,717)	Low for benefit	High study limitations, consistency unknown, direct, precise	Adjusted HR, 0.55; 95% CI, 0.39 to 0.77.
Costs of hospitalization	3; 2,151 (2,050)	Insufficient	Medium study limitations, inconsistent, direct, imprecise	Inconsistent direction of effect but consistent in lack of significant effect
	CHF or COPD: 1 (169,099 to 200,722)	Insufficient for CHF or COPD	High study limitations, consistency unknown, direct, imprecise	Differences range from -526 USD to 200 USD for CHF and COPD
	Diabetes: 1 (150,470)	Low for benefit for diabetes	High study limitations, consistency unknown, direct, precise	Differences range from -363 USD to -399 USD for diabetes
Length of hospital stay	RCT: 1 (208)	Insufficient	Low study limitations, consistency unknown, direct, imprecise	MTM reduced length of stay 1.8 days

Abbreviations: CAD = Canadian dollar; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; OR = odds ratio; RCT = randomized controlled trial; USD = U.S. dollar.

Over all three categories of outcomes, each of which had a substantial number of individual measures, MTM improved outcomes in only a few instances. Study limitations, lack of consistency, and lack of precision of the estimates of effects limited the strength of evidence considerably. As discussed later, even the minimal findings of effectiveness are at best only narrowly applicable.

### **KQ 3: Effectiveness of MTM by Intervention Features**

We found evidence from one study each on five intervention features: (1) access of pharmacists to patient records,<sup>69</sup> (2) intensity of care coordination and followup after comprehensive medication review,<sup>88</sup> (3) community pharmacy versus call center,<sup>79</sup> (4) level of intensity of intervention,<sup>57</sup> and (5) type of payer (private vs. Medicaid).<sup>58</sup> With the exception of the study on pharmacists' access to patient records, we rated these studies as high risk of bias.

Evidence was insufficient for most outcomes for the first two intervention features, with two exceptions. First, MTM delivered by community pharmacists increased the weighted generic dispensing ratio when compared with call-center pharmacists (low strength of evidence). Second, enhanced MTM with pharmacists' access to patient records reduced the mean number of adverse drug events; this finding suggested benefit when compared with basic MTM (low strength of evidence). We found insufficient evidence for all outcomes for intensity of intervention and type of payer.

#### **KQ 4: Effectiveness of MTM by Patient Characteristics**

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

#### **KQ 5: Harms of MTM Interventions**

Lack of precision and the limitations of a single high risk-of-bias study meant that evidence was insufficient to judge whether MTM resulted in greater or inconvenience<sup>70,71</sup> than usual care. We found no evidence on other prespecified harms, specifically including care fragmentation, patient decisional conflict, patient anxiety, increased (actual) adverse drug events, prescriber confusion, and prescriber dissatisfaction.

### **Findings in Relation to What Is Already Known**

Our findings contrast with conclusions that Chisholm-Burns and colleagues reached in a recent systematic review.<sup>95</sup> In that review, the authors concluded that “Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states.”<sup>95, p. 923</sup> Several differences between the Chisholm-Burns review and the current review may account for the discrepant conclusions. First, the Chisholm-Burns review included all studies that cited evidence of pharmacist involvement in direct patient care. The interventions examined included chronic disease management and prospective and retrospective drug utilization review; we excluded these types of efforts because of the clinical heterogeneity those interventions would have introduced into the review. Notably, the Chisholm-Burns review did not use the term “medication therapy management” to categorize the interventions in the articles they reviewed. Second, approximately 30 percent of the papers in the Chisholm-Burns review were conducted entirely in institutional settings. In contrast, we did not identify any studies within institutional settings that met our MTM intervention definition criteria. Third, the Chisholm-Burns review included a total of 298 articles and did not omit from their analyses studies with a high risk of bias; by contrast, we based our strength-of-evidence grades in this review on only those studies with no more than medium risk of bias. Thus, a direct comparison of findings between these two reviews would be ill advised.

The striking differences between the conclusions reached in these two reviews emphasize two important needs for efforts to systematically review MTM programs. The first is for researchers to specify the MTM intervention based on existing definitions, taxonomies, or service models. The second is to develop consensus guidelines for describing intervention features and fidelity of intervention delivery in publications reporting findings from evaluation studies. Progress on these two steps would enable systematic reviews to differentiate better between different types of services and avoid the problem of overgeneralizing review results.

## Applicability of the Findings

This body of evidence has significant clinical and methodological heterogeneity, which limits the ability to make any universal statements about effectiveness.<sup>36</sup> However, the range of study designs, which includes RCTs, nonrandomized trials, and cohort studies, enhances the applicability of findings for real-world settings. Included studies ranged from relatively small interventions in single clinics provided by a single interventionist to evaluations of MTM services delivered on a large scale through integrated health systems or health plans as a Medicare Part D or other drug plan benefit. This diversity of studies enhanced the applicability of findings to a wide variety of settings, including outpatient clinics, community pharmacies, and centralized pharmacy call centers. A few studies conducted outside the United States included MTM as part of a home visits program; findings from this model may not be directly applicable within the United States.

The studies in this review are broadly applicable to a range of chronically ill, adult patient populations. The majority of interventions were directed at populations with multiple and common chronic conditions, such as diabetes, chronic heart failure, and hypertension. Several specifically targeted adults aged 65 years or older. Few studies reported sociodemographic characteristics beyond age and sex; thus, the applicability of findings to specific populations (e.g., rural, low socioeconomic status, cognitively impaired, uninsured) is unknown. The nature of the MTM intervention, which includes involving patients as active participants in the process, limits the extent to which findings can be generalized beyond patients who agreed to participate in such interventions. Patients who agree to participate may be systematically different from those who decline to be in such a program. For that reason, the impact of such interventions at a population or health-plan level may be limited by the degree of uptake among interested patients.

The intervention used across most studies can be characterized as complex and moderately resource intensive. Components involve identifying applicable patients; initially assessing patients; providing counseling, education, and care coordination; and following patients over time. These services were provided per protocol in some studies and as needed or ad hoc in others. Most studies described intervention components in terms of “pharmaceutical care model” components or Medicare Part D MTM program criteria, but few provided detailed descriptions or measurement of implementation fidelity.

All studies included comparator arms with usual medical care or pharmacy care. Usual care does not typically include distinct MTM services by health care providers other than prescribing providers (not common for the time period covered by most of the studies). Models of collaborative health care delivery are evolving, and the changing roles and training of pharmacists increase the potential applicability of MTM interventions in future models of health care.

The broad sets of outcomes evaluated across this body of evidence spanned a substantial range of both intermediate and health outcomes as well as outcomes related to resource use. Proximal and intermediate outcomes included number of drugs, identification of drug therapy problems, appropriateness of medication prescribing, and laboratory or biometric markers of disease control (e.g., hypertension, hemoglobin A1c, low-density lipoprotein cholesterol). Patient-centered outcomes focused on numerous measures of quality of life as well as adverse drug events. Many studies also reported outcomes involving health care resource use and expenditures (e.g., number and costs of hospitalizations, emergency department visits, outpatient visits).

Most studies did not, however, clearly indicate the expected, desired, or intended direction of effect on most resource use outcomes, making the applicability of using these interventions to reduce drug-related or overall health care costs or expenditures difficult to assess. For example, whether one should expect the number of medications prescribed or drug costs for heart failure to increase or decrease under the careful scrutiny of an MTM intervention is not clear because the desired impact will be based on the goal of therapy for each individual.

The focus of outcome measurement in many studies was the short-term identification and characterization of drug therapy problems and their resolution; these endpoints are thought to be the outcomes most sensitive to change as a result of receiving MTM services. However, by design, because identification of drug therapy problems is a part of the MTM intervention itself, differences between the nature of the intervention and that of the control group mean that measuring these outcomes cannot be as rigorous in a usual care comparison group as it is in the intervention group. In fact, many studies were able to measure only changes in this outcome in the intervention group. Hence, many studies failed to demonstrate a direct analytic link between the resolution of drug therapy problems as a result of MTM and impact on intermediate outcomes, patient-centered outcomes, and resource utilization. Thus, the applicability of studies that demonstrate an impact on the resolution of drug therapy problems is limited.

## Implications for Clinical Practice and Policymakers

Although we found the evidence insufficient in general to draw definitive conclusions about the comparative effectiveness of MTM for most outcomes that we evaluated, our findings do suggest some implications for practice and policy. MTM is already in widespread practice and is now shaped in the United States largely by Medicare Part D policy: this presents both challenges and opportunities. MTM programs sponsored and administered by Part D drug benefit plans are often centrally administered and delivered primarily by phone and may be less integrated into routine health care than some of the interventions included in our review. MTM programs of the future have the potential to be more integrated into routine health care through participation in accountable care organizations or patient-centered medical home models. We were unable to answer definitively whether level of integration matters for effectiveness, but policymakers may need to consider expectations about the impact that MTM might have on patient-centered outcomes and resource use in the context of other health care delivery transformation activities or quality improvement initiatives that are also occurring. More integration of MTM services with other activities may be effective; however, the more integrated MTM becomes within routine medical care, the more difficult it becomes to isolate it as a discrete intervention for evaluation.

Policymakers could thus consider whether MTM services should be positioned as a *contributor* to overall improvement in processes of care, health status, and costs or positioned as an intervention to which effects can be discretely *attributed*. As noted earlier, improvements in medication appropriateness or drug therapy regimens may not always translate into improvements in health or costs, and even if they do, secular trends in related quality improvement (e.g., medication adherence interventions, regulatory requirements for medication reconciliation, electronic health record meaningful use incentives) may make measuring outcomes *attributable* to MTM very challenging.

Future training of MTM providers would benefit from a better understanding of which MTM components really matter. At the moment, such information is lacking. Policymakers and funders who wish to understand the comparative effectiveness of different MTM components could

encourage rigorous program evaluation designs that fit within the context of the real-world implementation of these programs. For example, positive deviance analyses<sup>96</sup> with rigorous measurement of implementation features or stepped wedge trial designs<sup>97</sup> may be useful approaches.

A typical approach for evaluating complex interventions is to identify the “core” components for standardization, while allowing for flexibility for peripheral components or variations in implementation. In complex practice-based innovations, such flexibility may reflect desirable (or unavoidable) adaptations to local circumstances. Policy governing MTM programs may warrant modifications to permit investigators to conduct rigorous and innovative evaluative designs to identify core components or effectiveness-enhancing modifications. As future research and evaluation elucidates these components or enhancements, policy will need to evolve to keep pace with best practices.

Finally, considering both patients’ and prescribers’ perspectives in future design and delivery of MTM services may be needed. In our current analytic framework, MTM interventions require a significant element of engagement by both patients and prescribers if the interventions are to have a reasonable likelihood of improving outcomes. Although “opt in” strategies may increase the reach of such interventions, keeping patients (and their prescribing providers) engaged in the intervention over a reasonable amount of time may be the key to translating the potential of MTM interventions into actual improvements. Further refinement of eligibility criteria based on evidence to provide interventions to those most at risk from drug-related problems and therefore most likely to benefit may also be warranted.

## **Limitations of the Comparative Effectiveness Review Process**

The constraints for populations, interventions, and settings that we imposed on this systematic review may limit its applicability as discussed above. During topic refinement and based on technical expert panel inputs and public comment, we expanded the scope by removing an exclusion criterion that would have required MTM interventions to have been directed at a patient population with two or more chronic conditions. As a result, we did include studies that focused on one chronic condition. Because of the prevalence of certain chronic conditions in the adult population, and particularly among Medicare beneficiaries, we think this decision was sensible and permitted us to examine a broader evidence base than would otherwise have been the case.

Although we tried to distinguish MTM from disease or case management interventions, making this distinction was challenging. We created a threshold for what intervention components were required to be present for this distinction. Specifically, we elected to emphasize whether the intervention entailed a comprehensive review of all medications; for that reason, we did not constrain studies of interest to those that targeted a single medication or drug regimen or that focused on a single condition such as diabetes or hypertension.

As described in the Methods chapter, when we were unable to determine which medications the interventionist had reviewed, we wrote to the authors for additional information. We chose to pursue authors in an effort to permit us to use studies that had been designed as MTM but did not describe the comprehensive medication review component in detail.

Our approach may have been overly inclusive because it led us to include studies that addressed a single disease, as long as the pharmacist reviewed all medications. For example, 10 of the 44 studies were relatively narrowly focused; two of these addressed patients with chronic



heart failure and two addressed patients with either hypertension or hypertension and diabetes. The remaining six studies focused on, patients with diabetes, HIV, glucocorticoid-induced osteoporosis, or hemodialysis. The fact that did not require patients to have more than one clinical condition resulted in an approach that was inclusive of these more narrowly focused (albeit often termed “MTM”) studies and may render our results less applicable to MTM interventions targeted to patients with a wide range of chronic conditions.

Also based on feedback during the process of setting out the scope of this review, we chose to include interventions that were broader than the Medicare Part D MTM-defined interventions. Put another way, we broadened our view of patient populations and intervention criteria, and we allowed studies not conducted in the United States into the evidence base. This decision led us to include interventions described as “pharmaceutical care,” which were generally based on the pharmaceutical care model principles;<sup>10</sup> it also permitted us to examine investigations with elements of pharmaceutical care or MTM that did not specifically label the intervention as either MTM or pharmaceutical care. These studies were often described as “clinical pharmacist interventions.”

Furthermore, all the non-U.S. studies involved interventions within single-payer health systems. Hence, the interventions in this review constitute a more heterogeneous group than if we had allowed only those labeled as Medicare Part D MTM programs. This is both a limitation and a strength. Although our approach makes results more challenging to interpret, it enhances our ability not to miss interventions that include MTM components but lack the descriptor term MTM.

Studies did not often explicitly describe certain MTM components. In cases when we could not determine whether investigators had provided certain MTM components (such as patient education and counseling, or coordination with other health care providers), we contacted the authors to gain additional information that would allow us to make an informed decision. We were fairly permissive in interpreting the presence of the MTM intervention components other than comprehensive medication review. The main reason is that we recognized that terms describing some components have evolved over time and may have been absent from the lexicon in earlier years or implicitly conveyed by authors by simply using the terms “MTM” or pharmaceutical care to describe their intervention.

Our approach to categorizing interventions for KQ 1 relied primarily on the short descriptions in published manuscripts and those we were able to obtain via email inquiries. Their similarities or differences substituted for any overarching taxonomy, because none that we considered seemed to fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for clinical heterogeneity among interventions. This approach limits our ability to make definitive statements about the effectiveness of various intervention components. We believe that the clusters and categorizations we used are useful heuristics, but some may regard them more as hypothesis generating than as reflecting settled principles of classification.

Finally, our search process was complicated by having to ensure coverage of all terms that could be used to describe MTM interventions over time. Adding to this challenge was our effort to examine the gray literature, where we thought we might find studies tilted toward effectiveness and real-world program evaluation. As it turned out, studies of these types of interventions were not indexed similarly; for that reason, we needed to rely heavily on hand searches of citation lists from key background articles to identify possibly relevant studies for inclusion. Thus, we may have missed some studies that might have qualified for inclusion. Given

the considerable diversity in the evidence base we did have, however, we do not think that any potentially missed studies would have changed our conclusions in any material way. No meta-analyses included more than five studies; as a result, we did not examine included studies for publication bias quantitatively.

## Limitations of the Evidence

As a body of evidence, the MTM literature evaluated in this review has measured numerous outcomes. As indicated in previous sections, very few outcomes, with the exception of harms, remain completely unexamined. Of the 44 studies in this review, we rated 28 as having medium, low, or mixed risk of bias. The 44 studies included 21 trials and 4 nonrandomized controlled studies. In other words, the literature on this topic is *not* marked by failure to consider important outcomes, universally high risk of bias, or pervasively weak designs.

Despite these advantages, we were unable to identify sufficient evidence on the majority of hypothesized outcomes of MTM. In several instances, our inability to rate evidence as higher than insufficient came from indirect, inconsistent, and imprecise evidence. The choice of outcome measures in this body of evidence limited our ability to come to conclusions in some instances. For example, some studies did not focus on changes that proponents might expect MTM services to produce. Because effective MTM can either increase or decrease expenditures or use of services based on the needs of the patient, studies that did not prespecify the expected direction of change had no way to interpret their results as an appropriate change. Studies that demonstrated inconsistent results in direction of change (i.e., some showing an increase in resource use and others showing a decrease) may well have been consistent in terms of appropriate change, but because they generally failed to establish a priori the direction in which they expected to find an effect, we rated such evidence as indirect and inconsistent.

Similarly, studies often used nonstandardized or idiosyncratic measures for outcomes such as adverse events, adherence, and expenditures or costs; this tendency limited our ability to meta-analyze results. When studies focused on specific outcomes, they were often significantly underpowered to detect differences between groups (that is, they did not meet optimal information size criteria). As a result, we rated several studies as imprecise.

MTM intervention studies are largely practice based and incorporate substantial heterogeneity in specific intervention elements and in patient populations targeted. Yet the evidence is sharply constrained in its ability to inform questions of the effectiveness of specific MTM components or intervention features (KQ 3 in our review) because study designs did not often capitalize on variants in MTM programs for a prospective evaluation of outcomes by those variants. Neither did they measure fidelity to intended MTM elements for post-hoc evaluation. Similarly, the relatively untargeted nature of the MTM interventions meant that, in many studies, only small numbers of patients had any one specific condition, and most studies did not measure patient characteristics beyond age and sex, thus limiting our ability to address KQ 4 in our review. For this reason, the evidence we identified for this review was most relevant for KQ 2.

## Research Gaps

In many bodies of research, questions regarding the *comparative* effectiveness of specific intervention components or implementation features are best answered after clear evidence of the effectiveness of the intervention relative to usual care has been established. Our review largely indicates insufficient evidence on the primary question of effectiveness relative to usual care. By definition, this limited what we could say about comparative effectiveness.

Nonetheless, the widespread implementation of MTM coexists with the urgent need for actionable information for policy, program policies, and training. This clinical and policy environment means that new research cannot afford to address causal claims relative to usual care first, followed by comparative effectiveness of the intervention elements in a relatively controlled environment, and finally, program evaluation of real-world implementation, all in sequential order.

In prioritizing among various research goals, therefore, funders may wish to consider the relative value of new evidence on overall effectiveness, effectiveness of implementation features, and program implementation and accountability. Trial research in narrow clinical settings can address questions of effectiveness but may lack applicability to real-world implementation. Likewise, evaluations of real-world programs with variable fidelity to interventions can answer questions about process and implementation, but they offer limited information on effectiveness. Research prioritization exercises will also need to account for already commissioned MTM intervention studies.

For new studies focusing on causal claims, a critical gap relates to the failure to specify the expected direction of effect. New research requires a strong theoretical foundation to help specify causal mechanisms and hypothesized effects. Without such an edifice, future research will continue to produce inconsistent and uninterpretable results.

Heightened attention to causal mechanisms will also help researchers convey their understanding of what outcomes these types of interventions are likely to influence. For instance, how should researchers wishing to establish direct causal links between MTM programs and outcomes evaluate distal outcomes such as patient-centered outcomes and resource utilization? This effort requires a better understanding of the relationship between proximal outcomes like “drug therapy problems identified and resolved” and distal outcomes. For instance, MTM may reduce outpatient visits to address side effects. MTM may also result in the need for further testing and evaluation for some patients, which could, in turn, result in more rather than fewer outpatient visits. Unless the nature of change resulting from MTM is specified in relation to goals of drug therapy, studies cannot assert benefit or harm. Further, drug therapy problems are diverse and may not all have the same causal relationship to health, quality of life, patient satisfaction, or resource use outcomes. Furthermore, a causal model of these distal outcomes may need to take into account the competing or complementary contributions of MTM, new models of health care delivery (e.g., patient-centered medical homes), and other quality improvement interventions.

Investigators embarking on new studies focusing on causal links between MTM and outcomes may wish to consider the limitations of studies based on secondary data from existing MTM programs that use opt-in/opt-out patient enrollment mechanisms. Although these studies may provide invaluable information on process measures such as patient engagement, underlying issues of confounding severely limit the validity of causal claims from such studies.

Regardless of the goal of their future research, investigators should consider issues of sample size to ensure precision of their results. This issue is particularly relevant when evaluating outcomes likely to occur in smaller subgroups defined by patient risk, context, or highly adapted intervention features. Innovative designs (e.g., stepped wedge trials, statistical process control, time series analysis, simulations, and factorial experiments) may permit both rigor and adequate sample size within the context of real-world implementation. With careful attention to fidelity, new studies may also inform questions of the effectiveness of intervention components and implementation features. Mixed-methods approaches may allow more information on variations

in context and implementation. Such designs may also help inform our understanding of critical training elements for MTM service providers.

Regarding research gaps for specific outcomes such as patient satisfaction, measures specific to the types of services provided through MTM (e.g., patient education about medications) or to the proximal outcomes that MTM is intended to achieve (e.g., reduced medication side effects, improved disease control) may offer better insights into the effects of MTM. Similarly, a medication-related instrument may better measure patients' concerns that are directly related to medication use (e.g., experience of side-effects, intrusiveness of the medication regimen) than generic tools.

## Conclusions

We included 44 eligible studies (21 randomized controlled trials, 4 controlled clinical trials, and 19 cohort studies) reported in 61 articles, described in detail in the report (KQ 1). Evidence was insufficient on the effect of MTM on most outcomes (KQ 2). In a few instances, described below, the evidence led us to conclude with a low strength of evidence either a benefit or lack of benefit. Specifically, we found evidence that MTM results in improvement when compared with usual care for some measures of medication adherence and appropriateness, medication dosing, health plan expenditures on medication costs, and the proportion and costs of hospitalization for patient with diabetes. Similarly, we conclude based on a low strength of evidence that MTM conferred no benefit for patient satisfaction and most measures of health-related quality of life. We found evidence on five intervention components and intervention features (KQ 3): one study provided information on each feature and yielded insufficient evidence for most outcomes with two exceptions. MTM programs with pharmacist access to brief clinical summaries from the medical record reduced the mean number of adverse drug events when compared with basic MTM programs without such access (low strength of evidence). Community pharmacists increase the generic dispensing ratio more than call-center-based pharmacists (low strength of evidence). We found no relevant studies on patient characteristics moderating the effect of MTM interventions (KQ 4). Similarly, the evidence on harms associated with MTM was limited to one study on inconvenience and was rated as insufficient (KQ 5).

The evidence base offers low evidence of benefit for a limited number of intermediate and health utilization outcomes. We graded the evidence for most outcomes as insufficient because of inconsistency in direction, magnitude, and precision, rather than lack of evidence. Wide variations in populations and interventions, both within and across studies, likely explain these inconsistencies. Given the widespread implementation of MTM and urgent need for actionable information, optimal investments in new research require a process of research prioritization in which the value of information from each proposed study is carefully considered. Studies designed to identify causal relationships between MTM interventions and their outcomes require adequate controls for confounding but may offer limited information on what explains program success or failure. Studies designed to explore the reasons for program success or failure using qualitative or single-arm designs may offer hypotheses-generating rather than hypotheses-confirming insights on MTM effectiveness. New research, regardless of specific focus, will likely continue to find inconsistent results until underlying sources of heterogeneity are accounted for.

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# Appendix A. Literature Search Strategies

## Published Literature

PubMed. Total of 1961 records retrieved; 1709 records imported after removing duplicates.

PubMed Search Update 1-9-14

211 additional results; 49 imported

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	<a href="#">610</a>
#2	Search "medication therapy management"	<a href="#">795</a>
#3	Search "comprehensive medication review"	<a href="#">22</a>
#4	Search "personal medication record"	<a href="#">14</a>
#5	Search ("medication" AND "action plan")	<a href="#">152</a>
#6	Search "medication therapy review"	<a href="#">11</a>
#7	Search "Medication Reconciliation"[Mesh]	<a href="#">252</a>
#8	Search (med* AND reconciliation)	<a href="#">335</a>
#9	Search "medication-related problems"	<a href="#">218</a>
#10	Search MTMP	<a href="#">34</a>
#11	Search prescriber intervention*	<a href="#">243</a>
#12	Search "drug utilization management"	<a href="#">6</a>
#13	Search "chronic care improvement "	<a href="#">13</a>
#14	Search "drug therapy services"	<a href="#">4</a>
#15	Search ("utilization management strategies" OR "utilization management strategy")	<a href="#">22</a>
#16	Search "optimized treatment outcomes"	<a href="#">6</a>
#17	Search ((patient OR patients) AND "medication understanding")	<a href="#">12</a>
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	<a href="#">34</a>
#19	Search "medication counseling"	<a href="#">133</a>
#20	Search "pharmaceutical case management"	<a href="#">12</a>
#21	Search "drug therapy management"	<a href="#">105</a>
#22	Search ("drug therapy problem" OR "drug therapy problems")	<a href="#">90</a>
#23	Search ("medicine management"[tiab] OR "medicines management"[tiab])	<a href="#">223</a>
#25	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Humans	<a href="#">2113</a>
#26	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Humans; English	<a href="#">1961</a>
#27	Search ((#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) AND ("retraction"[All Fields] OR "Retracted Publication"[pt])) Filters: Humans; English	<a href="#">0</a>
#28	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Publication date from 2012/11/04 to 2014/12/31; Humans; English	<a href="#">211</a>

## PubMed Search Update 11-4-13

### 390 additional results; 236 imported

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	<a href="#">579</a>
#2	Search "medication therapy management"	<a href="#">765</a>
#3	Search "comprehensive medication review"	<a href="#">22</a>
#4	Search "personal medication record"	<a href="#">13</a>
#5	Search ("medication" AND "action plan")	<a href="#">149</a>
#6	Search "medication therapy review"	<a href="#">11</a>
#7	Search "Medication Reconciliation"[Mesh]	<a href="#">234</a>
#8	Search (med* AND reconciliation)	<a href="#">326</a>
#9	Search "medication-related problems"	<a href="#">215</a>
#10	Search MTMP	<a href="#">34</a>
#11	Search prescriber intervention*	<a href="#">242</a>
#12	Search "drug utilization management"	<a href="#">6</a>
#13	Search "chronic care improvement "	<a href="#">13</a>
#14	Search "drug therapy services"	<a href="#">4</a>
#15	Search ("utilization management strategies" OR "utilization management strategy")	<a href="#">22</a>
#16	Search "optimized treatment outcomes"	<a href="#">6</a>
#17	Search (patient OR patients) AND "medication understanding")	<a href="#">12</a>
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	<a href="#">33</a>
#19	Search "medication counseling"	<a href="#">130</a>
#20	Search "pharmaceutical case management"	<a href="#">12</a>
#21	Search "drug therapy management"	<a href="#">105</a>
#22	Search ("drug therapy problem" OR "drug therapy problems")	<a href="#">88</a>
#23	Search ("medicine management"[tiab] OR "medicines management"[tiab])	<a href="#">218</a>
#24	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23)	<a href="#">2414</a>
#25	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Humans	<a href="#">2042</a>
#26	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Humans; English	<a href="#">1894</a>
#27	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) Filters: Publication date from 2012/02/27 to 2013/12/31; Humans; English	<a href="#">390</a>

### PubMed search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.

#### 149 additional results; all imported

Search String	Search Terms	Number of Results
#1	Search "medicine management"[tiab] OR "medicines management"[tiab] Filters: Humans; English	149

PubMed search revision 2-27-13: search re-run while keeping “wildcard” search terms.

**26 additional results; all imported**

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	<a href="#">475</a>
#2	Search "medication therapy management"	<a href="#">622</a>
#3	Search "comprehensive medication review"	<a href="#">18</a>
#4	Search "personal medication record"	<a href="#">13</a>
#5	Search ("medication" AND "action plan")	<a href="#">139</a>
#6	Search "medication therapy review"	<a href="#">10</a>
#7	Search "Medication Reconciliation"[Mesh]	<a href="#">168</a>
#8	Search (med* AND reconciliation)	<a href="#">27</a>
#9	Search "medication-related problems"	<a href="#">197</a>
#10	Search MTMP	<a href="#">31</a>
#11	Search prescriber intervention*	<a href="#">223</a>
#12	Search "drug utilization management"	<a href="#">5</a>
#13	Search "chronic care improvement "	<a href="#">13</a>
#14	Search "drug therapy services"	<a href="#">4</a>
#15	Search ("utilization management strategies" OR "utilization management strategy")	<a href="#">17</a>
#16	Search "optimized treatment outcomes"	<a href="#">6</a>
#17	Search ((patient OR patients) AND "medication understanding")	<a href="#">12</a>
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	<a href="#">33</a>
#19	Search "medication counseling"	<a href="#">122</a>
#20	Search "pharmaceutical case management"	<a href="#">11</a>
#21	Search "drug therapy management"	<a href="#">97</a>
#22	Search ("drug therapy problem" OR "drug therapy problems")	<a href="#">82</a>
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	<a href="#">1694</a>
#24	Search #23 Filters: Humans	<a href="#">1491</a>
#25	Search #23 Filters: Humans; English	<a href="#">1387</a>
#26	Search (#25 AND (2012/10:2013/12[edat]))	<a href="#">26</a>

**PubMed search revision 2-18-13: updated final PubMed/Medline “specific” MTM-and-MTM-components search conducted on 11/26/12 by using Entrez date limit of October 2012 to February 2013, which is the date each record was entered into PubMed, as opposed to limiting by publication date.**

**17 additional results; all imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Number of Results</b>
#1	Search "Medication Therapy Management"[Mesh]	472
#2	Search "medication therapy management"	621
#3	Search "comprehensive medication review"	18
#4	Search "personal medication record"	13
#5	Search ("medication" AND "action plan")	139
#6	Search "medication therapy review"	10
#7	Search "Medication Reconciliation"[Mesh]	162
#8	Search (med* AND reconciliation)	27
#9	Search "medication-related problems"	197
#10	Search MTMP	31
#11	Search prescriber intervention*	223
#12	Search "drug utilization management"	5
#13	Search "chronic care improvement "	13
#14	Search "drug therapy services"	4
#15	Search ("utilization management strategies" OR "utilization management strategy")	17
#16	Search "optimized treatment outcomes"	6
#17	Search ((patient OR patients) AND "medication understanding")	12
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	33
#19	Search "medication counseling"	122
#20	Search "pharmaceutical case management"	11
#21	Search "drug therapy management"	97
#22	Search ("drug therapy problem" OR "drug therapy problems")	82
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	1687
#24	Search #23 Filters: Humans	1476
#25	Search #23 Filters: Humans; English	1372
#26	Search (#25 AND (2012/10:2013/02[edat]))	17

**PubMed primary search 11-26-12 – 1190 results, all imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Number of Results</b>
#1	Search "Medication Therapy Management"[Mesh]	433
#2	Search "medication therapy management"	582
#3	Search "comprehensive medication review"	17
#4	Search "personal medication record"	13
#5	Search ("medication" AND "action plan")	134
#6	Search "medication therapy review"	10
#7	Search "Medication Reconciliation"[Mesh]	135
#8	Search (med* AND reconciliation)	27
#9	Search "medication-related problems"	193
#10	Search MTMP	31
#11	Search prescriber intervention*	217
#12	Search "drug utilization management"	5
#13	Search "chronic care improvement "	13
#14	Search "drug therapy services"	4
#15	Search ("utilization management strategies" OR "utilization management strategy")	17
#16	Search "optimized treatment outcomes"	6
#17	Search ((patient OR patients) AND "medication understanding")	9
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	33
#19	Search "medication counseling"	120
#20	Search "pharmaceutical case management"	11
#21	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)	1473
#22	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) Filters: Humans	1280
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) Filters: Humans; English MTM terms and specific component terms.	1190

Cochrane Library. Total of 408 records retrieved; 299 imported after removing duplicates.

**Cochrane Library search update 1-10-2014 – 97 results, 9 imported**

Search String	Search Terms	Number of Results
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	31
#2	"medication therapy management"	43
#3	"comprehensive medication review"	4
#4	"personal medication record"	1
#5	"medication" and "action plan"	94
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	18
#8	"medication reconciliation"	45
#9	"medication-related problems"	35
#10	MTMP	0
#11	"prescriber intervention" or "prescriber interventions"	0
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	156
#19	"medication counseling"	21
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	10
#23	("medicine management":ti or "medicine management":ab or "medicines management":ti or "medicines management":ab)	23
#24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	421
#25	MeSH descriptor: [Congresses] explode all trees	4
#26	MeSH descriptor: [Congresses as Topic] explode all trees	40
#27	congresses:pt	45
#28	#25 or #26 or #27	85
#29	#24 not #28 from 2012 to 2014	97



### Cochrane search update 11-4-2013 – 84 results, 40 imported

Search String	Search Terms	Number of Results
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	29
#2	"medication therapy management"	41
#3	"comprehensive medication review"	4
#4	"personal medication record"	1
#5	"medication" and "action plan"	92
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	16
#8	"medication reconciliation"	42
#9	"medication-related problems"	35
#10	MTMP	0
#11	"prescriber intervention" or "prescriber interventions"	0
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	152
#19	"medication counseling"	21
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	9
#23	("medicine management":ti or "medicine management":ab or "medicines management":ti or "medicines management":ab)	23
#24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	410
#25	MeSH descriptor: [Congresses] explode all trees	4
#26	MeSH descriptor: [Congresses as Topic] explode all trees	40
#27	congresses:pt	45
#28	#25 or #26 or #27	85
#29	#24 not #28	410
#30	#24 not #28 from 2012 to 2014	84

Cochrane Library search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.

### 21 additional results; all imported

Search String	Search Terms	Number of Results
#1	"medicine management":ti or "medicine management":ab or "medicines management":ti or "medicines management":ab	21

**Cochrane Library search revision 2-27-13: search re-run while removing “wildcard” search terms and conference papers and abstracts.**

**338 additional results; 337 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Number of Results</b>
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	19
#2	"medication therapy management"	30
#3	"comprehensive medication review"	3
#4	"personal medication record"	1
#5	"medication" and "action plan"	81
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	5
#8	"medication reconciliation"	21
#9	"medication-related problems"	32
#10	MTMP	0
#11	"prescriber intervention" or "prescriber interventions"	0
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	142
#19	"medication counseling"	19
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	8
#23	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	338
#24	MeSH descriptor: [Congresses] explode all trees	4
#25	MeSH descriptor: [Congresses as Topic] explode all trees	38
#26	congresses:pt	45
#27	#24 or #25 or #26	83
#28	#23 not #27	338

**Cochrane Library primary search 2-18-13: run concurrently with revised PubMed search, but eventually replaced with 2-27-13 search described above.**

**534 additional results; 532 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Number of Results</b>
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	19
#2	"medication therapy management"	30
#3	"comprehensive medication review"	3
#4	"personal medication record"	1
#5	"medication" and "action plan"	81
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	5
#8	med* and reconciliation	47
#9	"medication-related problems"	32
#10	MTMP	0
#11	prescriber intervention*	180
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	142
#19	"medication counseling"	19
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	8
#23	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	534

**International Pharmaceutical Abstracts (IPA): total of 756 records retrieved; 508 imported after removing duplicates.**

**IPA search update 1-10-2014 – 63 results, 16 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S24	S23	Limiters - Published Date: 20121101-20141231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	63
S23	S22	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	756
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,665
S21	TI ( "medicine management" OR "medicines management" ) AND AB ( "medicine management" OR "medicines management" )	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	40
S20	"drug therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	247
S19	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	149

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S18	"pharmaceutical case management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	14
S17	"medication counseling"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	236
S16	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	73
S15	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S14	"optimized treatment outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	0
S13	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	6

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S12	"drug therapy services"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2
S11	"chronic care improvement"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3
S10	"drug utilization management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	17
S9	"prescriber intervention" OR "prescriber interventions"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S8	MTMP	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S7	"medication-related problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	204

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S6	"medication reconciliation"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	367
S5	"medication therapy review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	82
S3	"personal medication record"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	12
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	15
S1	"medication therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	315

**IPA search update 11-4-13 – 105 results, 40 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S24	S23	Limiters - Published Date: 20120201-20131231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	<b>105</b>
S23	S22	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	739
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,648
S21	TI ( "medicine management" OR "medicines management" ) AND AB ( "medicine management" OR "medicines management" )	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	40
S20	"drug therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	246



<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S19	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	148
S18	"pharmaceutical case management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	14
S17	"medication counseling"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	235
S16	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	73
S15	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S14	"optimized treatment outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	0
S13	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	5
S12	"drug therapy services"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2
S11	"chronic care improvement"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3
S10	"drug utilization management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	17

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S9	"prescriber intervention" OR "prescriber interventions"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S8	MTMP	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S7	"medication-related problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	202
S6	"medication reconciliation"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	364
S5	"medication therapy review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	81
S3	"personal medication record"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	12
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	14
S1	"medication therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	308

**IPA search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.  
19 additional results; 18 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S1	TI ( "medicine management" OR "medicines management" ) AND AB ( "medicine management" OR "medicines management" )	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	19

**IPA search revision 2-27-13: search re-run while removing “wildcard” search terms.  
673 additional results; 666 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S22	S21	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	673
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,558
S20	"drug therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	243
S19	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	145
S18	"pharmaceutical case management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	14
S17	"medication counseling"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	232
S16	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	72
S15	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S14	"optimized treatment outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	0
S13	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S12	"drug therapy services"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Last Run Via</b>	<b>Number of Results</b>
S11	"chronic care improvement"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3
S10	"drug utilization management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	16
S9	"prescriber intervention" OR "prescriber interventions"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S8	MTMP	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S7	"medication-related problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	199
S6	"medication reconciliation"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	341
S5	"medication therapy review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	80
S3	"personal medication record"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	12
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	12
S1	"medication therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	289

**IPA primary search 2-18-13: run concurrently with revised PubMed search, but eventually replaced with 2-27-13 search described above.  
739 additional results; 679 imported**

<b>Search String</b>	<b>Search Terms</b>	<b>Limiters/Expanders</b>	<b>Number of Results</b>
S23	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	739
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	1,803
S21	"drug therapy management"	Search modes - Boolean/Phrase	243
S20	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	145
S19	"pharmaceutical case management"	Search modes - Boolean/Phrase	14
S18	"medication counseling"	Search modes - Boolean/Phrase	232
S17	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	72
S16	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	4
S15	"optimized treatment outcomes"	Search modes - Boolean/Phrase	0
S14	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	4
S13	"drug therapy services"	Search modes - Boolean/Phrase	2
S12	"chronic care improvement"	Search modes - Boolean/Phrase	3
S11	"drug utilization management"	Search modes - Boolean/Phrase	16
S10	prescriber intervention*	Search modes - Boolean/Phrase	95
S9	MTMP	Search modes - Boolean/Phrase	10
S8	"medication-related problems"	Search modes - Boolean/Phrase	199
S7	med* AND reconciliation	Search modes - Boolean/Phrase	508
S6	"medication reconciliation"	Search modes - Boolean/Phrase	341
S5	"medication therapy review"	Search modes - Boolean/Phrase	10
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	80
S3	"personal medication record"	Search modes - Boolean/Phrase	12
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	12
S1	"medication therapy management"	Search modes - Boolean/Phrase	289

# Gray Literature

Search update 11-4-13

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
ClinicalTrials.gov Expert Search Strategy	( "medication therapy management" OR "comprehensive medication review" OR "Medication Reconciliation" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems" OR "medicine management" OR "medicines management" )	[ALL-FIELDS] AND ( NOT NOTEXT ) [FIRST-RECEIVED-RESULTS-DATE] AND ( "03/04/2013" : "11/04/2013" ) [FIRST-RECEIVED-DATE]	5 (5)
WHO ICTRP	<u>Title search</u> : "medication therapy management" OR "comprehensive medication review" OR "Medication Reconciliation" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems" OR "medicine management" OR "medicines management"  <u>Intervention search</u> : "medication therapy management"	Registered from 3/4/2013 to 11/4/13	5 (5) (Title search);  2 (1) (Intervention search)
HSRProj Advanced search	"medication therapy management" OR "comprehensive medication review" OR "personal medication record" OR (medication AND "action plan") OR "medication therapy review" OR "Medication Reconciliation" OR "medication-related problems" OR "prescriber intervention" OR "drug utilization management" OR "chronic care improvement" OR "drug therapy services" OR "utilization management strategies" OR "utilization management strategy" OR "optimized treatment outcomes" OR ((patients OR patient) AND "medication understanding") OR "drug therapy outcome" OR "drug therapy outcomes" OR "medication counseling" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems" OR "medicine management" OR "medicines management" [Limited to Ongoing/Completed status]	Initial Year Range = 2011 – 2013	18 (7)
DOPHER (Database of Promoting Health Effectiveness Reviews)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems  2) "MTM" or "Medication Therapy Management"	None	0



Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
New York Academy of Medicine Gray Literature Report (greyLit.org)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems	Published from 2012-2013	0 for search string #1; 1 (0) for search string #2
	2) "MTM" or "Medication Therapy Management"		
CMS.gov	1) allintitle: "medication therapy management" site:cms.gov	"allintitle", which limited results to those in which "medication therapy management" appeared in title of retrieved websites	82 (82) total: 82 through CMS.gov directly; 6 indirectly through Google

**Search revision 6-28-13: added British terms ("medicine management" OR "medicines management") for MTM to account for the MEDMAN study. Total of 14 records retrieved, 13 imported after initial screening.**

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
ClinicalTrials.gov Expert Search Strategy	"medicine management" OR "medicines management"	[ALL-FIELDS] AND ( NOT NOTEXT ) [FIRST-RECEIVED-RESULTS-DATE]	2 (2)
WHO ICTRP	"medicine management" OR "medicines management"	None	10 (10)
HSRProj Advanced search	"medicine management" OR "medicines management"	None	0
NIH RePORTER Advanced search	"medicine management" OR "medicines management"	None	0
DOPHER (Database of Promoting Health Effectiveness Reviews)	"medicine management" OR "medicines management"	None	0
New York Academy of Medicine Gray Literature Report (greyLit.org)	"medicine management" OR "medicines management"	None	0
CMS.gov	"medicine management" OR "medicines management"	"allintitle", which limited results to 2 (1) those in which "medication therapy management" appeared in title of retrieved websites	

**Primary searches 3-4-13: 750 records retrieved, 596 imported after removing duplicates.**

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
ClinicalTrials.gov Expert Search Strategy	( "medication therapy management" OR "comprehensive medication review" OR "Medication Reconciliation" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems" )	[ALL-FIELDS] AND ( NOT NOTEXT ) [FIRST-RECEIVED-RESULTS-DATE]	119 (119)
WHO ICTRP	<u>Title search</u> : medication therapy management OR comprehensive medication review OR Medication Reconciliation OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems  <u>Intervention search</u> : was either 41,000+, with the shorter search (see Search Strings #1c and #1d), or no results for "medication therapy management" by itself.	None	5 (5) (Title search);  0 (Intervention search)
HSRProj Advanced search	"medication therapy management" OR "comprehensive medication review" OR "personal medication record" OR (medication AND "action plan") OR "medication therapy review" OR "Medication Reconciliation" OR "medication-related problems" OR "prescriber intervention" OR "drug utilization management" OR "chronic care improvement" OR "drug therapy services" OR "utilization management strategies" OR "utilization management strategy" OR "optimized treatment outcomes" OR ((patients OR patient) AND "medication understanding") OR "drug therapy outcome" OR "drug therapy outcomes" OR "medication counseling" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems" [Limited to Ongoing/Completed status]	None	87 (82)
NIH RePORTER Advanced search	medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems	None	234 (85)

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
DOPHER (Database of Promoting Health Effectiveness Reviews)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems  2) "MTM" or "Medication Therapy Management"	None	0 for all search strings
New York Academy of Medicine Gray Literature Report (greylit.org)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems  2) "MTM" or "Medication Therapy Management"	None	0 for search string #1;  1 (1) for search string #2
CMS.gov	1) "medication therapy management" OR "comprehensive medication review" OR "personal medication record" OR (medication AND "action plan") OR "medication therapy review" OR "Medication Reconciliation" OR "medication-related problems" OR "prescriber intervention" OR "drug utilization management" OR "chronic care improvement" OR "drug therapy services" OR "utilization management strategies" OR "utilization management strategy" OR "optimized treatment outcomes" OR ((patients OR patient) AND "medication understanding") OR "drug therapy outcome" OR "drug therapy outcomes" OR "medication counseling" OR "pharmaceutical case management" OR "drug therapy management" OR "drug therapy problem" OR "drug therapy problems"  2) allintitle: "medication therapy management" site:cms.gov	"allintitle", which limited results to those in which "medication therapy management" appeared in title of retrieved websites	304 (304) total: 295 through CMS.gov directly; 9 indirectly through Google

## Appendix B. Abstract and Full-Text Review Form Templates

### Abstract Review Form

Ref ID	Author	Year	Include or Exclude? (separate exclusion codes for publication type, PICOTS, and study design)	If ineligible, is manual review or hand search of full-text needed?	If ineligible, potential background reference?	NOTE: The following columns apply only to studies meeting our inclusion criteria	Study Design (RCT, NRCT, Other Study Design)	If "Other Study Design", which specific design does it use? (Cohort, Case-Control, Nonconcurrent Time Series, Other – describe in Comments column)	Comments (e.g., if reviewer included an abstract due to a lack of clarity within the abstract)

### Full-Text Review Form

Ref ID	First author's last name	Year	Study name (if applicable)	Include or Exclude? (separate exclusion codes for publication type, PICOTS, and study design)	Hand search references? (If so, marked with an "X")	BKG? (If so, marked with an "X")	Comments for INELIGIBLE studies (e.g., additional detail about exclusion reasons)	NOTE: The following columns apply only to studies meeting our inclusion criteria	Study Design (Dropdown list options: RCT, NRCT, Cohort, Case-Control)	KQ(s) (separate sub-columns for KQs 1, 2a, 2b, 2c, 3, 4, and 5, and relevant questions marked with an "X")	Comments for ELIGIBLE studies (e.g., for reviewers to describe "Other" study designs)

# Appendix C. Studies Excluded After Full-Text Level Review

X1 = Ineligible Publication

X2 = Ineligible or No Intervention

X3 = Ineligible Population

X4 = Ineligible Study Design

X5 = Ineligible Comparator

X6 = Ineligible Outcomes

X7 = Ineligible Setting

X8 = Insufficient Information to Determine Eligibility

1. Patients confirm that medication counseling helps. *Am J Hosp Pharm.* 1994 Jul 1;51(13):1606, 8. PMID: 7942886. Exclusion Code: X2.
2. The MEDMAN study: a randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease. *Fam Pract.* 2007 Apr;24(2):189-200. PMID: 17272285. Exclusion Code: X2.
3. MTM program increased statin use. *Dis Manag Advis.* 2008 Oct;14(10):suppl 1-3, 1. PMID: 19031586. Exclusion Code: X1.
4. What's expected for med reconciliation? *OR Manager.* 2008 Mar;24(3):21, 3. PMID: 18438074. Exclusion Code: X1.
5. Hospitals collaborate to reduce ED overuse. *Hosp Case Manag.* 2012 Oct;20(10):151-3. PMID: 23091842. Exclusion Code: X1.
6. First, do no harm: avoiding medication mishaps. *Johns Hopkins Med Lett Health After 50.* 2013 Summer;24(6):1-4. PMID: 24000429. Exclusion Code: X1.
7. Cut readmissions through med adherence. *Hosp Peer Rev.* 2013 Feb;38(2):19-20. PMID: 23513301. Exclusion Code: X1.
8. Optimising medicines management? *Drug Ther Bull.* 2013 Apr;51(4):37. PMID: 23575602. Exclusion Code: X1.
9. Aguiar PM, Balisa-Rocha BJ, Brito GC, et al. Pharmaceutical care in hypertensive patients: a systematic literature review (Provisional abstract). *DARE.* 2012(4):383-96. PMID: DARE-12013008032. Exclusion Code: X2.
10. Al-Ghamdi SA, Mahmoud MA, Alammari MA, et al. The outcome of pharmacist counseling at the time of hospital discharge: an observational nonrandomized study. *Ann Saudi Med.* 2012 Sep-Oct;32(5):492-7. PMID: 22871618. Exclusion Code: X2.
11. Alsuwaidan S, Malone DC, Billups SJ, et al. Characteristics of ambulatory care clinics and pharmacists in Veterans Affairs medical centers. IMPROVE investigators. Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers. *Am J Health Syst Pharm.* 1998 Jan 1;55(1):68-72. PMID: 9437478. Exclusion Code: X2.
12. Altman JS. Medication therapy management and the new practitioner. *Am J Health Syst Pharm.* 2007 Mar 15;64(6):590-2. PMID: 17353567. Exclusion Code: X1.
13. Anonymous. Prescribing and research in medicines management (UK & Ireland) Conference 2013 Imperial Hotel London January 24th 2013 "Intelligent polypharmacy ... It's not all about the number" abstract. *Pharmacoepidemiol Drug Saf.* 22:670. Exclusion Code: X1.
14. Armour CL, Reddel HK, LeMay KS, et al. Feasibility and effectiveness of an evidence-based asthma service in Australian community pharmacies: a pragmatic cluster randomized trial. *J Asthma.* 2013 Apr;50(3):302-9. PMID: 23270495. Exclusion Code: X2.
15. Asis ML, Greene R. A cost-effectiveness analysis of a peak flow-based asthma education and self-management plan in a high-cost population (Structured abstract). *J Asthma.* 2004(5):559-65. PMID: NHSEED-22004001183. Exclusion Code: X2.
16. Atkinson WL, Frey D. Integration of a medication management model into outcome-based quality improvement: a pilot program in a rural propriety home healthcare agency. Home

- Health Care Serv Q. 2005;24(1-2):29-45. PMID: 16236657. Exclusion Code: X4.
17. Avery AJ, Rodgers S, Cantrill JA, et al. Protocol for the PINCER trial: a cluster randomised trial comparing the effectiveness of a pharmacist-led IT-based intervention with simple feedback in reducing rates of clinically important errors in medicines management in general practices. *Trials*. 2009;10:28. PMID: 19409095. Exclusion Code: X2.
  18. Avery AJ, Rodgers S, Cantrill JA, et al. Correction: Protocol for the PINCER trial: a cluster randomised trial comparing the effectiveness of a pharmacist-led IT-based intervention with simple feedback in reducing rates of clinically important errors in medicines management in general practices. *Trials*. 2010:23. PMID: CN-00789806. Exclusion Code: X1.
  19. Bandres MA, Mendoza MA, Nicolas FG, et al. Pharmacist-led medication reconciliation to reduce discrepancies in transitions of care in Spain. p. 1083. Exclusion Code: X2.
  20. Bates DW. Role of pharmacists in the medical home. *Am J Health Syst Pharm*. 2009 Jun 15;66(12):1116-8. PMID: 19498128. Exclusion Code: X1.
  21. Bayoumi I, Howard M, Holbrook AM, et al. Interventions to improve medication reconciliation in primary care (Structured abstract). *Ann Pharmacother*. 2009(10):1667-75. PMID: DARE-12010000178. Exclusion Code: X2.
  22. Bell JS, Vaananen M, Ovaskainen H, et al. Providing patient care in community pharmacies: practice and research in Finland. *Ann Pharmacother*. 2007 Jun;41(6):1039-46. PMID: 17504836. Exclusion Code: X1.
  23. Bellone JM, Barner JC, Lopez DA. Postdischarge interventions by pharmacists and impact on hospital readmission rates. *J Am Pharm Assoc* (2003). 2012 May-Jun;52(3):358-62. PMID: 22618976. Exclusion Code: X2.
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## Appendix D. Evidence Tables

**Table D1. Study and patient-level characteristics**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	To identify actual and potential DRPs using a structured approach, and to resolve those problems in collaboration with PCPs using pharmacy-based interventions	1) Aged ≥65 2) Taking ≥4 prescribed medications 3) Oriented with respect to self, time, and place 4) Community-dwelling 5) Regular visitors to recruited community pharmacy	Housebound or resident in nursing /residential home	RCT: cluster-randomized	18 months	Multiple (Government, foundation, professional organizations, pharmaceutical companies)	NR	NR	Pooled sample Overall: NR G1: 57.9 G2: 57.3 Northern Ireland Overall: NR G1: 63.6 G2: 61.0	NR
Blakey, 2000 <sup>3</sup>	G1: Pharmacist evaluation plus usual medical care G2: Usual medical care	To recognize and resolve drug therapy problems, decrease drug therapy costs, and maintain positive clinical outcomes.	Patients age 65 and receiving care in VA geriatric clinic due to assistance required in activities of daily living, memory impairment, poor judgment, diagnosis of dementia, history of falls or difficulty walking, incontinence of bowel or bladder, or polypharmacy.	NR	NRCT	8 months	Unspecified	NR	NR	Overall: 0% G1: 0% G2: 0%	NR



**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Brummel, 2013 <sup>4</sup> ; Soliman, 2013 <sup>5</sup> ; Ramalho de Oliveira, 2010 <sup>6</sup>	G1: Fairview Pharmacy Services' MTM program (opt-in) G2: control group (did not opt-in)	Achievement of Optimal Diabetes Care benchmarks	Patients with diabetes who participated in an MTM demonstration project and had MTM visits to any Fairview clinic offering MTM services between January 1, 2007, and December 31, 2007. A random selection of 121 patients with diabetes who were eligible for the demonstration project but who did not actively participate in MTM services served as the control group. The final analysis included data on patients for whom all information on medications was available at baseline and all D5 quality measure components were available for 2006, 2007, and 2008.	NR	Cohort	36 months	Pharmaceutical	NR	Overall: NR G1: 58.44 G2: 58.19	Overall: NR G1: 52.07 G2: 51.46	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	To train community pharmacists to provide HTN monitoring and direct consultation to physicians and nurses	(1) Greater than 18 years of age, with essential HTN (one of the following: average diastolic blood pressure 90 mm Hg or above, average systolic blood pressure 140 mm Hg or above, or current therapy with antihypertensive drugs [controlled or uncontrolled blood pressure]); (2) Receiving care from a physician in the medical center or annex and prescriptions from the clinic pharmacy	(1) Secondary causes of HTN; (2) Unwilling or unable to return to clinic pharmacy for scheduled appointment; (3) Spouse or sibling enrolled in study; (4) BP >210 mm Hg systolic or >115 mm Hg diastolic; (5) Serious complicating disease so disabling that BP control was secondary or minor concern (e.g., terminal cancer, New York Heart Association class III or IV CHF)	Cohort	6 months	Unspecified	Overall: NR, but likely 100% rural G1: NR G2: NR	Mean (range) Overall: NR G1: 67.3 (47-80) G2: 68.5 (40-92)	NR	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Chris-chilles et al., 2004 <sup>9</sup>	G1: PCM provided by pharmacists G2: Did not receive PCM services	Avoid adverse drug events and the health system costs associated with these adverse events in a Medicaid population at high risk for adverse effects	Noninstitutionalized Iowa Medicaid patients taking four or more long-term medications, including at least one medication representing 1 of specified 12 diseases, were eligible (the 12 diseases were congestive heart disease, ischemic heart disease, diabetes mellitus, HTN, hyperlipidemia, asthma, depression, atrial fibrillation, osteoarthritis, gastroesophageal reflux, peptic ulcer disease, and chronic obstructive pulmonary disease) with pharmacy claims at one (or more) of the 117 participating pharmacies.	All patients who were not continuously eligible for Medicaid from 6 months before through 12 months after the date on which they became eligible for PCM.	Cohort	21 months	Multiple (Government and foundation funding)	NR	Overall: 52.5 (20.2) G1: 54.1 (0.8) G2: 48.4 (0.5)	Overall: 71.4 G1: 80.0 G2: 69.3	Overall: NR White G1: 89.1 G2: 90.0 Black G1: 5.9 G2: 5.5 Other G1: 1.0 G2: 2.1 Unknown G1: 4.0 G2: 2.4

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Christensen et al., 2007 <sup>10</sup>	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	To assess the feasibility of a pharmacist based medication therapy management service for North Carolina State Health Plan enrollees.	(1) Residence in Orange or Durham County, NC; (2) Among the 1,000 highest number of prescriptions used during the first 6 months of 2004.	NR	NRCT	6 months	Multiple (Third-party payor and foundation)	NR	G1: 67.7 (11.4) G2: 67.6 (12.2) G3: 66.0(12.1)	G1: 62.3 G2: 68.9 G3: 71.3	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Clifford et al., 2002 <sup>11</sup>	G1: Pharmaceutical care provided by a clinical pharmacist, which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	To improve glycemic control in diabetic patients without adversely affecting QOL or satisfaction with health care provided	Adult patients ≥18 years with type 1 or type 2 diabetes and at least one of the following features indicating high risk for development of diabetes complications: 1) Random blood glucose levels >11 mmol/L on ≥2 occasions in tertiary care setting within previous 12 months; 2) HbA1C >8% on ≥2 occasions in previous 12 months; 3) HTN (SBP >160 mm Hg and/or DBP >90 mm Hg) and/or taking drug therapy; 4) Dyslipidemia (total serum cholesterol >5.5 mmol/L and/or serum triglycerides >4.0 mmol/L); 5) Polypharmacy (>3 drugs)	See inclusion criteria	RCT: parallel, not clustered	6 months	Multiple (Pharmaceutical, professional organization)	NR	Overall: NR G1: 60 (12) G2: 61 (12) p=NS	Overall: NR G1: 42 G2: 52 p=NS	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Fischer et al., 2000 <sup>12</sup>	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists G2: Standard community pharmacy practice G3: Patients at eligible clinics who declined to receive intervention but were included in some analyses.	(1) To improve the amount of information patients received; (2) To improve the way patients self-administer medication; (3) To enhance awareness of side effects.	(1) HMO enrollees enrolled in a participating clinic; (2) Had asthma, COPD or heart disease identified via pharmacy or hospital data base medication records.	NR	NRCT	6 months	Foundation or non-profit	NR	Overall: NR G1: 67.2 G2: 68.3 G3: 58.9	Overall: NR G1: 54 G2: 52 G3: 50	% White Overall: NR G1: 98 G2: 96 G3: 92
Fischer et al., 2002 <sup>13</sup>	Pharmaceutical care based on Encara Practice System provided by pharmacists. Pharmacist-physician communication about pharmacist-identified DTPs. G2: Usual care with no additional interventions	To assess whether pharmaceutical care program decreases health care utilization, medication use, or charges	(1) Age ≥18; (2) Enrolled in participating HMO for ≥2 years with active prescriptions treating heart or lung disease; (3) Obtained prescriptions from participating pharmacy; (4) Must have filled prescriptions for one of several pre-specified medication types for heart or lung disease in 6 months before study	Died, disenrolled, or discontinued pharmacy benefit before end of study period	NRCT	2 years (1997-98) [one year before initiation and one year after]	Multiple (Pharmaceutical companies, third-party payors)	NR	Overall: NR G1: 57 G2: 58	Overall: NR G1: 50 G2: 51	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Fox et al., 2009 <sup>14</sup>	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	To reduce LDL-C and improve HEDIS goal attainment among patients with diabetes on lipid-lowering medications	FHCP enrollees who: 1) Were Medicare Part D members; 2) Were diagnosed with ≥3 chronic diseases; 3) Used ≥4 maintenance medications; 4) Were likely to have Part D medication costs ≥\$4000 per year; 5) Were eligible for inclusion in 2008 HEDIS CDC administrative dataset	None specified	Cohort	21 months	Unspecified	NR	Overall: NR G1: 67.6 (7.2) G2: 68.3 (6.1)	Overall: NR G1: 45.5 G2: 57.9	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Gattis et al., 1999 <sup>15</sup>	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	To improve outcomes in outpatients with heart failure.	Patients with a diagnosis of heart failure with LVEF < 45% in a general cardiology clinic at a University Medical Center.	Life expectancy < 6 months; currently participating in a drug trial, primary residence was a skilled nursing facility, marked dementia or other psychological disorder that prevented participation in patient education or follow-up.	RCT: parallel, not clustered	24 weeks	Multiple (Foundation and academic)	NR	Overall: 71.5 (25%: 60, 75% : 77) G1: 63.0 (25%: 55, 75% : 72)	Overall: NR G1: 31 G2: 33	White Overall: NR G1: 80 G2: 79



**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Grymonpre, 2001 <sup>16</sup>	G1: Comprehensive drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensive drug therapy review only with referral to usual pharmacist	Identify and address drug-related issues with an non-institutionalized elderly population	Age 65 or older, NR non-institutionalized, taking 2 or more prescribed or non-prescribed medications		RCT: parallel, not clustered	6 months	Unspecified	Overall: NR G1: NR G2: NR	Overall: N-R G1: 76.9(8.4) G2: 77.2(8.8)	Overall: NR G1: 75 G2: 83	Overall: NR G1: 100% Caucasian G2: 100% Caucasian

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Hanlon et al., 1996 <sup>17</sup> Cowper, 1998 <sup>18</sup>	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	To evaluate the effect of sustained clinical pharmacist interventions involving elderly outpatients with polypharmacy and their primary care physicians on: prescribing appropriateness, health-related quality of life, adverse drug events, medication compliance and knowledge, number of medications used, patient satisfaction, and physician receptivity	(1) Age ≥65; (2) Had evidence of polypharmacy operationally defined as prescribed 5+ regularly scheduled medications by a VA physician; (3) Receiving primary care in the General Medicine Clinic.	1) Nursing home residence; 2) Patients with cognitive impairment, as determined by the Mental Status Questionnaire; 3) No caregiver available to be involved in the intervention	RCT: parallel, clustered	One year	Government	NR	Overall: NR G1: 69.7 (3.5) G2: 69.9 (4.1)	Overall: NR G1: 1.9 G2: 0	White Overall: NR G1: 79 G2: 74.8

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Hirsch, 2011 <sup>19</sup> Hirsch, 2009 <sup>20</sup> Rosenquist, 2010 <sup>21</sup> (methods)	G1: Patients served at nonpilot pharmacies G2: Patients served at pilot pharmacies	Examining an HIV/AIDS pharmacy MTM compensation pilot program in a sample of Medi-Cal beneficiaries by describing the associations between use of pilot pharmacies and (a) adherence to ART regimens; (b) medication utilization; (c) occurrence of opportunistic infections; and (d) all-cause pharmacy and medical costs	Medi-Cal beneficiaries aged ≥18, who were continuously enrolled from January 1, 2004 through December 31, 2007 and diagnosed with HIV/AIDS. In each study year, patients were identified as pilot pharmacy patients if they filled 50% or more of their ART prescriptions at 1 of the 10 pilot pharmacies. Comparison group patients met the same inclusion and exclusion criteria as study patients except they filled less than 50% of their ART prescriptions at 1 of the 10 pilot pharmacies	Individuals enrolled in managed care plans, dual-eligible Medicare patients, who died at any time from 2004 through 2007	Cohort	3 years	Government	NR	Overall: NR G1: 44.7 (8.1) G2: 45.4 (7.8)	Overall: NR G1: 32.8 G2: 28.0	Non-Latino White Overall: NR G1: 40.3 G2: 42.7  African American Overall: NR G1: 33.0 G2: 31.4  Latino Overall: NR G1: 16.2 G2: 16.3  Other Overall: NR G1: 10.5 G2: 9.6

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Isetts et al., 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	(1) To provide MTM services to patients; (2) to measure clinical effects associated with MTM, (3) to measure percent of patients achieving goals for HTN and hyperlipidemia in MTM vs. comparison; and 4) to compare patients' total health expenditures for the year before and after MTM	Patients in intervention group: 1) Enrolled in Blue Plus insurance product of Blue Cross BlueShield of Minnesota; (2) Age ≥18 years; (3) Receiving medical care at one of 6 clinics in Fairview, MN where MTM services provided; (4) Diagnosed with ≥1 of 12 study medical conditions, (5) ≥2 health care claims related to 12 study conditions in 6-month period before the start of the study.	NR	Cohort	12	Academic	NR	Overall: NR G1: 14% were age 65 or older G2: NR	Overall: NR G1: 66 G2: NR	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup>	Pharmacotherapy and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	To simplify the pharmacologic regimen, improve effectiveness of the regimen, and decrease side effects. Secondary goal to decrease cost without adversely affecting the first three goals. Improved clinical outcomes (decreased number of medications, decreased number of doses per day, monthly cost of medications, patient self-reported compliance, drug regimen convenience, fewer side effects and problems).	All patients at a Family Health Center seen during a 1 year period with 2 or more risk factors: 5 or more medications, 12 or more daily doses, 4 or more medication changes in last 12 months, more than 3 disease states, documented medication noncompliance, medications that require therapeutic monitoring.	Active alcohol or illicit drug use, unwilling or unable to return for a pharmacotherapy consultation, medication regimen primarily managed by an outside provider, terminally ill, less than 18 years of age.	RCT: parallel, not clustered	6 months	Multiple (Foundation or non-profit, academic, and pharmaceutical)	NR	Overall: 60.5 G1: NR G2: NR	Overall: 80 G1: NR G2: NR	African American Overall: 28 G1: NR G2: NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Jeong et al., 2007 <sup>24</sup> Jeong, 2009 <sup>25</sup>	G1: Kaiser Permanente 2006 pharmacist-managed MTMP G2: Patients without Medicare Part D as their primary drug benefit and likely to incur drug costs greater than or equal to \$4000 per year with a similar disease burden.	Provide Medicare Part D MTM benefit to eligible beneficiaries to improved medication use and decrease adverse events.	Patients who: 1) Were likely to incur >\$4,000 in drug costs per year 2) Received ≥2 Part D medications 3) Had ≥2 chronic conditions 4) Had a diagnosis of hyperlipidemia, diabetes, or CAD for LDL-C analysis 5) Had a diagnosis of diabetes for HbA1c analysis 6) Had a lab (LDL-C or HbA1c) within 6 months before and 6 months after index date 7) were at least 65 years old as of Jan 1, 2006 and had a dx of DM, HTN or CAD in 2005. 8) continuous membership with drug benefits during 12 months study period	See inclusion criteria	Cohort	12 months	Integrated health care system (Kaiser Permanente)	NR	Overall: NR G1: 75.1 (6.5) G2: 73.8 (7.0) p< 0.0001	Overall: NR G1: 54 G2:51 p= 0.04	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Jeong <sup>26</sup> Jeong, 2012 <sup>27</sup>	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	To optimize therapeutic outcomes through improved medication use and to reduce the risk of adverse events.	1) at least 3 chronic conditions 2) on at least 5 Medicare Part D drugs 3) Incurred costs for Part D drugs >=\$3,000.	NR	Cohort	12 months	Integrated health care system (Kaiser Permanente)	NR	Overall: NR G1: 74.98 (8.67) G2: 74.67 (9.47) G3: 78.34 (10.78)	NR	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Krska et al., 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	To study the effect of medication review led by a pharmacist on resolution of pharmaceutical care issues costs, use of health and social services and health-related quality of life	Patients aged at least 65 years with at least two chronic disease states, taking at least 4 prescribed medicines regularly	Dementia, being considered by the GP to be unable to cope with the study	RCT: parallel, not clustered	3 months	Government	NR	Overall: NR G1: 74.8 (6.2) G2: 75.2 (6.6) p=0.972	Overall: NR G1: 56.5 G2: 64.6 p=0.132	NR



**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Malone, 2000 <sup>29</sup> Ellis, 2000 <sup>30</sup> Malone, 2001 <sup>31</sup> Ellis, 2000 <sup>32</sup> IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	Determine if clinical pharmacists could change resource use and humanistic outcomes among Veterans identified at high risk for medication-related problems.	1) High risk for drug-related problems (were taking 5 or more drugs, 12 or more doses/day, had 3 or more chronic medical conditions, 4 or more changes in their drug regimen over the past year, history of nonadherence or taking an agent that required therapeutic drug monitoring); 2) Received care at the VA within the past 12 months and anticipated continued VA care for the duration of the study; 3) Lived close/had transportation to VA.	1) Participation in a pharmacist managed clinic within previous 12 months; 2) Terminal condition/ poor life expectancy; 3) Required mental health services; 4) Poor spoken or written English; 5) Visually impaired.	RCT: parallel, not clustered	12 months	Pharmaceutical	Overall: 67 (10.1) G1: 66.8 (10.2) G2: 66.6 (10.0)	Overall: NR G1: 3.6 G2: 3.8	NR	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year, Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Marques, 2013 <sup>33</sup>	G1: Intervention group: Dader method pharmacotherapy follow-up intervention monthly over 3-month follow-up period G2: Control group: monthly pharmacist visits without pharmacotherapy follow-up intervention	Clinical improvement of depression and anxious symptoms	Female gender, age 18-65 years, diagnosis of depression at the initial stage of treatment (first treatment, no previous antidepressant), prescribed new antidepressant	Insurmountable difficulties scheduling visits, Beck Depression Inventory < 11 points, dependence on illicit drugs, schizophrenia diagnosis, cognitive impairment	RCT: parallel, clustered	3 months	Unspecified	Overall: NR G1: NR G2: NR	Overall: NR G1: 40.8 (12.2) G2: 44.2 (13.9)	Overall: NR G1: 100 G2: 100	Overall: NR G1: NR G2: NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup>	<b>CHF</b> G1: enrolled in Medicare PDP receiving MTM with a CMR G2: enrolled in PDP receiving MTM, no CMR G3: enrolled in MA-PD receiving MTM with CMR G4: enrolled in MA-PD, receiving MTM, no CMR <b>COPD</b> G5: enrolled in Medicare PDP receiving MTM with a CMR G6: enrolled in PDP receiving MTM, no CMR G7: enrolled in MA-PD receiving MTM with CMR G8: enrolled in MA-PD, receiving MTM, no CMR	Investigate how enrollment in a standalone PDP or MA-PD MTM program with or without receipt of a CMR influenced adherence, quality of prescribing, resource utilization, and costs for Medicare beneficiaries with CHF, COPD, and diabetes.	G1-G12: Part D beneficiaries with 2009 risk data; have CHF, COPD, or diabetes; have at least one PDE claim in 2010; enrolled in contract that passed data validation for MTM section; enrolled in one MTM program in 2010; enrolled in a MTM program at least one day in 2010; new to MTM in 2010; same contract reported in MTM Beneficiary-Level file and Part D enrollment file; continuously enrolled in Part D during study period; enrolled in the same contract during outcome period. G13-G18: Constructed from the pool of beneficiaries in the	Did not have ESRD in 2009; Non-LTI in 2010; Not new in risk file;	Cohort	12 months	Government	NR	G1: ≤65: 25.2 66-75: 33.4 76-85: 30.7 >85: 10.7 G2: ≤65: 13.8 66-75: 31.8 76-85: 36.8 >85: 17.6 G3: ≤65: 8.0 66-75: 35.8 76-85: 41.9 >85: 14.3 G4: ≤65: 11.9 66-75: 35.1 76-85: 38.3 >85: 14.6 G5: ≤65: 34.2 66-75: 34.7 76-85: 24.6 >85: 6.5 G6: ≤65: 23.1 66-75: 35.7 76-85: 30.7 >85: 10.4	G1: 68.2 G2: 59.7 G3: 52.3 G4: 54.8 G5: 69.2 G6: 61.8 G7: 54.6 G8: 56.7 G9: 68.8 G10: 59.4 G11: 53.3 G12: 56.4 G13: 63.3 G14: 59.1 G15: 64.7 G16: 62.4 G17: 60.9 G18: 57.8	<b>White</b> G1: 74.8 G2: 82.5 G3: 79.8 G4: 79.1 G5: 81.4 G6: 85.6 G7: 84.0 G8: 84.4 G9: 76.3 G10: 80.7 G11: 75.1 G12: 76.5 G13: 81.8 G14: 79.2 G15: 86.1 G16: 83.7 G17: 77.3 G18: 72.2  <b>Black</b> G1: 19.0 G2: 11.3 G3: 11.6 G4: 13.3 G5: 13.7 G6: 9.1 G7: 9.3 G8: 9.8 G9: 16.2

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup> (continued)	<b>Diabetes</b> G9: enrolled in Medicare PDP receiving MTM with a CMR G10: enrolled in PDP receiving MTM, no CMR G11: enrolled in PA-PD receiving MTM with CMR G12: enrolled in MA-PD, receiving MTM, no CMR <b>Comparison - CHF</b> G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care <b>Comparison - COPD</b> G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care		same disease cohort. To narrow the set of beneficiaries in the comparison group to include only beneficiaries with chronic conditions and drug utilization levels similar to those experienced by MTM enrollees, used variations in MTM eligibility rules and implementation methods set by Part D sponsors.						G7: ≤65: 10.1 66-75: 38.8 76-85: 40.1 >85: 10.9 G8: ≤65: 15.6 66-75: 40.9 76-85: 34.2 >85: 9.2 G9: ≤65: 28.6 66-75: 36.1 76-85: 27.8 >85: 7.6 G10: ≤65: 16.5 66-75: 40.1 76-85: 33.4 >85: 10.0 G11: ≤65: 8.9 66-75: 45.5 76-85: 37.6 >85: 8.0 G12: ≤65: 13.2 66-75: 45.8 76-85: 33.4 >85: 7.6		G10: 10.6 G11: 12.4 G12: 12.9 G13: 12.6 G14: 13.9 G15: 9.1 G16: 10.1 G17: 13.7 G18: 16.5 <b>Hispanic</b> G1: 3.5 G2: 2.6 G3: 3.5 G4: 4.0 G5: 2.6 G6: 2.1 G7: 2.9 G8: 3.0 G9: 3.9 G10: 3.0 G11: 4.2 G12: 5.0 G13: 2.5 G14: 3.4 G15: 2.1 G16: 2.9 G17: 3.7 G18: 4.6

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup> (continued)	<b>Comparison - Diabetes</b> G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care								G13: ≤65: 16.7 66-75: 28.7 76-85: 34.8 >85: 19.8 G14: ≤65: 12.5 66-75: 32.6 76-85: 38.0 >85: 16.9 G15: ≤65: 24.9 66-75: 33.0 76-85: 29.9 >85: 12.2 G16: ≤65: 17.9 66-75: 37.3 76-85: 34.0 >85: 10.7 G17: ≤65: 22.2 66-75: 37.6 76-85: 30.5 >85: 9.7 G18: ≤65: 14.7 66-75: 43.9 76-85: 33.4 >85: 8.0		<b>Other/Unkn own</b> G1: 2.7 G2: 3.6 G3: 5.2 G4: 3.7 G5: 2.3 G6: 3.2 G7: 3.8 G8: 2.8 G9: 3.6 G10: 5.7 G11: 8.3 G12: 5.6 G13: 3.1 G14: 3.4 G15: 2.7 G16: 3.2 G17: 5.3 G18: 6.6

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
McDonough et al., 2005 <sup>36</sup>	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of dose, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	To reduce risk of glucocorticoid osteoporosis.	Patients 18 years of age or older who had been on the equivalent of at least 7.5 mg of prednisone for at least 6 months	NR	RCT: cluster-randomized	9 months	Multiple (Pharmaceutical company and academic)	NR	NR	Overall: NR G1: 57.7 G2: 74.3	Caucasian or Asian Overall: NR G1: 92.3 G2: 84.3

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Intervention s and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Moczygemba, 2011 <sup>37</sup> Moczygemba, 2008 <sup>38</sup> Moczygemba, 2012 <sup>39</sup>	G1: Opt-in telephone- based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	To identify and resolve medication and health- related problems	Medicare Part D beneficiaries of the Scott & White Health Plan with: 1) ≥2 chronic diseases 2) ≥2 Part D drugs 3) ≥\$4000 in Part D drug costs 4) Received ≥1 MTM consultation	Patients ≥90 years of age due to patient privacy concerns	Cohort	9 months	Foundation or non-profit	NR	Mean (SD) Overall: NR G1: 71.2 (7.5) (range: 53- 86) G2: 73.9 (8.0) (range: 46- 88) p: 0.06	Overall: NR G1: 48.3 G2: 71.7 p: 0.009	White Overall: NR G1: 78.3 G2: 91.7 p: 0.29

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Moore, 2013 <sup>40</sup>	G1: MTM program (opt-in) G2: control group (refusers)	To improve drug therapy adherence and clinical outcomes	Patients over the age of 18 who had 14 or more claims within a 120-day period and/or had claims showing the absence of a recommended therapy or the presence of a conflicting therapy in the treatment of conditions such as, but not limited to, asthma, diabetes, heart failure, or heart disease	NR	Cohort	24 months	Other	NR	Mean (SE) G1: 74.1 (0.226) G2: 73.7 (0.259) p: 0.277	Overall: 60 G1: 60 G2: 60	NR



**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Pai, 2009 <sup>41</sup> ; Pai, 2009 <sup>42</sup>	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	To investigate the impact of a pharmaceutical care program managed by clinical pharmacists on drug use, hospitalization rates, and drug-related problems (DRPs) in ambulatory patients undergoing hemodialysis.	To participate in the study, patients had to speak English, and be older than 18 years and undergoing a stable hemodialysis regimen for at least 3 months. Informed consent was obtained from each patient before starting the study, with a consent rate of 70%.	If patients elected not to consent or were unable to provide informed consent, they continued to receive the care that their shift was assigned; however, no data from these patients were collected or analyzed.	RCT: cluster-randomized	2 years	Foundation or non-profit	NR	Overall: 59.0 (15.0) G1: 56.3 (15) G2: 60.5 (14.7)	Overall: 48.1 G1: 38.6 G2: 59.6	Caucasian Overall: 27.9 G1: 22.8 G2: 34.0 Hispanic Overall: 30.8 G1: 29.8 G2: 31.9 Native American Overall: 17.3 G1: 22.8 G2: 10.6 Other Overall: 24.0 G1: 24.6 G2: 23.4
Park et al., 1996 <sup>43</sup>	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	Improve blood pressure and quality of life for patients with HTN.	Patients with HTN either currently taking anti-hypertensive medication or with a BP > 140/90.	Bedridden; non-English speaking; had another family member enrolled in the study.	RCT: parallel, not clustered	4 months	Unspecified	NR	Overall: NR G1: 57.3 (range 29-82) G2: 63.0 (Range 23-88)	Overall: NR G1: 44 G2: 41	% white G1: 81 G2: 69

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Pindolia et al., 2009 <sup>44</sup>	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors). G2: Usual medical care (refusers)	To 1) ensure that safest, most efficacious, and cost-effective drug therapy is provided by collaborating physicians and patients/care givers in the development of an optimal drug regimen that meets both medical and patient needs; (2) educate patients on all aspects of their drug therapy; and (3) improve adherence to drug therapy regimens	In 2006: 1) Diagnosed with 2 of 26 selected chronic diseases; 2) Filled ≥2 prescriptions as identified by pharmacy claims data; 3) Likely to incur annual costs of ≥\$4000 for all Medicare Part D-covered medications based on quarterly prescription drug expenditures of \$1000 In 2007: 1) Diagnosed with 3 of 21 selected chronic diseases; 2) Filled ≥4 prescriptions as identified by pharmacy claims data; 3) Likely to incur annual costs of ≥\$4000 for all Medicare Part D-covered medications based on monthly prescription drug expenditures of \$334	NR	Cohort	2 years	Unspecified	NR	2006 Mean (SD) [range] Overall: NR G1: 73.5 (9.7) [42-92] G2: 74.2 (9.8) [32-96] p: 0.229 2007 Mean (SD) [range] Overall: NR G1: 73.0 (9.1) [39-93] G2: 73.9 (9.8) [33-98] p: 0.168	2006 Overall: NR G1: 64 G2: 60 p: 0.175 2007 Overall: NR G1: 54 G2: 63 p: 0.01	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Planas et al., 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	To improve BP and antihypertensive medication adherence in patients with both diabetes and HTN	Members of MCO already enrolled in concurrent study of community pharmacy-based diabetes management program.  Criteria for diabetes study: (1) Lack of diabetes control (i.e., most recent A1C within last 6 months >7.0%) (2) ≥18 years old (3) Currently insured by MCO (4) Able and willing to come to periodic visits during a 9-month period  Criteria for HTN study: (1) Present at baseline diabetes study visit (2) BP ≥130/80 mm Hg or currently taking antihypertensive therapy	(1) Pregnant; (2) Currently enrolled in another diabetes program	RCT: parallel, clustered	9 months	Multiple (Foundation and pharmacy chain)	NR	Overall: NR G1: 64.2 (10.5) G2: 65.2 (14.1)	Overall: NR G1: 65.6 G2: 60.0	White Overall: NR G1: 75.0 G2: 90.0 Black Overall: NR G1: 21.9 G2: 10.0 Hispanic Overall: NR G1: 3.1 G2: 0

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Roughead et al., 2009 <sup>46</sup>	G1: HMR, a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	To reduce time to next hospitalization for HF among Australian war veterans and war widows with HF	Community-dwelling elderly who: 1) Had all health services fully subsidized by Australian Government's DVA; 2) Were dispensed beta-blocker subsidized for HF in 6 months before the HMR; 3) Were aged ≥65 years at the time of home review	1) Residents in aged-care facilities	Cohort	40 months	Government	Region of residence Remote Overall: NR G1: 0 G2: 1 Outer regional Overall: NR G1: 12 G2: 9 Inner regional Overall: NR G1: 29 G2: 31	Median (SD) Overall: G1: 81.6 (4.8) G2: 81.6 (4.8)	Overall: NR G1: 30 G2: 26	NR
Sellors et al., 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes	Reducing regimen complexity and improving patient outcomes	1) Community dwelling; 2) 65 years or older; 3) taking 5 or more medications; 4) had been seen by their physician within the past 12 months; 5) had no evidence of cognitive impairment; and 6) could understand English	1) Had planned surgery, 2) were on a nursing home waiting list or 3) were receiving palliative care	RCT: cluster-randomized	3 months	Multiple (Government and hospital)	NR	Overall: NR G1: 74.0 (6.1) G2: 74.0 (6.0)	Overall: NR G1: 64.3 G2: 61.4	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Sellors, 2003 <sup>48</sup>	G1: Pharmaceutical consultation G2: Usual care	Pilot study for a larger randomized trial investigating the efficacy and cost-effectiveness of a pharmacist consultation program for elderly patients in family practice	Eligible participants were at least 65 years of age and were taking at least four medications regularly, which in addition prescribed oral medications included insulin, inhalers, creams, drops and ointments, OTC medications, and herbal remedies.	NR	RCT: parallel, not clustered	6 months	Unspecified	Overall: NR G1: NR G2: NR	Overall: NR G1: 76.4 (6.5) G2: 75.5 (6.4)	Overall: NR G1: 60.6 G2: 69.7	Overall: NR G1: NR G2: NR
Shimp, 2012 <sup>49</sup>	G1: MTM program for University of Michigan beneficiaries, entitled FOM G2: Usual care (not described)	To leverage the University's investment in employee health by introducing a patient-centered MTM program offered to employees, retirees, and their dependents to optimize drug therapy	University of Michigan beneficiaries (employees, retirees, and their dependents), taking seven or more prescription medications. Patients with a University of Michigan PCP were preferentially invited.	NR	RCT: parallel, not clustered	12 months	Academic	Overall: NR G1: NR G2: NR	Overall: NR G1: 70 G2: NR	Overall: NR G1: 55 G2: NR	Overall: NR G1: NR G2: NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Sidel et al., 1990 <sup>50</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	To determine the prevalence of use of prescription and OTC medications and home remedies, to characterize medication taking behaviors and practices, and to assess the impact of in-home pharmacist intervention in identifying and correcting problems with medication use	(1) All Medicare recipients 65 years or older living in the Norwood area eligible; (2) Patients who were considered "high risk" by baseline RAP questionnaire	(1) Patients considered reluctant or difficult; (2) Those who died or moved during identification and assignment	RCT: parallel, clustered	6-11 months	Government	Overall: 0	65-74 years G1: 48.4% G2: 48.1% 75-84 years G1: 38.5% G2: 41.4% 85 years and older G1: 13.2% G2: 10.6%	Overall: NR G1: 76.9 G2: 77.9	Non-White G1: 7.7 G2: 6.7 Hispanic G1: 4.4 G2: 7.7

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Staresinic et al., 2007 <sup>51</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	To ensure that drugs prescribed to beneficiaries are appropriately used to optimize therapeutic outcomes and lower the risks of adverse drug events and drug interactions.	(1) PDP beneficiaries who fill at least two Part D covered drugs for ≥2 chronic diseases of interest, including, but not limited to, asthma, CD, CHF, diabetes, dyslipidemia, and HTN (specific disease states varied by PDP); (2) Additional independent eligibility criteria included an extrapolated annual drug cost (set by the Secretary of DHHS) of \$4000 or more by the end of the plan year. Long-term care residents eligible.	CMS-mandated exclusions including any one of following: use of OTC drugs, vitamins, drugs for cosmetic use, medication to treat cold or cough symptoms, fertility agents, DESI drugs, and drugs not covered under Part D.	Cohort	NR	Unspecified	NR	<45 years Overall: 6.8% G1: 2.1% G2: 7.7% 45-64 years Overall: 29.2% G1: 25.9% G2: 29.9% ≥65 years Overall: 63.9% G1: 72.0% G2: 62.4%	Overall: 61.3 G1: 58.2 G2: 61.9	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Taylor, Byrd, and Krueger, 2003 <sup>52</sup>	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	Prevention, detection and resolution of medication-related problems in high-risk patients in a rural community.	(1) Age ≥18 years; (2) Receiving care at participating clinic; (3) Identified as high risk for medication-related adverse event (defined as ≥3 of following risk factors: 5+ medications, 12+ doses per day, 4+ medications changes in the previous year, 3+ concurrent diseases, history of medication noncompliance, presence of drugs that require therapeutic monitoring)	(1) Significant cognitive impairment; (2) History of missed office visits; (3) Scheduling conflicts; (4) Life expectancy of <1 year	RCT: parallel, not clustered	12 months	Foundation or non-profit	Overall: 100	Overall: NR G1: 64.4 (13.7) G2: 66.7 (12.3)	Overall: NR G1: 63.6 G2: 72.2	White Overall: NR G1: 60.6 G2: 61.1



**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Touchette et al., 2012 <sup>53</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	To improve the safety of medication by reducing ADEs and DRPs; Also to reduce health care, especially ED visits.	1) Age ≥65 years; (2) Primary use of English for written and oral communication; (3) Telephone access for the study's duration; (4) Presence of ≥3 comorbid chronic conditions associated with increased health care use; (5) >2 visits to clinic provider during previous year; (6) >6 chronic prescription medications during 6 months before enrollment; (7) >1 recent situations placing patient at higher risk of DRP (i.e., ≥3 different health care providers visited in the last 12 months; any medication change, new physician visit, ED visit, hospitalization; or invasive procedure [requiring stopping medications] in previous 30 days).	1) Presence of a terminal condition with life expectancy of 6 months or less; 2) Previous enrollment in MTM program involving comprehensive medication review in previous 12 months.	RCT: parallel, clustered	6 months	Government	NR	Overall: 74.6 (6.7) G1: 74.5 (6.6) G2: 74.8 (6.8) G3: 74.6 (6.8)	Overall: 66.2 G1: 63.0 G2: 67.0 G3: 68.3	Black Overall: 51.2 G1: 48.3 G2: 49.1 G3: 56.3 Hispanic Overall: 4.4 G1: 6.2 G2: 2.3 G3: 4.8 Asian Overall: 0.8 G1: 0.5 G2: 0.9 G3: 1.0 American Indian Overall: 0.3 G1: 0 G2: 0 G3: 1.0

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup>  PREP	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	Authors describe the goal of pharmaceutical care as the "improvement of patient outcomes and quality of life." They add study objective to describe changes in intermediate and primary outcomes after the provision of pharmaceutical care.	Pharmacies: 1) Participation of pharmacists working >8 hours a week dispensing medications; 2) Agreement to participate in practice enhancement program; 3) Agreement to conform with professional standards developed by Alberta Pharmaceutical Association; 4) Alberta Blue Cross Billings represented at least one-third of pharmacy billings; 5) Located ≤200 miles of Edmonton. Patients: (1) >65 years; (2) Prescription medication coverage under Alberta Health and Wellness' Senior Health Plan; (3) Use ≥3 medications concurrently; (4) Residing in Alberta for 12 of 15 study months; (5) Agree to receive prescription medications only from study pharmacy during study period	Patients: 1) Individuals with terminal disease; 2) Could not communicate in English; 3) Could not complete telephone interviews.	RCT: cluster-randomized	12 to 13 months	Multiple (Government, foundation, and pharmaceutical)	NR	Mean (SD) Overall: 74 (NR) G1: 73.9 (6.1) G2: 73.2 (6.1)	Mean (SD) Overall: NR G1: 63.5 G2: 69.6	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Welch et al., 2009 <sup>56</sup>	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	To reduce mortality, inpatient hospitalizations, ED visits, and Part D-covered medication costs	1) MTM-eligible KPCO beneficiaries; 1) Had ≥2 chronic conditions, one of which was considered high risk; 2) Receiving 5 or more Part D-covered medications; 3) Likely to incur at least \$4000 in total costs for Part D-covered medications.	KPCO beneficiaries with end-stage renal disease (ESRD)	Cohort	180 days	Integrated health care system (Kaiser Permanente Colorado)	NR	Mean (SD) Overall: NR G1: 68.8 (10.7) G2: 68.9 (11.3) p=0.949	Overall: NR G1: 56.6 G2: 54.5 p=0.541	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Williams et al., 2004 <sup>57</sup>	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	To promote regimen changes to simplify regimens in elders taking multiple medications and to see whether these changes improved functioning.	1) Age ≥65 years; 2) Cognitively intact (no evidence of dementia or cognitive dysfunction in the medical record); 3) Minimum of 5 prescription medications, of which 2 had to be potentially problematic for geriatric patients.	NR	RCT: parallel, not clustered	6 weeks	Unspecified	NR	G1: 73.5 (5.9) G2: 73.9 (5.6)	G1: 65.1 G2: 50.6	White G1: 79.4 G2: 76.6 Non-White G1: 20.6 G2: 23.4

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Winston and Lin, 2009 <sup>58</sup>	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Describe experiences with MTM services delivered to beneficiaries of Mirixa's health plan clients	Patients who qualified for MTM services between April 1, 2007 and June 30, 2007. MTM qualification determined by each participating health plan; generally patients who had increased cardiovascular risk due to diabetes and HTN and/or dyslipidemia	(1) Patients whose coverage was discontinued for any reason; (2) Patients who received additional pharmacist-provided services (i.e., formulary review or other MTM) during intervention period.	Cohort	Unclear	Private MTM and pharmacy-delivered service provider	NR	Overall: NR G1: 67.4 (13.1) G2: 67.8 (12.8) G3: 66.5 (13.4)	Overall: NR G1: 70.4 G2: 70.5 G3: 69.5	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/Ethnicity %
Witry, Doucette, and Gainer, 2011 <sup>59</sup>	G1: PCM provided by community pharmacists to lowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	To decrease the risk of DRPs	(1) Patients ≥1 chronic condition (i.e., who filled a medication commonly used to treat 1 of 12 chronic conditions, as defined by Medicaid PCM program, at least twice during 3 months prior to screening date); (2) Must have filled ≥4 unique, nontopical medications during 3 months prior to screening date; (3) Patrons of study pharmacies, meaning that ≥50% of patients' prescription claims were paid to those pharmacies	See inclusion criteria	Cohort	21 months	Foundation or non-profit	NR	Mean (SD) Overall: NR G1: 54.1 (0.8) G2: 58.9 (7.51)	Mean (SD) Overall: NR G1: 80 G2: 68.1	NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Intervention s and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Wittayanukorn, 2013 <sup>60</sup>	G1: Intervention group: Pharmacist provided face-to-face MTM services for 30-60 minutes per encounter, not always including a follow-up visit G2: Control group: Patients who did not receive MTM services (economic analyses only)	To improve cardiovas- cular outcomes and improve direct and indirect costs among employees working for large, self- insured employers.	IG: Medical claims data with ICD-9-CM codes showing least 1 diagnosis code for CVD conditions. For economic analysis: enrollment in the insurance plan for ≥6 months before and ≥6m after date of first MTM encounter, ≥1 pharmacy claim for a CVD-related medication during 6 months prior to MTM visit and ≥1 during 6 months after MTM visit. Clinical analysis: ≥1 clinical measurement during the 6 months pre- MTM and ≥1 measure in the 6 months post-MTM. Control group: matched-pair patients who did not receive MTM services but were diagnosed with CVD conditions and had CVD-related medications.	Age <19 years	Cohort	6 months	Unspecified	Overall: NR G1: NR G2: NR	Overall: N-R G1:56.8 (9.3) G2: 56.9 (9.6) 61.3	Overall: N-R G1: IG: 61.9 G2: CG: 61.3	Overall: NR G1: NR G2: NR

**Table D1. Study and patient-level characteristics (continued)**

Author, Year Trial Name	Intervention s and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Yamada 2012 <sup>61</sup>	G1: Kaiser- Permanente MTM enrolled patients G2: Kaiser patients enrolled in Medicare part D, but not in MTM program matched to control on age, gender, region and DCG risk	Not stated, explicitly stated, but this was an evaluation of an existing MTM program.	Intervention Group: Enrolled in the MTM program between Jan 2006 and Dec 2010. Received a CMR. Met all matching criteria.	For both groups: Cancer diagnosis within one year of study entry Residing in a nursing home for more than 20 days, or less than 30 days at index date and a repeat stay within one year. Gap of more than 2 months of member- ship coverage within 12 months prior to index date.	Cohort	Up to 4 years	Other	Overall: NR G1: NR G2: NR	Overall: 75 (8) G1: NR G2: NR	Overall: 58 G1: NR G2: NR	Overall: NR G1: NR G2: NR

Abbreviations: ADE = adverse drug event; ART = antiretroviral therapy; BP = blood pressure; CAD = coronary artery disease; CDC = comprehensive diabetes care; CHF = chronic heart failure; CMR = comprehensive medication review; CMS = Centers for Medicare and Medicaid Services; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; DHHS = Department of Health and Human Services; DM = diabetes mellitus; DRP = drug-related problem; DTP = drug therapy problem; DVA = Department of Veterans' Affairs; ED = emergency department; ESRD = end-stage renal disease; FHCP = Federal Hazard Communication Program; FOM = Focus on Medicines; G = group; GP = general practitioner; HbA1c = hemoglobin A1c; HF = heart failure; HMO = health maintenance organization; HMR = home medication review; HTN = hypertension; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IG = intervention group; IQR = interquartile range; KPCO = Kaiser Permanente Colorado; LDL-C = low-density lipoprotein-cholesterol; MA-PD = Medicare Advantage Part D; MCO = managed care organization; Mg = milligram; mm Hg = milligrams mercury; mmol/L = milligrams per liter; MTM = medication therapy management; MTMP = Part-D medication therapy management; NR = not reported; NRCT = non-randomized controlled trial; OTC = over-the-counter; PCM = pharmaceutical case management; PCP = primary care provider; PDP = Medicare Part D Plan; PREP = Pharmaceutical Care Research and Education Project; QOL = quality of life; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; VA = Veterans' Administration.



**Table D2. Other patient-level and clinical characteristics**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	RCT: cluster- randomized	Pooled sample Patients living alone (%) Overall: NR G1: 37.2 G2: 37.7 Patients requiring help with daily activities (%) Overall: NR G1: 50.9 G2: 47.4 Northern Ireland Patients living alone (%) Overall: NR G1: 30.9 G2: 26.9 Patients requiring help with daily activities (%) Overall: NR G1: 43.1 G2: 55.7	NR	NR	Pooled sample Overall: NR G1: 7.1 (2.5) G2: 7.0 (2.5) p=NS Northern Ireland Overall: NR G1: 5.9 (1.9) G2: 6.7 (1.9) p<0.05	NR
Blakey, 2000 <sup>3</sup>	G1: Pharmacist evaluation plus usual medical care G2: Usual medical care	NRCT	NR	NR	NR	Overall: G1: 10.6 (SD not reported) G2: 7.4 (SD not reported) p< 0.0001	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Brummel, 2013 <sup>4</sup> ; Soliman, 2013 <sup>5</sup> ; Ramalho de Oliveira, 2010 <sup>6</sup>	G1: Fairview Pharmacy Services' MTM program (opt-in) G2: control group (did not opt-in)	Cohort	% Medicare G1: 12.73 G2: 20.59 % Medicaid G1: 5.45 G2: 1.96	Charlson index score G1: 3.7 G2: 2.72 p < 0.001 % with diabetic complications G1: 95.04 G2: 15.53 p < 0.001 % with insulin therapy G1: 53.33 G2: 34.95 P=0.005	Diabetes G1: 100 G2: 100	% on statins + others G1: 36.36 G2: 23.3 p=0.03 % on ACE/ARB+ others G1: 56.20 G2: 58.25	NR
Carter et al., 1997 <sup>7</sup> ; Barnette et al., 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	Cohort	NR	N of comorbid conditions Overall: NR G1: 3.5 (2.4) G2: 3.2 (2.0) p=0.47	No. (%) with controlled blood pressure at baseline	Overall: NR G1: 13 (52) G2: 14 (54)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Chrischilles et al., 2004 <sup>9</sup>	G1: PCM provided by pharmacists G2: Did not receive PCM services	Cohort	NR	NR	NR	Overall: NR G1: 7.5 (0.2) G2: 6.9 (0.1)	NR
Christensen et al., 2007 <sup>10</sup>	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	NRCT	NR	NR	Patients younger than 65: Hypertension G1: 48.1 G2: 47.9 G3: 46.4 >1 Condition G1: 42.8 G2: 34.0 G3: 38.3 Diabetes G1: 37 G2: 31.7 G3: 37.7  Patients older than 65: Hypertension G1: 62.5 G2: 41.5 G3: 48.5 Cardiovascular Disease G1: 55.0 G2: 48.4 G3: 50.2 >1 Condition G1: 46.3 G2: 39.7 G3: 39.9 Diabetes G1: 45.0 G2: 36.8 G3: 33.7	Patients younger than 65: G1: 40.3 (15.3) G2: 37.2 (17.5) G3: 36.9 (17.3)  Patients older than 65: G1: 41.7 (16.3) G2: 38.4 (16.3) G3: 41.7 (16.2)	Differences in % with selected conditions and in number of baseline medications were not significant among the three groups.

**Table D2. Other patient-level and clinical characteristics (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Design</b>	<b>Other Baseline Characteristics</b>	<b>Measure of Co- Morbidity</b>	<b>Diagnosed Conditions or Diseases (%)</b>	<b>Baseline Number of Prescribed Medications</b>	<b>Other Patient Clinical Characteristics</b>
Clifford et al., 2002 <sup>11</sup>	G1: Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	RCT: parallel, not clustered	NR	NR	Type 1 or 2 Diabetes Overall: 100 G1: 100 G2: 100 Type 1 Diabetes Overall: NR G1: 29.2 G2: 20.0 Type 2 Diabetes Overall: NR G1: 70.8 G2: 80.0 Hypertension: NR Dyslipidemia: NR	NR	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Fischer et al., 2000 <sup>12</sup>	G1: Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists. G2: Standard Community Pharmacy Practice G3: A set of refusers surveyed and included in some analyses among those who were at eligible clinics but initially declined to participate.	NRCT	% Married Overall: NR G1: 68 G2: 71 G3: 72 % Education < HS Overall: NR G1: 9 G2: 18 G3: 20 % Income < 10K Overall: NR G1: 3 G2: 9 G3: 9	% in Fair or Poor Health Overall: NR G1: 28 G2: 26 G3: 35	% Heart/HTN problems Overall: NR G1: 68 G2: 61 G3: 65 % Asthma/Lung Problems Overall: NR G1: 49 G2: 52 G3: 42	Overall: NR G1: 5.2 G2: 4.6 G3: 4.3	Mean N non- prescription meds: Overall: NR G1: 2.2 G2: 1.8 G3: 1.7
Fischer et al., 2002 <sup>13</sup>	Pharmaceutical care based on the Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care with no additional interventions.	NRCT	Annual health care charges Overall: NR G1: \$9,600 G2: \$11,000	Charlson Index G1: 1.2 G2: 1.3	Heart disease (%) Overall: NR G1: 43 G2: 40	Overall: NR G1: 9.1 G2: 9.4	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Fox et al., 2009 <sup>14</sup>	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	Cohort	NR	NR	Diabetes: 100	Number of PMPM in 2007 Overall: NR G1: 9.4 G2: 8.8	NR
Gattis et al., 1999 <sup>15</sup>	G1: Clinical pharmacy services, including not an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	RCT: parallel, clustered	NR	NR	Heart Failure Overall: 100 G1: 100 G2: 100	Overall: NR G1: 6.5 (25%: 5, 75%: 8) G2: 6 (25%: 4.5, 75%: 8)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Grymonpre, 2001 <sup>16</sup>	G1: Comprehensive drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensive drug therapy review only with referral to usual pharmacist.	RCT: parallel, not clustered	Education Overall: NR G1: <9th grade: 24.6% grades 9-12: 47.8% some college: 17.4% college graduate: 10.1% G2: <9th grade: 21.2% grades 9-12: 43.9% some college: 18.2% college graduate: 16.7%  Lives alone Overall: NR G1: 61% G2: 77%  Annual income Overall: NR G1: <\$15K: 40.6% \$15-30K: 27.5% >\$30K: 14.5% not available: 17.4% G2: <\$15K: 54.5% \$15-30K: 22.7% >\$30K: 6.0% not available: 16.7%  Financial hardship Overall: NR G1: 16% G2: 27%	Overall: NR G1: NR G2: NR	Overall: NR G1: NR G2: NR	Overall: NR G1: 5.9 (3.1) G2: 6.5 (3.4)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Hanlon, 1996 <sup>17</sup> Cowper, 1998 <sup>18</sup>	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	RCT: parallel, not clustered	Married (%) Overall: NR G1: 65.7 G2: 85.4 Mean years of education (SD) Overall: NR G1: 10.2 (3.8) G2: 9.9 (4.2)	N of chronic conditions Overall: NR G1: 9.2 (3.7) G2: 9.0 (3.0)	NR	Overall: NR G1: 7.6 (2.8) G2: 8.2 (2.7) These were limited to medications prescribed by a VA physician.	% of medications for which compliant Overall: NR G1: 73% G2: 74%
Hirsch, 2011 <sup>19</sup> Hirsch, 2009 <sup>20</sup> Rosenquist, 2010 <sup>21</sup> (methods)	G1: Patients served at nonpilot pharmacies G2: Patients served at pilot pharmacies	Cohort	NR	Overall: NR G1: NR G2: NR	Overall: NR G1: NR G2: NR	Overall: NR G1: 14.46 (5.16) G2: 14.79 (5.34) G3: 13.97 (5.74)	NR



**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Isetts et al., 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	Cohort	NR	Mean Number of Conditions Overall: NR G1: 6.4 (NR) G2: NR	NR	Overall: NR G1: 14% were age 65 or older G2: NR	These variables were not reported for the HEDIS comparison group other than a statement that says "...were similar to intervention group patients in terms of age, gender, and presence of study medical conditions." (bottom of page 205)
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup>	Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clustered	NR	More than 3 chronic diseases Overall: NR G1: 70% G2: 76%	NR	5 or more long-term medications (%) Overall: NR G1: 89 G2: 90	NR
Jeong, 2007 <sup>24</sup> Jeong, 2009 <sup>25</sup>	G1: Kaiser Permanente 2006 pharmacist-managed MTMP G2: Patients without Medicare Part D as their primary drug benefit and likely to incur drug costs greater than or equal to \$4000 per year with a similar disease burden	Cohort	NR	NR	Diabetes G1: 48 G2: 51  HTN G1: 86 G2: 83  CAD OR DM G1: 54 G2: 59	NR	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Jeong <sup>26</sup> Jeong, 2012 <sup>27</sup>	G1: Kaiser- Permanente MTM program participants (2010) G2: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	Cohort	NR	NR	NR	Overall: NR G1: 14.46 (5.16) G2: 14.79 (5.34) G3: 13.97 (5.74)	NR
Krska et al., 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	NR	Overall: NR G1: 3.9 (1.4) G2: 3.8 (1.4) p=0.968	NR	Repeat medicines on computer records Overall: NR G1: 7.4 (2.7) G2: 7.7 (2.8) p: 0.951	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Malone, 2000 <sup>29</sup>	G1:	RCT:	% Married	Mean number of	Hypertension	Overall: NR	NR
Ellis, 2000 <sup>30</sup>	Pharmaceutical	parallel,	Overall: NR	chronic conditions	Overall: NR	G1: 8.4 (4.4)	
Malone, 2001 <sup>31</sup>	care provided by	not	G1: 68.5	Overall: NR	G1: 68.5	G2: 8.0 (4.0)	
Ellis, 2000 <sup>32</sup>	clinical	clustered	G2: 67.8	G1: 4.0 (2.0)	G2: 66.5		
IMPROVE	pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care			G2: 3.8 (1.9)	Angina Overall: NR G1: 46.1 G2: 46.7 Hyperlipidemia Overall: NR G1: 39.8 G2: 43.1		

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Marques, 2013 <sup>33</sup>	G1: Intervention group: Dader method pharmacotherapy follow-up intervention monthly over 3- month follow-up period G2: Control group: monthly pharmacist visits without pharmacotherapy follow-up intervention	RCT: parallel, not clustered	Marital status Overall: NR G1: Married: 72.7% Not married: 27.3% G2: Married: 65.4% Not married: 34.6%  Schooling Overall: NR G1: Until 9 years: 59.1% >10 years: 40.9% G2: Until 9 years: 46.2% >10 years: 53.9%  Occupation Overall: NR G1: Homemaker: 50.0% Other: 50.0% G2: Homemaker: 30.8% Other: 69.2%  Religion Overall: NR G1: Catholic: 40.9% Other: 59.1% G2: Catholic: 80.8% Other: 19.2%	Overall: NR G1: NR G2: NR	Depression (mild, moderate, severe) Overall: NR G1: Mild: 18.2% Moderate: 59.1% Severe: 22.7% G2: Mild: 30.8% Moderate: 50.0% Severe: 19.2% p=0.59  Depression (first episode, relapse) Overall: NR G1: First episode: 31.8% Relapse: 68.2% G2: First episode: 23.1% Relapse: 76.9% p=0.53	Overall: NR G1: 1.5 (0.6) G2: 1.7 (0.8)	Mean treatment time (on drugs) before starting study: G1: 60 days G2: 30 days p=0.53

Table D2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup>	<b>CHF</b> G1: enrolled in Medicare PDP receiving MTM with a CMR G2: enrolled in PDP receiving MTM, no CMR G3: enrolled in MA-PD receiving MTM with CMR G4: enrolled in MA-PD, receiving MTM, no CMR <b>COPD</b> G5: enrolled in Medicare PDP receiving MTM with a CMR G6: enrolled in PDP receiving MTM, no CMR G7: enrolled in MA-PD receiving MTM with CMR G8: enrolled in MA-PD, receiving MTM, no CMR <b>Diabetes</b> G9: enrolled in Medicare PDP receiving MTM with a CMR G10: enrolled in PDP receiving MTM, no CMR G11: enrolled in PA-PD receiving	Cohort	<b>LIS eligible</b> G1: 71.1% G2: 44.1% G3: 22.4% G4: 36.7% G5: 77.0% G6: 54.1% G7: 25.0% G8: 38.9% G9: 68.0% G10: 42.8% G11: 22.5% G12: 36.1% G13: 52.1% G14: 37.0% G15: 56.1% G16: 41.7% G17: 56.4% G18: 36.5% <b>Disabled</b> G1: 27.9% G2: 15.6% G3: 9.8% G4: 14.0% G5: 37.1% G6: 25.4% G7: 12.2% G8: 18.0% G9: 31.0% G10: 18.3% G11: 10.7% G12: 15.3% G13: 18.5% G14: 14.6% G15: 27.1% G16: 20.4% G17: 24.3% G18: 16.7%	NR	<b>CHF</b> G1-G4, G13, G14: 100.0% <b>COPD</b> G5-G8, G15, G16: 100.0% <b>Diabetes</b> G9-G12, G17, G18: 100.0%	<b>≤8 Maintenance Drugs</b> G1: 8.2% G2: 17.4% G3: 15.5% G4: 20.6% G5: 11.5% G6: 23.5% G7: 22.5% G8: 30.3% G9: 16.8% G10: 29.7% G11: 27.6% G12: 34.7% G13: 20.8% G14: 26.3% G15: 28.7% G16: 34.7% G17: 29.0% G18: 33.0% <b>9-10 Maintenance Drugs</b> G1: 17.4% G2: 22.4% G3: 21.9% G4: 23.4% G5: 19.1% G6: 21.9% G7: 22.3% G8: 22.8% G9: 26.6% G10: 27.9% G11: 28.1% G12: 27.8% G13: 27.0% G14: 29.3% G15: 25.9% G16: 27.9%	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup> (continued)	MTM with CMR G12: enrolled in MA-PD, receiving MTM, no CMR <b>Comparison - CHF</b> G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care <b>Comparison - COPD</b> G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care <b>Comparison - Diabetes</b> G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care					G17: 34.0% G18: 35.7% <b>11-12 Maintenance Drugs</b> G1: 22.0% G2: 22.1% G3: 24.4% G4: 23.0% G5: 21.9% G6: 19.8% G7: 22.5% G8: 19.3% G9: 24.0% G10: 20.5% G11: 22.4% G12: 19.7% G13: 22.4% G14: 21.4% G15: 19.7% G16: 18.8% G17: 19.4% G18: 18.2% <b>&gt;12 Maintenance Drugs</b> G1: 52.4% G2: 38.0% G3: 38.2% G4: 33.0% G5: 47.4% G6: 34.9% G7: 32.7% G8: 27.6% G9: 32.6% G10: 21.9% G11: 22.0% G12: 17.8% G13: 29.8% G14: 23.0%	

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup> (continued)						G15: 25.7% G16: 18.6% G17: 17.6% G18: 13.1%	
McDonough et al., 2005 <sup>36</sup>	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of doses, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster- randomiz ed	NR	NR	NR	Overall: G1: 5.6 (3.1) G2: 7.0 (3.2)	At baseline, the treatment group was significantly less likely to report alcohol use and more likely to be post-menopausal.

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Moczygemba et al., 2011 <sup>37</sup> ; Moczygemba et al., 2008 <sup>38</sup>	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	Cohort	NR	Number of chronic dx Mean (SD) Overall: NR G1: 6.5 (2.3) G2: 7.0 (2.1) p: 0.18	Hypertension Overall: NR G1: 95 G2: 95 Dyslipidemia Overall: NR G1: 77 G2: 87 Diabetes Overall: NR G1: 55 G2: 60	Mean (SD) Overall: NR G1: 13.0 (3.2) G2: 13.2 (3.4)	MRCI Mean (range) Overall: NR G1: 21.5 (8-43) G2: 22.8 (9-43) p: 0.32
Moore, 2013 <sup>40</sup>	G1: MTM program (opt-in) G2: control group (refusers)	Cohort	NR	NR	Hypertension G1: 87.6 G2: 86.4  Dyslipidemia G1: 67.3 G2: 58.8  Diabetes G1: 27.0 G2: 30.4	Mean (SE) G1: 55.3 (0.485) G2: 69.2 (0.656) p<0.001	NR



**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology- trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	RCT: cluster- randomized	Mean Time on Hemodialysis in years (SD) Overall: 2.6 (2.0) G1: 2.8 (1.8) G2: 2.4 (2.2)	NR	ESRD etiology - Diabetes mellitus Overall: 43.3 G1: 38.6 G2: 48.9 ESRD etiology - Hypertension Overall: 28.9 G1: 31.6 G2: 25.5 ESRD etiology - Other Overall: 27.9 G1: 29.8 G2: 25.5	Overall: 10 (4) G1: 10 (4) G2: 10 (4)	NR
Park et al., 1996 <sup>43</sup>	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	RCT: parallel, not clustered	NR	NR	NR	NR	Mean number of antihypertensives Overall: NR G1: 1.4 G2: 1.3

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Pindolia et al., 2009 <sup>44</sup>	G1: Telephone- based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors). G2: Usual medical care (opt-out)	Cohort	2006 Part D type (%) <u>Donut hole</u> G1: 68 G2: 60 <u>Nondonut hole or coverage gap</u> G1: 6 G2: 8 <u>Low income subsidy</u> G1: 18 G2: 24 <u>Institutionalized</u> G1: 8 G2: 7 Overall p: 0.054 2007 Part D type (%) <u>Donut hole</u> G1: 93 G2: 63 <u>Nondonut hole or coverage gap</u> G1: 1 G2: 9 <u>Low income subsidy</u> G1: 6 G2: 26 <u>Institutionalized</u> G1: 0 G2: 2 Overall p: 0.001	2006 N of qualifying diseases (mean, SD) Overall: NR G1: 5.9 (2.2) G2: 5.6 (2.1) p: 0.047 2007 N of qualifying diseases (mean, SD) Overall: NR G1: 5.8 (2.0) G2: 5.9 (2.0) Overall p: 0.701	NR	2006 Unique prescriptions filled (mean, SD) Overall: NR G1: 16.7 (7.2) G2: 14.8 (6.1) p: 0.001 2007 Unique prescriptions filled (mean, SD) Overall: NR G1: 14.4 (6.2) G2: 14.9 (6.2) p: 0.223	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Planas et al., 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clustered	Overweight (25-29.9 kg/m <sup>2</sup> ), %: Overall: NR G1: 15.6 G2: 42.1 p: NR Obese (≥30 kg/m <sup>2</sup> ), %: Overall: NR G1: 68.8 G2: 47.4 p: NR	NR	Hypertension: 100 Diabetes: 100	NR	NR
Roughead et al., 2009 <sup>46</sup>	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	Cohort	Socioeconomic index of disadvantage (%) <u>Lowest disadvantage</u> Overall: NR G1: 31 G2: 25 <u>Medium/low disadvantage</u> Overall: NR G1: 25 G2: 25 <u>Medium/high disadvantage</u> Overall: NR G1: 24 G2: 25 <u>Highest disadvantage</u> Overall: NR G1: 20 G2: 25 Overall p: 0.01	N of co-morbidities (median, SD) Overall: NR G1: 8 (2) G2: 7 (2) p: <0.0001	NR	N (range) of prescriptions in last year Overall: NR G1: 95 (69-123) G2: 76 (54-104) p: <0.0001	Changes in medicines during 6-month period in previous year (N, SD) Overall: NR G1: 3 (2-6) G2: 3 (1-5) p: <0.0001

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Sellors et al., 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: cluster-randomized	Education: highest level attained (%) <u>Elementary School</u> Overall: NR G1: 26.9 G2: 24.1 <u>High school graduate</u> Overall: NR G1: 50.8 G2: 51.0 <u>Some college</u> Overall: NR G1: 22.2 G2: 24.9 % married FPL/ common-law spouse Overall: NR G1: 58.2 G2: 63.1	NR	Hypertension G1: 54.3 G2: 55.7 Osteoarthritis G1: 46.4 G2: 48.3 IHD G1: 36.0 G2: 38.0	NR	NR
Sellors, 2003 <sup>47</sup>	G1: Pharmaceutical consultation G2: Usual care	RCT: parallel, not clustered	NR	NR	NR	NR	NR
Shimp, 2012 <sup>49</sup>	G1: MTM program for University of Michigan beneficiaries, entitled Focus on Medicines G2: Usual care (not described)	RCT: parallel, not clustered	NR	NR	Overall: NR G1: Dyslipidemia: 44% Hypertension: 31% Gastroesophageal reflux disease: 22% G2: NR	Overall: NR G1: 9.2 (3.2) G2: NR	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Sidel et al., 1990 <sup>50</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clustered	Income (%) Overall: NR <u>Under \$5000</u> G1: 23.3 G2: 22.2 <u>\$5000-\$15000</u> G1: 61.0 G2: 63.3 <u>&gt;\$15000</u> G1: 15.9 G2: 14.4  Education: % with 9 or more years Overall: NR G1: 62.2 G2: 54.8 % with Self-Assessed Health Fair or Poor Overall: NR G1: 44.0 G2: 42.7 % with Problems with Activities of Daily Living Overall: NR G1: 33.0 G2: 34.6 % with Symptoms of Depression Overall: NR G1: 10.8 G2: 22.6 % with Cognitive Impairment Overall: NR G1: 15.4 G2: 21.4	Number of medical conditions (%) Overall: NR <u>None</u> G1: 3.3 G2: 2.9 <u>1-3</u> G1: 58.2 G2: 70.2 <u>4 or more</u> G1: 38.5 G2: 29.9	NR	Overall: 65.3% (mean 2.4, range 1- 10) G1: NR G2: NR	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Staresinic et al., 2007 <sup>51</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	Cohort	Dual eligible (%) G1: 6 G2: 25	NR	Hypertension/CHF Overall: 96.1 G1: 96.5 G2: 96.0 Hyperlipidemia Overall: 70.7 G1: 75.9 G2: 69.8 Diabetes Overall: 51.2 G1: 51.4 G2: 51.1	NR	NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup>	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	RCT: parallel, not clustered	Median years of education (Range) Overall: NR G1: 12 (4-16) G2: 12 (8-16) No insurance coverage for Rx medications Overall: 17% G1: NR G2: NR Marital status: % married Overall: NR G1: 75.8 G2: 72.2	NR	Hypertension: Overall: 51 Dyslipidemia: Overall: 40 Diabetes Mellitus: Overall: 27	Mean N of medications (SD) Overall: NR G1: 6.3 (2.2) G2: 5.7 (1.7)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Touchette et al., 2012 <sup>53</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clustered	NR	Number of comorbidities Overall: 4.9 (1.6) G1: 5.0 (1.6) G2: 5.0 (1.6) G3: 4.9 (1.6)	Hypertension Overall: 90.9 G1: 89.6 G2: 90.8 G3: 92.3 Dyslipidemia Overall: 77.7 G1: 76.3 G2: 80.7 G3: 76.0 Arthritis Overall: 70.2 G1: 68.2 G2: 73.4 G3: 68.8	Mean (SD) Overall: 8.0 (2.4) G1: 8.2 (2.6) G2: 7.7 (2.3) G3: 8.0 (2.3)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup>	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	RCT: cluster- randomized	All Overall %'s NR Education (%) <u>Some high school</u> G1: 46 G2: 50 <u>Completed high school</u> G1: 17 G2: 18 <u>Some trade school/college</u> G1: 19 G2: 17 <u>Completed college</u> G1: 17 G2: 14 Annual income (%; CAD) <u>&lt; \$20,000</u> G1: 40 G2: 40 <u>\$20,000 - \$39,000</u> G1: 40 G2: 43 <u>\$40,000 - \$59,000</u> G1: 11 G2: 11 <u>≥\$60,000</u> G1: 8 G2: 5 Living situation (%) <u>Live alone</u> G1: 34 G2: 29 <u>Live with spouse/partner</u> G1: 57 G2: 61 <u>Live with other relative</u> G1: 7 G2: 6 <u>Live with unrelated person</u> G1: 2 G2: 2	Mean number of conditions (SD) G1: 3.3 (1.7) based on study interview and 10 (4.8) based on data collected by treatment pharmacist. G2: NR	NR	Mean (SD) Overall: NR G1: 4.7 (2.8) G2: 3.9 (2.5) p < 0.05	NR



**Table D2. Other patient-level and clinical characteristics (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Design</b>	<b>Other Baseline Characteristics</b>	<b>Measure of Co- Morbidity</b>	<b>Diagnosed Conditions or Diseases (%)</b>	<b>Baseline Number of Prescribed Medications</b>	<b>Other Patient Clinical Characteristics</b>
Welch et al., 2009 <sup>56</sup>	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	Cohort	NR	NR	NR	NR	Mean Chronic Disease Score (SD) (ranges from 0-35, with larger scores indicating increasing burden of chronic diseases under treatment) Overall: NR G1: 8.8 (3.1) G2: 8.2 (3.5) p: 0.016 NOTE: Difference represents, on average, less than one additional chronic disease per patient  Median (IQR) baseline medication cost (\$) G1: 3149 (2378 to 4806) G2: 3186 (2363 to 5123) Mean baseline medication cost (\$) (no SD reported) G1: 4465 G2: 5197 p: 0.525

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Williams et al., 2004 <sup>57</sup>	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clustered	<u>Education (%)</u> Had not completed high school G1: 33.3 G2: 32.5 High school or some college G1: 25.4 G2: 19.5 Completed college G1: 41.3 G2: 48.1  <u>Marital status (%)</u> Married G1: 47.6 G2: 53.2 Living Alone G1: 38.1 G2: 33.8	NR	NR	G1: 6.6 (1.8) G2: 7.7 (2.3)	Baseline number of non-prescription drugs G1: 5.1 (3.1) G2: 4.6 (2.5)

**Table D2. Other patient-level and clinical characteristics (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Design</b>	<b>Other Baseline Characteristics</b>	<b>Measure of Co- Morbidity</b>	<b>Diagnosed Conditions or Diseases (%)</b>	<b>Baseline Number of Prescribed Medications</b>	<b>Other Patient Clinical Characteristics</b>
Winston and Lin, 2009 <sup>58</sup>	G1: MTM provided in a community pharmacy (i.e., care in face-to- face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist- staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient- specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	NR	NR	NR	Overall: NR G1: 9.8 (3.2) G2: 9.8 (2.9) G3: 9.7 (2.9)	NR

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Witry, Doucette, and Gainer, 2011 <sup>59</sup>	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual- group insurance	Cohort	NR	NR	NR	Mean (SD) Overall: NR G1: 7.9 (3.8) G2: 4.7 (2.2) p: <0.001	NR
Wittayanukorn, 2013 <sup>60</sup>	G1: Intervention group: Pharmacist provided face-to- face MTM services for 30-60 minutes per encounter, not always including a follow-up visit G2: Control group: Patients who did not receive MTM services (economic analyses only)	Cohort	NR	Charlson comorbidity index score (Range) Overall: NR G1: IG: 1.00 (0-7) G2: CG: 0.90 (0-5)	Hypertension Overall: NR G1: IG: 87.3 G2: CG: 79.0  Dyslipidemia Overall: NR G1: IG: 74.6 G2: CG: 72.6  Hypertension with dyslipidemia Overall: NR G1: IG: 61.9 G2: CG: 51.6	Number of CVD- related medications (SD): G1: 1.9(0.9) G2: 1.7(1.1)	Number of pharmacy claims (SD) Overall: NR G1: IG: 2.9 (2.1) G2: CG: 2.4 (2.0)  Mean number of all- cause medical claims (SD): G1: 5.2 (6.1) G2: 4.5(3.1)

**Table D2. Other patient-level and clinical characteristics (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co- Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Yamada 2012 <sup>61</sup>	G1: Kaiser- Permanente MTM enrolled patients G2: Kaiser patients enrolled in Medicare part D, but not in MTM program matched to control on age, gender, region and DCG risk	Cohort	NR	Mean Dx CG score: Overall: 1.8 (1.3) Mean Charlson comorbidity score G1: 2.1 (2.7) G2: 1.3 (2.0) p< 0.001  Hospitalization rate G1: 27% G2: 22% p< 0.001	% with CHF: G1: 13 G2: 7 p< 0.001  % with ESRD: G1: 20% G2: 13% p< 0.001  % with Diabetes G1: 30% G2: 15% p< 0.001	Overall: NR G1: NR G2: NR	Drug Costs: G1: \$4,220 G2: \$921 p<0.001

Abbreviations: ACE/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CAD = coronary artery disease; CMR = comprehensive medication review; DM = diabetes mellitus; dx = diagnosis; ESRD = end-stage renal disease; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HTN = hypertension; IG = intervention group; IQR = interquartile range; MA-PD = Medicare Advantage Part D; MRCI = Medication Regimen Complexity Index; MTM = medication therapy management; MTMP = medication therapy management program; NR = not reported; NS = not sufficient; NRCT = non-randomized controlled trial; PCM = pharmaceutical case management; PCP = primary care provider; PDP = prescription drug plan; PMPM = prescriptions per member per month; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; VA = Veterans Affairs

**Table D3. Number of study participants**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Bernsten, 2001 <sup>1</sup> ; Sturgess, 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	RCT: cluster- randomized	Pooled sample Overall: 2,454 G1: 1,290 G2: 1,164	Overall: 2,454 G1: 1,290 G2: 1,164	Overall: 1,340 G1: 704 G2: 636	Overall: 1,340 G1: 704 G2: 636
Blakey, 2000 <sup>3</sup>	G1: Pharmacist evaluation plus usual medical care G2: Usual medical care	NRCT	Overall: 178 G1: 106 G2: 72	Overall: 178 G1: 106 G2: 72	Overall: 178 G1: 106 G2: 72	Overall: 178 G1: 106 G2: 72
Brummel, 2013 <sup>4</sup> ; Soliman, 2013 <sup>5</sup> ; Ramalho de Oliveira, 2010 <sup>6</sup>	G1: Fairview Pharmacy Services' MTM program (opt-in) G2: control group (did not opt- in)	Cohort	Overall: 248 G1: 127 G2: 121	Overall: 224 G1: 121 G2: 103	Overall: 224 G1: 121 G2: 103	Overall: 224 G1: 121 G2: 103
Carter 1997 <sup>7</sup> , Barnette 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	Cohort	Overall: NR G1: NR G2: NR	Overall: 55 G1: 29 G2: 26	Overall: 51 G1: 25 G2: 26	Overall: 51 G1: 25 G2: 26
Chrischilles, 2004 <sup>9</sup>	G1: PCM provided by pharmacists G2: Did not receive PCM services	Cohort	Overall: 2,211 G1: 524 G2: 1,687	Overall: 2,211 G1: 524 G2: 1,687	Overall: 2,211 G1: 524 G2: 1,687	Overall: 2,211 G1: 524 G2: 1,687

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Christensen, 2007 <sup>10</sup>	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	NRCT	Overall: NR G1: 1,000 G2: NR	Overall: 1,639 G1: 80 G2: 689 G3: 870	Overall: 1,589 G1: 30 G2: 689 G3: 870	Overall: 1,626 G1: 67 G2: 689 G3: 870
Clifford, 2002 <sup>11</sup>	G1: Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	RCT: parallel, not clustered	NR	Overall: 73 G1: 48 G2: 25	NR	Overall: 73 G1: 48 G2: 25
Fischer, 2000 <sup>12</sup>	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists G2: Standard community pharmacy practice G3: Patients at eligible clinics who declined to receive intervention but were included in some analyses.	NRCT	Overall: 1,051 G1: NR G2: NR	Overall: 748 G1: 244 G2: 504	Overall: 578 G1: 210 G2: 368	Overall: 578 G1: 210 G2: 368

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Fischer, 2002 <sup>13</sup>	G1: Pharmaceutical care based on Encara Practice System provided by pharmacists. Pharmacist-physician communication about pharmacist-identified DTPs. G2: Usual care with no additional interventions	NRCT	Overall before death, disenrollment, or discontinuation of pharmacy benefits: 1,070 G1: 553 G2: 517  Overall after death, disenrollment, or discontinuation of pharmacy benefits: 921 G1: 477 G2: 444	Overall: 675 (enrolled + control) or 921 (intention-to-treat) G1: 231 (enrolled) or 477 (intention-to-treat: enrolled +refused) G2: 444	Overall: 675 (enrolled + control) or 921 (intention-to-treat) G1: 231 (enrolled) or 477 (intention-to-treat: enrolled +refused) G2: 444	Overall: 675 (enrolled + control) or 921 (intention-to-treat) G1: 231 (enrolled) or 477 (intention-to-treat: enrolled +refused) G2: 444
Fox, 2009 <sup>14</sup>	G1: Florida Health Care Plans (FHCP) MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	Cohort	Overall: 311 G1: 255 G2: 56	Overall: 311 G1: 255 G2: 56	NR	Overall: 311 G1: 255 G2: 56
Gattis, 1999 <sup>15</sup>	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	RCT: parallel, not clustered	Overall: 192 G1: NA G2: NA	Overall: 181 G1: 90 G2: 91	Overall: 181 G1: 90 G2: 91	Overall: 181 G1: 90 G2: 91



**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Grymonpre, 2001 <sup>16</sup>	G1: Comprehensive drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensive drug therapy review only with referral to usual pharmacist	RCT: parallel, not clustered	Overall: 190 G1: NR G2: NR	Overall: 131 G1: 69 G2: 66	Overall: 114 G1: 56 G2: 58	Overall: 131 G1: 69 G2: 66
Hanlon, 1996 <sup>17</sup> Cowper, 1998 <sup>18</sup>	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	RCT: parallel, not clustered	Overall: 228 G1: NR G2: NR	Overall: 208 G1: 105 G2: 103	Overall: 172 G1: 88 G2: 84	Overall: 208 G1: 105 G2: 103
Hirsch, 2011 <sup>19</sup> Hirsch, 2009 <sup>20</sup> Rosenquist, 2010 <sup>21</sup> (methods)	G1: Patients served at nonpilot pharmacies G2: Patients served at pilot pharmacies	Cohort	Overall: 2,234 G1: 132 G2: 2,102	Overall: 2,234 G1: 132 G2: 2,102	Overall: 2,234 G1: 628 G2: 1,606	Overall: 2,234  2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606
Isetts, 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	Cohort	Overall: NR G1: 2,834 G2: NR	Overall: NR G1: 285 G2: NR	Overall: NR G1: NR G2: NR	For goals of drug therapy and number of DTPs resolved Overall: 541 G1: 285 G2: 256  For HEDIS outcomes Overall: 154 G1: 128 G2: 126

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Jameson, 1995 <sup>23</sup>	G1: Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clustered	NR	Overall: 64 G1: 34 G2: 30	Overall: 56 G1: 27 G2: 29	Overall: 56 G1: 27 G2: 29
Jeong, 2007 <sup>24</sup> Jeong, 2009 <sup>25</sup>	G1: Kaiser Permanente 2006 pharmacist-managed MTMP G2: Patients without Medicare Part D as their primary drug benefit and likely to incur drug costs greater than or equal to \$4000 per year with a similar disease burden.	Cohort	Overall: 5,031 G1: 2,780 G2: 2,251	Overall: 5,031 G1: 2,780 G2: 2,251	Overall: 5,031 G1: 2,780 G2: 2,251	For HbA1c analysis Overall: 2,464 G1: 1,323 G2: 1,141 For LDL analysis Overall: 2,838 G1: 1,515 G2: 1,323 For BP analysis Overall: 2,283 G1: 1,301 G2: 982
Jeong <sup>26</sup> Jeong, 2012 <sup>27</sup>	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	Cohort	Overall: 39,680 G1: NA G2: NA G3: NA	Overall: 39,680 G1: 23,638 G2: 14,232 G3: 1,810	Overall: 39,680 G1: 23,638 G2: 14,232 G3: 1,810	Overall: 39,680 G1: 23,638 G2: 14,232 G3: 1,810
Krska, 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	Overall: 420 G1: NA G2: NA	Overall: 381 G1: 192 G2: 189	Overall: 332 G1: 168 G2: 164	Overall: 332 G1: 168 G2: 164

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Malone, 2000 <sup>29</sup> ; Ellis, 2000 <sup>30</sup> (interventions); Malone, 2001 <sup>31</sup> (detailed QOL outcomes); Ellis, 2000 <sup>32</sup> (dyslipidemia subgroup intermediate and utilization outcomes);	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	RCT: parallel, not clustered	NR	Overall: 1,054 G1: 523 G2: 531	Overall: 931 G1: 447 G2: 484	Overall: 1,043 G1: 523 G2: 531
Marques, 2013 <sup>33</sup>	G1: Intervention group: Dader method pharmacotherapy follow-up intervention monthly over 3-month follow-up period G2: Control group: monthly pharmacist visits without pharmacotherapy follow-up intervention	RCT: parallel, not clustered	Overall: 58 G1: NA G2: NA	Overall: 58 G1: 31 G2: 27	Overall: 48 G1: 26 G2: 22	Overall: 48 G1: 26 G2: 22

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Marrufo, 2013 <sup>34</sup> , Perlroth, 2013 <sup>35</sup>	<p><b>CHF</b></p> <p>G1: enrolled in Medicare PDP receiving MTM with a CMR</p> <p>G2: enrolled in PDP receiving MTM, no CMR</p> <p>G3: enrolled in MA-PD receiving MTM with CMR</p> <p>G4: enrolled in MA-PD, receiving MTM, no CMR</p> <p><b>COPD</b></p> <p>G5: enrolled in Medicare PDP receiving MTM with a CMR</p> <p>G6: enrolled in PDP receiving MTM, no CMR</p> <p>G7: enrolled in MA-PD receiving MTM with CMR</p> <p>G8: enrolled in MA-PD, receiving MTM, no CMR</p> <p><b>Diabetes</b></p> <p>G9: enrolled in Medicare PDP receiving MTM with a CMR</p> <p>G10: enrolled in PDP receiving MTM, no CMR</p> <p>G11: enrolled in PA-PD receiving MTM with CMR</p> <p>G12: enrolled in MA-PD, receiving MTM, no CMR</p> <p><b>Comparison - CHF</b></p> <p>G13: enrolled in PDP, usual care</p> <p>G14: enrolled in MA-PD, usual care</p> <p><b>Comparison - COPD</b></p> <p>G15: enrolled in PDP, usual care</p> <p>G16: enrolled in MA-PD, usual care</p> <p><b>Comparison - Diabetes</b></p> <p>G17: enrolled in PDP, usual care</p> <p>G18: enrolled in MA-PD, usual care</p>	Cohort	NR	NR	NR	<p>G1: 12,658</p> <p>G2: 103,080</p> <p>G3: 11,260</p> <p>G4: 62,983</p> <p>G5: 16,372</p> <p>G6: 110,042</p> <p>G7: 10,575</p> <p>G8: 64,637</p> <p>G9: 16,545</p> <p>G10: 149,803</p> <p>G11: 13,527</p> <p>G12: 95,299</p> <p>G13: 156,441</p> <p>G14: 51,938</p> <p>G15: 184,350</p> <p>G16: 73,623</p> <p>G17: 133,925</p> <p>G18: 53,912</p>

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
McDonough, 2005 <sup>36</sup>	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of doses, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster-randomized	Overall: 163 G1: NR G2: NR	Overall: 96 G1: 70 G2: 26	Overall: 80 G1: 61 G2: 19	Overall: 80 G1: 61 G2: 19
Moczygemba, 2011 <sup>37</sup>	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	Cohort	Overall: 1,971	Overall: 132	NR	Overall: 120
Moczygemba, 2008 <sup>38</sup>			G1: 95	G1: 72		G1: 60
Moczygemba, 2012 <sup>39</sup>			G2: 1,876	G2: 60		G2: 60
Moore, 2013 <sup>40</sup>	G1: MTM program (opt-in) G2: control group (refusers)	Cohort	Overall: 13,092 G1: 2,966 G2: 10,126	Overall: 8,723 G1: 2,260 G2: 6,463	Overall: 8,723 G1: 2,260 G2: 6,463	Overall: 4,500 G1: 2,250 G2: 2,250
Pai, 2009 <sup>41</sup> ; Pai, 2009 <sup>42</sup>	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	RCT: cluster-randomized	NR	Year 1 Overall: 104 G1: 57 G2: 47  Year 2 Overall: 107 G1: 61 G2: 46	Year 1 Overall: 80 G1: 44 G2: 36  Year 2 Overall: 46 G1: 24 G2: 22	Year 1 Overall: 80 G1: 44 G2: 36  Year 2 Overall: 46 G1: 24 G2: 22

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Park, 1996 <sup>43</sup>	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	RCT: parallel, not clustered	Overall: NR G1: NR G2: NR	Overall: 64 G1: 32 G2: 32	Overall: 53 G1: 27 G2: 26	Overall: 53 G1: 27 G2: 26
Pindolia, 2009 <sup>44</sup>	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors). G2: Usual medical care (refusers)	Cohort	Overall: 2,696 G1: NA G2: NA  2006 Overall: 1,388 G1: NA G2: NA  2007 Overall: 1,308 G1: NA G2: NA	2006 Overall: 1,388 G1: 307 G2: 1,081  2007 Overall: 1,308 G1: 228 G2: 1,080	NR	2006 Overall: 1,373 G1: 292 G2: 1,081  2007 Overall: 1,308 G1: 228 G2: 1,080
Planas, 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clustered	Overall: 52 G1: 32 G2: 20	Overall: 52 G1: 32 G2: 20	Overall: 33 G1: 20 G2: 13	Overall: 40 G1: 25 G2: 15

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Roughead, 2009 <sup>46</sup>	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	Cohort	NR	Overall: 5,717 G1: 273 G2: 5,444	NA	Overall: 5,717 G1: 273 G2: 5,444
Sellors, 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes	RCT: cluster-randomized	Overall: 1,279 G1: NR G2: NR	Overall: 889 G1: 431 G2: 458	Overall: NR G1: 379 G2: 409	NR
Sellors, 2003 <sup>47</sup>	G1: Pharmaceutical consultation G2: Usual care	RCT: parallel, not clustered	Overall: 191 G1: NR G2: NR	Overall: 132 G1: 66 G2: 66	Overall: 121 G1: 61 G2: 60	Overall: 121 G1: 61 G2: 60
Shimp, 2012 <sup>49</sup>	G1: MTM program for University of Michigan beneficiaries, entitled FOM G2: Usual care (not described)	RCT: parallel, not clustered	Overall: 1,862 G1: NR G2: NR	Overall: 133 G1: NR G2: NR	Overall: 128 G1: NR G2: NR	Overall: NR G1: NR G2: NR
Sidel, 1990 <sup>50</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clustered	Overall: 2,540 G1: NR G2: NR	Overall: 284 G1: 141 G2: 143	Overall: NR G1: 113 G2: 104	Overall: NR G1: 92 G2: 104

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Staresinic, 2007 <sup>51</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	Cohort	Overall: 1,890 G1: NA G2: NA	Overall: 1,826 G1: 282 G2: 1,544	Overall: 1,682 G1: 138 G2: 1,544	Overall: 1,826 G1: 282 G2: 1,544
Taylor, 2003 <sup>52</sup>	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	RCT: parallel, not clustered	Overall: NR G1: NR G2: NR	Overall: 81 G1: NR G2: NR	Overall: 69 G1: 33 G2: 36	Overall: 69 G1: 33 G2: 36
Touchette, 2012 <sup>53</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clustered	Overall: 1,941 G1: NA G2: NA	Overall: 637 G1: 211 G2: 218 G3: 208	Overall: 556 G1: 183 G2: 190 G3: 183	Overall: 637 G1: 211 G2: 218 G3: 208
Volume, 2001, PREP (Pharmaceutical Care Research and Education Project), #2579 and #2631 Kassam	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	RCT: cluster- randomized	Overall: Approximately 960 G1:NR G2: NR	Overall: 363 G1: NR G2: NR	Overall: 292 G1: NR G2: NR	Overall: 292 G1: 159 G2: 204



**Table D3. Number of study participants (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Design</b>	<b>N Eligible</b>	<b>N Randomized (trials) or N Enrolled (observational studies)</b>	<b>N Completers</b>	<b>N Analyzed</b>
Welch, 2009 <sup>56</sup>	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	Cohort	Overall: 1,231 G1: NR G2: NR	Overall: 904 G1: 539 G2: 365	Overall: 795 G1: 459 G2: 336	Overall: 795 G1: 459 G2: 336
Williams, 2004 <sup>57</sup>	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clustered	Overall: 144 G1: NA G2: NA	Overall: 140 G1: 63 G2: 77	Overall: 133 G1: 57 G2: 76	Overall: 133 G1: 57 G2: 76
Winston, 2009 <sup>58</sup>	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	Overall: 101,846 G1: 33,954 G2: 3,961 G3: 63,931	Overall: 95,736 G1: 31,347 G2: 3,787 G3: 60,602	Overall: NR G1: NR G2: NR	Overall: 73,793 G1: 21,336 G2: 3,436 G3: 49,021

**Table D3. Number of study participants (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Design	N Eligible	N Randomized (trials) or N Enrolled (observational studies)	N Completers	N Analyzed
Witry, 2011 <sup>59</sup>	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	Cohort	Overall: NR G1: NR G2: 250	Overall: 615 G1: 524 G2: 91	Overall: 615 G1: 524 G2: 91	Overall: 615 G1: 91 G2: 524
Wittayanukorn, 2013 <sup>60</sup>	G1: Intervention group: Pharmacist provided face-to-face MTM services for 30-60 minutes per encounter, not always including a follow-up visit G2: Control group: Patients who did not receive MTM services (economic analyses only)	Cohort	Overall: 3,233 G1: NA G2: NA	Overall: 125 G1: 63 G2: 62	Overall: 125 G1: 63 G2: 62	Overall: 125 G1: 63 G2: 62
Yamada 2012 <sup>61</sup>	G1: Kaiser-Permanente MTM enrolled patients G2: Kaiser patients enrolled in Medicare part D, but not in MTM program matched to control on age, gender, region and DCG risk	Cohort	Overall: 172,534 G1: 34,352 G2: 138,182	Overall: 172,534 G1: 34,352 G2: 138,182	Overall: 172,534 G1: 34,352 G2: 138,182	Overall: 172,534 G1: 34,352 G2: 138,182

Abbreviations: BP = blood pressure; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; DCG = diagnostic cost group; DTP = drug therapy problem; FHCP = Florida Health Care Plans; FOM = focus on medicine; G = group; HbA1c = hemoglobin A1c; HEDIS = Healthcare Effectiveness Data and Information Set; HMR = home medication review; LDL = low-density lipoprotein; MA-PD = Medicare Advantage Part D; MTM = medication therapy management; N = number; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; PCM = pharmaceutical case management; PCP = primary care provider; PREP = Pharmaceutical Care Research and Education Project; QOL = quality of life; RCT = randomized controlled trial

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup>  7 European countries: Denmark, Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland, and Sweden	<i>Intervention:</i> Structured pharmaceutical care provided by community pharmacists.  <i>Level of Integration with Usual Care:</i> Pharmacists were encouraged to use the patient's GP to obtain information, but specific details regarding pharmacist access to clinical information was NR. Rationalizing and simplifying drug regimens in collaboration with the patient's general practitioner was structured using drug use profiles, however specific details regarding the communication between pharmacist and physicians was NR.	Personal recruitment by pharmacists within pharmacy, or via GP records or pharmacy records	<i>Setting:</i> Community pharmacies, but also included some home visits.  <i>Mode of delivery:</i> NR  <i>Frequency and interval of follow-up:</i> NR	Health care systems varied by country, but all featured single payer systems.  <i>Reimbursement characteristics:</i> NR
Blakey et al., 2000 <sup>3</sup>  Georgia, US	<i>Intervention:</i> Interdisciplinary team provided geriatric medical care that included a clinical pharmacist  <i>Level of Integration with Usual Care:</i> Pharmacists were members of the interdisciplinary care team.	Pharmacist review of scheduled patients, identification during care team meetings, provider referral for services.	<i>Setting:</i> Outpatient geriatric medicine clinic.  <i>Mode of delivery:</i> Face-to-face  <i>Frequency and interval of follow-up:</i> initial consultation and at least one follow-up at 3 months.	Single Veterans Health Administration Medical Center  <i>Reimbursement characteristics:</i> NR
Brummel et al., 2013 <sup>4</sup> Soliman et al., 2013 <sup>5</sup> Ramalho de Oliveira et al., 2010 <sup>6</sup>  Minnesota, US	<i>Intervention:</i> Standardized MTM program provided by pharmacists.  <i>Level of Integration with Usual Care:</i> MTM pharmacists staff medical clinics and have collaborative practice agreements to initiate, modify, or discontinue drug therapy or order laboratory tests.	Patients "opt in" to MTM through direct referral, mailed letters, and telephone outreach.	<i>Setting:</i> Outpatient medical clinics  <i>Mode of delivery:</i> Face-to-Face  <i>Frequency and interval of follow-up:</i> No specific frequency or interval by design, median number of visits per year was 4.	Clinics were part of a large, integrated health system with its own pharmacy services  <i>Reimbursement characteristics:</i> NR

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Chrischilles et al., 2004 <sup>9</sup>  Iowa, US	<p><i>Intervention:</i> Pharmaceutical case management provided by pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in medical record NR. Pharmacist written communication with physicians about problems identified. A collaboratively determined action plan can be implemented by the pharmacist without requiring a patient visit to a physician.</p>	Claims data or pharmacy prescription profile records	<p><i>Setting:</i> Community pharmacy.</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and interval of follow-up:</i> Initial consultations with follow-up contacts as needed and routine re-assessments every 6 months by design.</p>	<p>Health plan intervention that included a payment reform to allow for reimbursement of multiple participating pharmacies and providers across different systems.</p> <p><i>Reimbursement characteristics:</i> provided as a Medicaid benefit using state and federal matching funds.</p>
Christensen et al., 2007 <sup>10</sup>  North Carolina, US	<p><i>Intervention:</i> Medication therapy management services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record NR. Pharmacist contacted prescribing physicians to discuss drug therapy problems and implemented any resulting approved action plan.</p>	Eligible patients identified through claims data, then recruited through a letter sent inviting them to participate.	<p><i>Setting:</i> Some patients received services within their medical clinic, some received services within a community pharmacy setting.</p> <p><i>Mode of delivery:</i> Face-to-face and telephone</p> <p><i>Frequency and interval of follow-up:</i> study designed as one initial visit and one follow-up, 37.5% of enrolled patients received follow-up contact.</p>	<p>Health plan intervention involving multiple health systems.</p> <p><i>Reimbursement characteristics:</i> Pharmacists compensated through study-related funding (e.g., grant).</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Fischer et al., 2000 <sup>12</sup>  Midwest, US	<p><i>Intervention:</i> Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record NR. Information to and consultation with physicians on behalf of patients mentioned but specific operational details NR.</p>	<p>Claims data or pharmacy prescription profile records to identify eligible participants who were then invited by letter.</p>	<p><i>Setting:</i> Pharmacies located within clinics</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and interval of follow-up:</i> NR</p>	<p>Health maintenance organization with clinics and on-site pharmacies.</p> <p><i>Reimbursement for services:</i> NR</p>
Fischer et al., 2002 <sup>13</sup>  Minnesota, US	<p><i>Intervention:</i> Pharmaceutical care based on the Encara Practice System provided by pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record NR. Communication with the patient's physician about drug therapy problems identified, but specific operational details NR.</p>	<p>Claims data or pharmacy prescription profile records to target eligible participants.</p>	<p><i>Setting:</i> Pharmacies located within clinics and free-standing pharmacies</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and interval of follow-up:</i> With each prescription refill (as designed); actual frequency and interval NR.</p>	<p>Health maintenance organization clinics and free-standing pharmacies.</p> <p><i>Reimbursement characteristics:</i> NR</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
State (Province) or Country				
Fox et al., 2009 <sup>14</sup> Florida, US	<p><i>Intervention:</i> MTM services provided by staff clinical pharmacist as part of a Medicare Part D MTM program.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist had access to clinical information in the medical record, including laboratory data. Pharmacist documented findings on a form, which was sent to the patient's physician.</p>	<p>Claims data or pharmacy prescription profile records to target eligible participants.</p>	<p><i>Setting:</i> Health plan pharmacy, unclear whether a single centralized center or outpatient clinic-based pharmacies used.</p> <p><i>Mode of delivery:</i> Primarily telephone, supplemented by mailed written materials.</p> <p><i>Frequency and interval of follow-up:</i> Initial consultation, and up to 3 follow-up contacts if a drug therapy problem identified or based on clinical need.</p>	<p>Mixed-staff model health maintenance organization that combines pharmacist services, primary care, and specialty medical care with a Medicare Advantage Part D Plan.</p> <p><i>Reimbursement characteristics:</i> Medicare Part D drug benefit</p>
Grymonpre et al., 2001 <sup>16</sup> Manitoba, Canada	<p><i>Intervention:</i> Pharmaceutical care provided by team of non-pharmacist staff or volunteers, a BS level pharmacist, and supervision by pharmacist with geriatric medicine experience.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record NR. Pharmacist recommendations sent via letter to prescribing physicians, who may not have been known or geographically close.</p>	<p>Self-referral or referral by a home health service program.</p>	<p><i>Setting:</i> Patient's home or a private office</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and interval of follow-up:</i> Initial consultation with follow-up as needed (as designed); actual frequency and interval NR.</p>	<p>Community-based interdisciplinary health clinic.</p> <p><i>Reimbursement characteristics:</i> NR</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
State (Province) or Country				
Hanson et al., 1996 <sup>17</sup> North Carolina, US	<p><i>Intervention:</i> Pharmaceutical care provided by a clinical pharmacist</p> <p><i>Level of Integration with Usual Care:</i> Pharmacists had access to clinical information in medical record. Pharmacist recommendations were presented orally and in writing to the patient's primary physician, pharmacist reinforced and amplified the primary physician's instructions.</p>	Computerized and manual chart audits to identify eligible subjects	<p><i>Setting:</i> Outpatient medical clinic</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> NR</p>	<p>Single Veterans Health Administration Medical Center</p> <p>Reimbursement characteristics: NR</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Isetts et al., 2008 <sup>22</sup> Minnesota, US	<p><i>Intervention:</i> Medication therapy management services provided by staff pharmacists, including the establishment of goals of therapy.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacists had access to clinical information in medical record. Pharmacist urgently consulted with primary care provider for potentially harmful drug therapy problems, but details regarding routine communication were NR.</p>	<p>Claims data or pharmacy prescription profile records used to identify eligible participants who were then invited by letter and provider referral.</p>	<p><i>Setting:</i> Outpatient medical clinics</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> NR (at least 1 follow-up visit was required for inclusion in the evaluation)</p>	<p>Integrated health system with an established pharmaceutical care program involving pharmacist certification in pharmaceutical care and a specific pharmaceutical care documentation system.</p> <p><i>Reimbursement characteristics:</i> Costs of providing services were funded through research grants, demonstration projects, third-party payer pilot programs, and internal health system funding.</p>
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup> Michigan, US	<p><i>Intervention:</i> Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record was NR. Pharmacist met with treating physician to discuss findings and new regimen was developed collaboratively with the physician.</p>	<p>Medical records of patients seen in an outpatient clinic were randomly screened for risks of adverse medication outcomes.</p>	<p><i>Setting:</i> Outpatient medical clinic</p> <p><i>Mode of Delivery:</i> Face-to-face and telephone</p> <p><i>Frequency and interval of Follow-up:</i> 1 initial visit and 1 follow-up visit 1 month later (by design); actual frequency and interval of follow-up NR.</p>	<p>Single family health clinic that was part of a family medicine residency program.</p> <p><i>Reimbursement characteristics:</i> NR</p>



**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Jeong et al., 2009 <sup>25</sup> California, US	<i>Intervention:</i> MTM services provided by clinical ambulatory care pharmacists and health care support staff.  <i>Level of Integration with Usual Care:</i> Pharmacist work under collaborative practice agreements to initiate, titrate, and discontinue medications and order laboratory tests. Patient data and interventions entered into an internal database (not clear if this accessible to care team).	NR	<i>Setting:</i> Centralized pharmacy  <i>Mode of delivery:</i> Telephone  <i>Frequency and interval of Follow-up:</i> Initial consultation and two additional follow-ups, interval NR.	Integrated health care delivery system providing MTM services to eligible beneficiaries  <i>Reimbursement characteristics:</i> Presumably Medicare Part D drug benefit.
Jeong et al., 2012 <sup>26</sup> Jeong et al., 2012 <sup>27</sup> California, US	<i>Intervention:</i> MTM services provided by clinical ambulatory care pharmacists and support staff  <i>Level of Integration with Usual Care:</i> Pharmacist work under collaborative practice agreements to initiate, titrate, and discontinue medications and order laboratory tests.	NR	<i>Setting:</i> Centralized pharmacy  <i>Mode of delivery:</i> Telephone  <i>Frequency and interval of follow-up:</i> NR	Integrated health care delivery system providing MTM services to eligible beneficiaries.  <i>Reimbursement characteristics:</i> Presumably Medicare Part D drug benefit.
Krska et al., 2001 <sup>28</sup> United Kingdom	<i>Intervention:</i> Medication reviews led by clinically trained pharmacists.  <i>Level of Integration with Usual Care:</i> Pharmacist had access to medical notes and practice computer records. Copies of the pharmaceutical care plan developed by the pharmacist were inserted into the patient's medical record and given to the patients' GP, who was asked to indicate level of agreement with recommendations.	Provider referral required but enrollment limited to 70 patients from each participating practice; selection process unclear	<i>Setting:</i> Home visits  <i>Mode of Delivery:</i> Initial consultation was face-to-face; follow-up consultation NR  <i>Frequency and Interval of Follow-up:</i> Two contacts, 3 months apart as designed; actual frequency and interval NR.	General medicine clinics that were part of a single payer health care system.  <i>Reimbursement characteristics:</i> NR

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> (dyslipidemia subgroup intermediate and utilization outcomes)  Multiple states, US	<p><i>Intervention:</i> Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist had access to medical record information. Pharmacist communication with primary care physician or other prescribers NR.</p>	Pharmacy prescription records to identify patients at high risk for drug-related problems.	<p><i>Setting:</i> Outpatient medical clinic</p> <p><i>Mode of Delivery:</i> Face-to-face (76.6% of contacts) and telephone (23.4%)</p> <p><i>Frequency and Interval of Follow-Up:</i> At least 3 visits over 12 months as designed. Actual frequency: mean (SD) number of visits was 3.5 (2.3). 27.7% did not complete the minimum number of visits (3) as designed</p>	<p>Multiple Veterans Health Administration Medical Centers with established ambulatory clinical pharmacy services</p> <p><i>Reimbursement characteristics:</i> Services provided as part of patient's VHA health care benefits</p>
Moczygemba et al., 2011 <sup>37</sup> Moczygemba et al., 2008 <sup>38</sup>  Texas, US	<p><i>Intervention:</i> Medication therapy management services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist had access to medical record information, including laboratory information. Patients are encouraged to share the Personal Medication Record and Medication Action Plan developed in the course of MTM consultation with their health care providers and patients are requested to contact their physicians regarding pharmacist's recommendations. Copies are kept in the patient's MTM file, but no MTM documentation goes back to the patient's medical record.</p>	Eligible patients are identified quarterly and mailed MTM Program information and instructions for opting in to the program.	<p><i>Setting:</i> centralized MTM program</p> <p><i>Mode of Delivery:</i> Telephone</p> <p><i>Frequency and Interval of Follow-Up:</i> one initial consultation by design with follow-up scheduled as needed. Actual frequency and interval of follow-up NR.</p>	<p>Health plan intervention provided by a regional Medicare Part D MTM Provider.</p> <p><i>Reimbursement characteristics:</i> Medicare Part D drug benefit.</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Moore et al., 2013 <sup>40</sup> Multiple states, US	<p><i>Intervention:</i> Medication therapy management services provided by a large pharmacy benefits management company.</p> <p><i>Level of Integration with Usual Care:</i> Patients had to send validated lab data to pharmacist before initial appointment. With patient authorization, pharmacist faxed recommendations to prescribing provider (unless patient was referred by case or disease manager).</p>	Patients with claims data showing more than 14 pharmacy claims within 4 months or absence of claims for recommended therapy or evidence of conflicting therapy were sent a letter offering enrollment.	<p><i>Setting:</i> Centralized pharmacy</p> <p><i>Mode of delivery:</i> Telephone</p> <p><i>Frequency and interval of follow-up:</i> Initial consultation with at least two follow-up contacts within 12 months.</p>	<p>Health plan intervention with a pharmacy benefits management company.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Perlroth et al., 2013 <sup>35</sup> Multiple states, US	<p><i>Intervention:</i> Medicare Part D MTM Programs</p> <p><i>Level of Integration with Usual Care:</i> Varies by program sponsor.</p>	Varies by program sponsor.	<p><i>Setting:</i> Varies by program sponsor</p> <p><i>Mode of delivery:</i> Varies by program sponsor</p> <p><i>Frequency and interval of follow-up:</i> Varies by program sponsor</p>	<p>Varies by program sponsor</p> <p><i>Reimbursement characteristics:</i> Medicare Part D</p>
Pindolia et al., 2009 <sup>44</sup> Michigan, US	<p><i>Intervention:</i> Medication therapy management services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacists had access to clinical information in the medical record. Communications with physicians were by telephone, face-to-face, or e-mail.</p>	Monthly query of clinical care management systems for eligible patients with subsequent letter mailed and follow-up phone call to enroll patients.	<p><i>Setting:</i> Integrated healthcare delivery system</p> <p><i>Mode of Delivery:</i> telephone</p> <p><i>Frequency and Interval of Follow-Up:</i> NR</p>	<p>Health plan intervention within an Integrated health system with an established pharmaceutical care program.</p> <p><i>Reimbursement characteristics:</i> Medicare Part D drug benefit.</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Sellors et al., 2003 <sup>47</sup> Ontario, Canada	<i>Intervention:</i> Clinical pharmacy consultations provided to elderly patients by pharmacists.  <i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in medical record was NR. Pharmacists provided a consultation letter to physician and subsequently met with physician to review the letter. They met again in 3 months to discuss progress in implementing recommendations.	About 20 randomly chosen eligible senior citizens per practice were recruited by the office staff of the practice, selection process for recruitment not reported.	<i>Setting:</i> Outpatient medical clinic  <i>Mode of Delivery:</i> Face-to-face and telephone  <i>Frequency and Interval of Follow-Up:</i> Initial contact plus 2 follow-up contacts at 1 and 3 months as designed. Actual frequency and interval of contact NR.	Family medicine practices within a single-payer health care system.  <i>Reimbursement characteristics:</i> NR
C. Sellors et al., 2003 <sup>48</sup> Ontario, Canada	<i>Intervention:</i> Clinical pharmacy consultations provided to elderly patients by pharmacist.  <i>Level of Integration with Usual Care:</i> Pharmacist reviewed information in patient's medical record. Pharmacist met with provider to discuss written recommendations.	Patients identified during office visits or through review of practice rosters.	<i>Setting:</i> Outpatient medical clinic  <i>Mode of delivery:</i> Face-to-face and telephone  <i>Frequency and interval of follow-up:</i> Initial consultation, follow-up at 2 weeks, then monthly for 6 months	Family medicine practices within a single-payer health care system.  <i>Reimbursement characteristics:</i> NR
Shimp et al., 2012 <sup>49</sup> Michigan, US	<i>Intervention:</i> Medication therapy management services provided by pharmacists as part of an employee health program.  <i>Level of Integration with Usual Care:</i> Pharmacist may have had access to clinical information in medical records for some enrolled patients. With patient approval, pharmacist recommendations were communicated to providers via the EHR.	Pharmacy benefits manager identified eligible individuals on a quarterly basis. From this list, individuals were randomly selected for an invitation to participate.	<i>Setting:</i> employer-based  <i>Mode of delivery:</i> Telephone and face-to-face  <i>Frequency and interval of follow-up:</i> Initial history taken by study staff by phone, with two follow-up visits face-to-face with pharmacist, interval NR	Large university and its associated pharmacy benefits management organization.  <i>Reimbursement characteristics:</i> NR

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Sidel et al., 1990 <sup>50</sup> New York, US	<i>Intervention:</i> Home visits by pharmacists to identify and correct problems associated with medication use.  <i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in medical record was NR. No information about communication with providers was reported.	Study population identified from a combination of the following: Medicare recipients living in the region, Senior Centers, houses of worship, Meals-on-Wheels, hospital admissions records and voter registration rolls.	<i>Setting:</i> Community setting  <i>Mode of delivery:</i> home visits and telephone  <i>Frequency and Interval of Follow-Up:</i> 2 visits over a 12 month period as designed. Actual frequency and interval of follow-up NR.	Implemented outside the health care system through a multidisciplinary research program on aging.  <i>Reimbursement characteristics:</i> NR
Staresinic, 2007 <sup>51</sup> Wisconsin, US	<i>Intervention:</i> Medication therapy management services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist.  <i>Level of Integration with Usual Care:</i> Pharmacists request lab data from participants; access to clinical information in medical records was NR. Pharmacists send a tailored letter by fax to each of the patient's health care providers.	Pharmacy claims based algorithm identifies eligible beneficiaries with invitation letters mailed within 2 weeks of identifying eligibility.	<i>Setting:</i> centralized MTM program  <i>Mode of Delivery:</i> telephone  <i>Frequency and Interval of Follow-Up:</i> One initial contact and one follow-up contact at 3 months as designed. Actual frequency and interval of follow-up NR.	Health plan intervention provided by a regional Medicare Part D MTM Provider  <i>Reimbursement characteristics:</i> Medicare Part D drug benefit.
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> Alabama, US	<i>Intervention:</i> Pharmaceutical care provided by pharmacists.  <i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in medical record was NR, but visits with pharmacist occurred 20 minutes before seeing the physician in the same clinic. Recommendations to physicians were communicated through discussions or progress notes.	Patients were identified by the participating pharmacists through manual evaluation of clinic medical records and review of computerized medical records in physician offices.	<i>Setting:</i> Outpatient medical clinic  <i>Mode of Delivery:</i> Face-to-face  <i>Frequency and Interval of Follow-Up:</i> Before each scheduled physician visit by design. Actual frequency and follow-up interval NR.	Three community-based family medicine clinics affiliated with an academic medical center.  <i>Reimbursement characteristics:</i> NR

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Touchette et al., 2012 <sup>53</sup>  Multiple States, US	<p><i>Intervention:</i> Patient-safety focused medication therapy management services provided by pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Two versions of the intervention were evaluated. In the enhanced version, pharmacists were provided with a clinical summary excerpted from the patient's medical record. No such summary was provided to pharmacists in the basic version. Drug therapy problems were communicated to physicians via fax, except urgent issues were communicated by telephone.</p>	Administrative and pharmacy databases and provider referral used for initial eligibility determination followed up with letter or phone call or in clinic for recruitment/enrollment	<p><i>Setting:</i> Outpatient medical clinic</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> 1 initial contact and a follow-up contact at 3 months as designed.</p> <p>Actual: 89.9% completed 1 contact and 75.7% completed 2 contacts in the enhanced MTM arm, 88.6% and 73.8% completed the first and second contacts respectively in the basic MTM arm.</p>	<p>Three academic medical centers in three different states.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Volume et al., 2001 <sup>54</sup> and Kassam et al., 2001 <sup>55</sup> PREP  Alberta, Canada	<p><i>Intervention:</i> Pharmaceutical care using a nine-step process as defined by Hepler and Strand provided by community pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record NR. Details regarding communication with physicians regarding drug therapy problems NR.</p>	Pharmacies evaluated 60 consecutive patients during one week for eligibility. Eligible patients were asked in person or by phone about interest in participating.	<p><i>Setting:</i> community pharmacy</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-Up:</i> Initial contact plus frequent follow-up at unspecified intervals as designed. Actual frequency and interval of follow-up NR.</p>	<p>Community-pharmacy intervention within a non-US single-payer healthcare system.</p> <p><i>Reimbursement characteristics:</i> NR</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Follow-up	Health Care System and Reimbursement Context
Welch et al., 2009 <sup>56</sup> Colorado, US	<p><i>Intervention:</i> Medication therapy management services provided by clinical pharmacists as part of a Medicare Part D MTM program.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacists had access to clinical information in the medical record. Pharmacists forwarded copies of consultation notes to providers and also placed a copy in the patient's medical record.</p>	Medicare beneficiaries identified as eligible using a computerized system.	<p><i>Setting:</i> centralized MTM program</p> <p><i>Mode of Delivery:</i> Telephone</p> <p><i>Frequency and interval of Follow-Up:</i> Initial consult with follow-up depending on clinical situation as designed. Actual frequency and interval of follow-up NR.</p>	<p>Group-model health maintenance organization using a centralized clinical pharmacy call center.</p> <p><i>Reimbursement characteristics:</i> Medicare Part D drug benefit.</p>
Williams et al., 2004 <sup>57</sup> North Carolina, US	<p><i>Intervention:</i> Medication review and optimization provided by a consulting pharmacist.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist had access to clinical information in the medical record. A MAT comprised of a physician, nurse, and consultant pharmacist met to discuss pharmacy recommendations.</p>	Patients were recruited from practices and through community print and radio advertisements and mass mailings, and presentations to community groups.	<p><i>Setting:</i> Outpatient medical clinic</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-Up:</i> Initial contact with follow-up contact as needed as designed. Actual frequency and interval of follow-up contact NR.</p>	<p>General medicine clinic of an academic medical center.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Winston and Lin, 2009 <sup>58</sup> Multiple States, US	<p><i>Intervention:</i> Medication therapy management services provided by either community pharmacists or call center pharmacists as part of a Medicare Part D MTM Program.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record was NR. Pharmacist contacted prescribers on behalf of the patients by phone or fax for medication adjustments related to cost or safety.</p>	Health plan used pharmacy prescription profile records identify eligible patients. Information on eligible patients was communicated to pharmacies by fax or email.	<p><i>Setting:</i> community pharmacy and centralized pharmacy call center</p> <p><i>Method of Delivery:</i> Face-to-face or telephone</p> <p><i>Frequency and Interval of Follow-up:</i> NR</p>	<p>Health plan intervention provided by a national Medicare Part D MTM provider.</p> <p><i>Reimbursement characteristics:</i> Medicare Part D drug benefit</p>

**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Follow-up	Health Care System and Reimbursement Context
Witry, Doucette, and Gainer, 2011 <sup>59</sup>  Iowa, US	<i>Intervention:</i> Pharmaceutical case management provided by community pharmacists.  <i>Level of integration with Usual Care:</i> Pharmacist access to clinical information in the medical record was NR. Pharmacists faxed a one-page summary of findings to physician.	Health plan used pharmacy prescription profile records identify eligible patients. This was sent to each pharmacy. The health plan also sent letters to inform eligible patients about the PCM service benefit, and an article about PCM appeared in the health plan newsletter. Pharmacies also sent letters and telephoned eligible patients.	<i>Setting:</i> community pharmacy  <i>Mode of Delivery:</i> Face-to-face and telephone  <i>Frequency and Interval of Follow-Up:</i> Initial contact with additional follow-up contacts as needed as designed. Actual frequency and interval of follow-up: 46% received 1 contact, 24% received 2 contacts, 16% received 3 contacts, 13% received 4 or more contacts	Health plan intervention executed by pharmacies that had previously participated in a similar intervention sponsored by Medicaid.  <i>Reimbursement characteristics:</i> Participating pharmacies were reimbursed for services provided by study grant.
Wittayanukorn et al., 2013 <sup>60</sup>  Southeast US	<i>Intervention:</i> Medication therapy management provided by pharmacists.  <i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record was NR. Provider communication and follow-up NR.	Patients were identified by pharmacists, referred by providers, or self-referred.	<i>Setting:</i> Pharmaceutical care center for employees of a self-insured employer  <i>Mode of delivery:</i> Face-to-face  <i>Frequency and interval of follow-up:</i> NR	Employer-based intervention within a university setting.  <i>Reimbursement characteristics:</i> Self-insured employer paid for cost of MTM services



**Table D4. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)**

Author, Year  State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Follow-up	Health Care System and Reimbursement Context
Yamada et al., 2012 <sup>61</sup>  California, US	<p><i>Intervention:</i> MTM services provided by clinical ambulatory care pharmacists and health care support staff.</p> <p><i>Level of Integration with Usual Care:</i> NR, but other evaluations of this MTM program reported that pharmacist work under collaborative practice agreements to initiate, titrate, and discontinue medications and order laboratory tests. Patient data and interventions entered into an internal database (not clear if this accessible to care team).</p>	NR	<p><i>Setting:</i> Centralized pharmacy</p> <p><i>Mode of delivery:</i> Telephone</p> <p><i>Frequency and interval of follow-up:</i> NR</p>	<p>Integrated health care delivery system providing MTM services to eligible beneficiaries</p> <p><i>Reimbursement characteristics:</i> Presumably Medicare Part D drug benefit.</p>

Abbreviations: GP = general practitioner; MAT = medication adjustment team; MTM = Medication Therapy Management; NR = not reported; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; QOL = quality of life; SD = standard deviation; US = United States; VHA = Veterans Health Administration.

**Table D5. Key Question 1: Components and features of medication therapy management interventions: Narrow focused studies**

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup>  Illinois, US	<p><i>Focus:</i> Hypertension</p> <p><i>Intervention:</i> Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized.</p> <p><i>Level of Integration with Usual Care:</i> The pharmacist had access to patients' medical records, diagnostic data, and laboratory data, and had face-to-face interaction with the clinic physicians and nurses.</p>	Patients were identified through a computerized profile review, details NR.	<p><i>Setting:</i> Outpatient primary care clinic</p> <p><i>Mode of delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> Monthly contacts for 6 months as designed. Actual frequency and interval of follow-up NR.</p>	<p>Rural medical clinic co-located in same building as a privately owned pharmacy.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Clifford et al., 2002 <sup>11</sup>  Australia	<p><i>Focus:</i> Diabetes</p> <p><i>Intervention:</i> Pharmaceutical care provided by a clinical pharmacist, which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist had access to patient's case notes. Pharmaceutical care was provided in cooperation with the patient's diabetes physicians and other diabetes health team members.</p>	Medical records were screened for eligible patients. Eligible patients were telephoned about their willingness to participate.	<p><i>Setting:</i> Outpatient hospital diabetes clinic</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-Up:</i> Initial visit followed by follow-up visits at 6 week intervals for 6 months as designed. Actual frequency and interval of follow-up NR.</p>	<p>Non-US, single payer health care system</p> <p><i>Reimbursement characteristics:</i> NR</p>

**Table D5. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)**

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Gattis et al., 1999 <sup>15</sup> North Carolina, US	<p><i>Focus: Chronic heart failure</i></p> <p><i>Intervention:</i> Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients.</p> <p><i>Level of integration with usual care:</i> Pharmacist had access to patient medical records and verbally recommendations regarding optimization of therapy with attending physician.</p>	Patients seen in a general cardiology clinic meeting inclusion criteria were recruited for enrollment.	<p><i>Setting:</i> Outpatient cardiology clinic</p> <p><i>Mode of Delivery:</i> Initial visit was face-to-face and follow-up visits were by telephone</p> <p><i>Frequency and Interval of Follow-Up:</i> 3 visits, baseline, two weeks, and 24 weeks by design. Actual frequency and interval of follow-up NR.</p>	<p>Single clinic within an academic medical center.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Hirsch et al., 2011 <sup>19</sup> Hirsch et al., 2009 <sup>20</sup> California, US	<p><i>Focus: HIV/AIDS</i></p> <p><i>Intervention:</i> Medication therapy management services provided by pharmacist.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacist access to clinical information in the medical record was NR. Follow-up and communication with providers was at the discretion of the pharmacy.</p>	Patients filling prescriptions at participating pharmacies were eligible to receive MTM services, but actual selection criteria were left to discretion of pharmacy.	<p><i>Setting:</i> Specialty HIV/AIDS community pharmacies (90 percent or more of population served are individuals with HIV/AIDS.)</p> <p><i>Mode of delivery:</i> Face-to-Face</p> <p><i>Frequency and interval of follow-up:</i> NR</p>	<p>Plan-level intervention provided by state Medicaid agency.</p> <p><i>Reimbursement characteristics:</i> Compensation provided to participating pharmacies on a per prescription basis by the state Medicaid agency.</p>

**Table D5. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)**

Author, Year	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Country/ Region				
Marques et al., 2013 <sup>33</sup>  Brazil	<p><i>Focus:</i> Depression and anxiety</p> <p><i>Intervention:</i> Dader method of pharmacotherapy follow-up provided by pharmacist. Includes establishing a plan of action for medications with a goal of enhancing or preserving health.</p> <p><i>Level of Integration with Usual Care:</i> Interventions with referring psychiatrist were provided as needed, but specific details NR.</p>	Psychiatrist referral to the pharmaceutical assistance service.	<p><i>Setting:</i> Outpatient psychiatry and psychology clinics</p> <p><i>Mode of Delivery:</i> Face to face in patient's home</p> <p><i>Frequency and Interval of Follow-up:</i> Initial visit and at least one follow-up every 30 days for 3 months (or sooner if needed)</p>	Specialty clinics of an academic medical center in a single payer system
McDonough et al., 2005 <sup>36</sup>  Iowa, US	<p><i>Focus:</i> Glucocorticoid-induced osteoporosis</p> <p><i>Intervention:</i> Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of doses, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education was also provided.</p> <p><i>Level of Integration With Usual Care:</i> Pharmacist access to patient medical records NR. A standardized physician communication form was used by pharmacists to communicate information to prescribing physicians.</p>	Claims data or pharmacy prescription profile records used to identify eligible patients who were then contacted by mail or telephone to participate.	<p><i>Setting:</i> community pharmacy</p> <p><i>Mode of Delivery:</i> NR</p> <p><i>Frequency and Interval of Follow-Up:</i> NR</p>	<p>Network of independent and retail chain pharmacies. Some pharmacies located within a clinic, while others are freestanding.</p> <p><i>Reimbursement characteristics:</i> Pharmacists were reimbursed using a web-based claims system, but entity providing reimbursement was NR.</p>

**Table D5. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)**

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>  New Mexico, US	<p><i>Focus:</i> Hemodialysis</p> <p><i>Intervention:</i> Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education.</p> <p><i>Level of Integration with Usual Care:</i> The pharmacist had access to patient's medical record and laboratory data. The pharmacists provided cognitive services during weekly rounds and during monthly formal reviews of the patients with the multidisciplinary health care team.</p>	Patients on stable hemodialysis regimen for the previous 3 months were approached for participation.	<p><i>Setting:</i> Outpatient hemodialysis clinic</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-Up:</i> Every 8 weeks for two years by design. Actual frequency and interval of follow-up NR.</p>	<p>University-affiliated outpatient dialysis clinic</p> <p><i>Reimbursement characteristics :</i> NR</p>

**Table D5. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)**

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Park et al., 1996 <sup>43</sup> Wisconsin and Illinois, US	<p><i>Focus:</i> Hypertension</p> <p><i>Intervention:</i> Comprehensive pharmaceutical care including drug therapy monitoring and patient education provided by a community pharmacy resident.</p> <p><i>Level of Integration with Usual Care:</i> Pharmacists access to patient medical records, or labs or vital signs from clinic was NR. Communication with provider was via fax or mail after each pharmacist visit, unless urgency required telephone communication.</p>	Claims data or pharmacy prescription profile records	<p><i>Setting:</i> Community pharmacy</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> 4 visits scheduled 1 month apart by design. Actual frequency and interval of follow-up NR.</p>	<p>Chain pharmacy with community pharmacy residents.</p> <p><i>Reimbursement characteristics:</i> NR</p>
Planas et al., 2009 <sup>45</sup> Oklahoma, US	<p><i>Focus:</i> Patients with both hypertension and diabetes</p> <p><i>Intervention:</i> Medication therapy management services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure.</p> <p><i>Level of integration with usual care:</i> Pharmacist access to patient medical records, or labs, or vital signs from clinic was NR. Providers were contacted via fax or telephone when drug therapy problems were identified in order to make recommendations.</p>	Three methods were used: managed care organization identification of patients with uncontrolled diabetes through lab data screening, screening for uncontrolled diabetes at a health fair for employees sponsored by the managed care organization, provider referral of patients with uncontrolled diabetes.	<p><i>Setting:</i> Community pharmacy</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-up:</i> Monthly visits for 9 months by design. Actual frequency and interval of follow-up NR.</p>	<p>Services provided through a collaboration between a managed care organization and a regional retail chain pharmacy.</p> <p><i>Reimbursement characteristics:</i> NR</p>

**Table D5. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)**

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Roughead et al., 2009 <sup>46</sup> Australia	<p><i>Focus:</i> Chronic heart failure</p> <p><i>Intervention:</i> HMR, a collaborative model of pharmaceutical care. HMRs are conducted by accredited pharmacists.</p> <p><i>Level of Integration with Usual Care:</i> NR for this study specifically, but the HMR model is that the GP provides pharmacist with diagnosis, current medications, relevant test results and medical history. Pharmacist conducts the HMR and submits a written and verbal report to the GP for assistance in developing or revising a management plan.</p>	HMRs are conducted upon request of a provider. Claims data or pharmacy prescription profile records	<p><i>Setting:</i> Outpatient clinic and home visits</p> <p><i>Mode of Delivery:</i> Face-to-face</p> <p><i>Frequency and Interval of Follow-Up:</i> NR</p>	<p>Non-US, single payer health care system</p> <p><i>Reimbursement characteristics:</i> services reimbursed through payer's home medicine review benefit.</p>

Abbreviations: CHF = chronic heart failure; GP = general practitioner; HIV/AIDS= human immunodeficiency virus/acquired immune deficiency syndrome HMR = home medication review; MTM = medication therapy management; NR = not reported; US = United States.

**Table D6. Anticoagulation: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Taylor, Byrd, and Krueger, 2003 RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 4 G2: 6 (Was only assessed among patients on anticoagulation)	Percent of patients at goal INR (goal was INR 2-3) at 12 months	G1: 100 G2: 16.7 P=0.048

Abbreviations: G = group; INR= international normalized ratio.



**Table D7. Hemoglobin A1c: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Clifford et al. 2002 <sup>11</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 48 G2: 25	Mean (SD) HbA1c at six months.	Baseline: G1: 8.4 (1.4) G2: 8.5 (1.6) p: NS  6 months G1: 8.2 (1.5) G2: 8.1 (1.6)  Calculated mean difference: -0.20, 95% CI, -0.93 to 0.53 (assuming pre- post correlation of 0.5) p=0.590
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 13 G2: 16 (Study included more subjects, but this outcome was only assessed among patients with diabetes within each study arm)	Percent with HbA1c at goal (defined as less than or equal to 7.5 percent) at baseline and at 12 months.	Baseline: G1: 23.1 G2: 56.3 p=0.071 Calculated OR: 0.2 95% CI, 0.05 to 1.19  Follow-up G1: 100 G2: 26.7 p=0.001  Calculated OR: 56.5 95% CI, 2.81 to 1,133.91 p=0.008

**Table D7. Hemoglobin A1c: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Brummel et al. 2013 <sup>4</sup> , Soliman, 2013 et al. <sup>5</sup> Ramalho de Oliveira et al., 2010 <sup>6</sup>	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage with HbA1c at goal (defined as less than 7) after 12 months of demonstration	Baseline: G1: 43.80 G2: 63.11 p=0.62
Cohort study/Medium				12 months (during demonstration) G1: 73.55 G2: 72.82 p=0.9
				Calculated OR: 1.038 95% CI 0.574 to 1.879, p=0.901 (unadjusted)
				Adjusted difference-in-difference coefficient: 2.44 95% CI 1.22 to 4.86, p=0.01
			Percentage with HbA1c at goal (defined as less than 7) after 24 months (i.e., 12 months after end of demonstration study)	24 months (12 months post-demonstration) G1: 42.15 G2: 59.22 p=0.01
				Calculated OR: 0.502 95% CI 0.294 to 0.855, p=0.011 (unadjusted)
				Adjusted difference-in-difference coefficient: NR

**Table D7. Hemoglobin A1c: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong et al., 2009 <sup>25</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects.	G1: 1,323 G2: 1,141 (Study included more subjects but this outcome was assessed among only patients with diabetes within each study arm)	Mean (SD) and mean change (SD) in HbA1c at 6 months	Baseline G1: 6.74 (1.13) G2: 6.84(1.21)  6 months G1: 6.76 (1.08) G2: 6.88 (1.23)  Mean Change G1: 0.02 (0.96) G2: 0.04 (1.09) p= NS  Calculated mean difference: -0.020 (0.041) 95% CI: -0.101 to 0.061 p=0.628
			Percentage with HbA1c less than 7 percent at 6 months	Baseline: G1: 66 G2: 63 p: NS  6 months: G1:65 G2:62 p=NS  Calculated OR: 1.142 95% CI: 0.969 to 1.347 p=0.114
Pindolia et al., 2009 <sup>44</sup> Cohort study/High	G1: Opted in to a telephone based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR (Was only assessed among patients with DM in each study arm and N for this outcome was not reported)	Change in percent of patients with HbA1c less than 7 percent at 6 months	G1: +3 G2: +7 Between-group p: inferred to be NS, exact p NR Within-group p: NR

Abbreviations: CI = confidence interval; DM = diabetes mellitus; G = group; HbA1C = hemoglobin A1C or glycosylated hemoglobin; MTM = Medication Therapy Management; N = number; NR = not reported; NS = not significant; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation; vs. = versus

**Table D8. LDL cholesterol: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	Baseline G1: 19 G2: 19 (Was only assessed among patients with dyslipidemia in each study arm)	Percent of patients at LDL-C goal based on ATPIII criteria at 12 months.	Baseline: G1: 10.5 G2: 15.8 Calculated OR: 0.6; 95% CI, 0.09 to 4.25; □p=0.631
		Follow-up (N inferred from percent in results) G1: 18 G2: 17		Follow-up G1: 77.8 G2: 5.9 Calculated OR: 56.0; 95% CI, 5.58 to 561.75; □p: 0.001
Brummel et al. 2013 <sup>4</sup> , Soliman, 2013 et al. <sup>5</sup> Ramalho de Oliveira et al., 2010 <sup>6</sup>  Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage with LDL-C at goal (defined as less than 100 mg/dl) after 12 months of demonstration	Baseline: G1: 63.64 G2: 65.05 p=0.82
				12 months: G1: 83.47 G2: 73.79 p=0.07
				Unadjusted calculated OR: 1.794 95% CI 0.936 to 3.438, p=0.078
				Adjusted difference in difference coefficient: 1.95, 95% CI 0.81, 4.84, p=0.13
				24 months: G1: 79.34 G2: 73.79 p=0.32
				Unadjusted calculated OR: 1.362 95% CI 0.733 to 2.540, p=0.328
				Adjusted difference-in-difference coefficient: NR

**Table D8. LDL cholesterol: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong et al., 2009 <sup>25</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program (opted in to program) G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects.	G1: 1,515 G2: 1,323 (Study included more subjects but this outcome was assessed among only patients with diabetes or CAD within each study arm)	Mean change (SD) in LDL cholesterol at 6 months  Percentage with LDL cholesterol at goal (Less than 100 mg/dl)	G1: -5.4 (26.2) G2: -1.3(25.8) Calculated mean difference: -4.1 95% CI -6.019 to -2.181 p< 0.001  Baseline G1: 74 G2: 75  6 months: G1: 82 G2: 76 Calculated OR at 6 months: 1.392 95% CI: 1.160 to 1.670 p<0.001
Isetts et al., 2008 <sup>22</sup> Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percent of patients meeting HEDIS measures related to cholesterol control after cardiovascular event at 12 months.	G1: 52 G2: 30 Calculated OR: 2.5; 95% CI, 1.52 to 4.26; p: 0.001
Pindolia et al., 2009 <sup>44</sup> Cohort study/High	G1: Opted in to a telephone based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR (Was only assessed among patients with coronary artery disease in each study arm)	Change in percent of patients with LDL-C less than 100 mg/dl at 6 months.	G1: -5 G2: +7 p: NR and could not be calculated

**Table D8. LDL cholesterol: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Fox et al. 2009 <sup>14</sup> Cohort study/High	G1: MTM program, provided through a health plan	G1: 255	Percent of patients with diabetes with LDL-C less than 100 mg/dl at 12 to 24 months.  Mean (SD) LDL-C at 12 to 24 months.	G1: 69
	G2: Usual medical care (eligible but opt-out from MTM program)	G2: 56		G2: 50 Calculated OR: 2.2; 95% CI, 1.24 to 4.01; p=0.008
		G1: 215 G2: 46		G1: 83.4 (31.1) G2: 90.8 (31.0) Calculated mean difference: -7.4, 95% CI, -17.30 to 2.50 p=0.33 as reported by study authors, p=0.143 as calculated

Abbreviations: ATPIII=Adult Treatment Panel III (Expert Panel on Detection, Evaluation; and Treatment of High Blood Cholesterol); CAD = coronary artery disease; CI = confidence interval; G = group; HEDIS= Healthcare Effectiveness Data and Information Set; LDL = low density lipoprotein; LDL-C= low density lipoprotein cholesterol; mg/dl = milligrams per deciliter; MTM = Medication Therapy Management; N = number; NR = not reported; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation; vs. = versus.

**Table D9. Blood pressure: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 24 G2: 29 (Was only assessed among patients with HTN in each study arm)	Percent of patients with SBP and DBP at goal at 12 months.	Baseline: G1: 12.5 G2: 31.0 p=0.109  Follow-up: G1: 91.7 G2: 27.6 p=0.001 Calculated OR: 28.875; 95% CI, 5.486 to 151.993; p<0.001

**Table D9. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al. 1996 <sup>43</sup> RCT/High	G1: Community-pharmacy based pharmaceutical care program G2: Usual care	G1: 23 G2: 26	Mean (SD) SBP (mm Hg) at four months.	Baseline: G1: 155.5 (21.1) G2: 147.9 (19.6) p: NS (between-group difference)  Follow up: G1: 143.2 (11.5) (p<0.05 for within group difference as compared to baseline) G2: 148.6 (20.1)  Calculated mean difference: -13.0; 95% CI, -23.739 to -2.261; p=0.018
			Mean (SD) DBP (mm Hg) at four months	Baseline: G1: 87.8 (9.9) G2: 83.3 (8.5) p: NS (between group difference)  Follow-up: G1: 83.2 (8.0) (p<0.05 for within group difference as compared to baseline) G2: 83.7 (10.9)  Calculated mean difference: -4.90; 95% CI, -10.3 to 0.50; p=0.075
			Percent of patients who were normotensive (SBP<140 and DBP<90)	Baseline: G1: 17.4 G2: 26.9 Calculated p: 0.428  Follow-up: G1: 52.2 (p<0.02 for within group difference compared to baseline) G2: 30.1 Calculated OR: 2.455; 95% CI, 0.764 to 7.888; p=0.132



**Table D9. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Planas et al. 2009 <sup>45</sup> RCT/High	G1: Community pharmacy- based hypertension MTM program for patients with diabetes G2: Control group (BP recorded, informed of BP goals at three time during study)	G1: 25 G2: 15	Mean (SD) change in SBP (mm Hg) at nine months	G1: -17.3 G2: 2.7 Between-group difference (95% CI): -20.0 (-32.7 to -7.4) p: 0.003
			Percent of patients at BP goal at nine months.	Baseline G1: 16.0 G2: 20.0 Calculated p: 0.714
				9 months G1: 48.0 G2: 6.7 p: 0.007
			OR for intervention group participant achieving BP goal relative to control group. (95% CI)	OR : 12.9 (1.5 to 113.8) p: 0.021

**Table D9. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Brummel et al. 2013 <sup>4</sup> , Soliman, 2013 et al. <sup>5</sup> Ramalho de Oliveira et al., 2010 <sup>6</sup>  Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage achieving BP goal (defined as less than 130/80) after 12 months of demonstration and after 24 months of demonstration (i.e., 12 months after end of demonstration)	Baseline G1: 66.12 G2: 61.17 p=0.44  12 months G1: 71.07 G2: 72.82 p=0.77 Unadjusted calculated OR: 0.917 95% CI 0.511 to 1.647, p=0.773  Adjusted difference in difference coefficient: 0.73, 95% CI 0.32 to 1.65, p=0.45  24 months G1: 76.03 G2: 69.9 p=0.3 Unadjusted calculated OR: 1.366 95% CI 0.755 to 2.471, p=0.303  Adjusted difference-in-difference coefficient: NR

**Table D9. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong et al., 2009 <sup>25</sup> Cohort/Medium	G1: Participants in Part D Medicare MTM program	G1: 1,301	Percentage with BP control (defined as < 130/80 mmHg)	Baseline
	G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects.	G2: 982 (Study included more subjects but this outcome was assessed among only patients with diabetes and HTN within each study arm)		G1: 48 G2: 43  6 months G1: 48 G2: 49 p=NS (adjusted for baseline BP status) Calculated OR: 0.953, 95% CI 0.808 to 1.125, p=0.571
		G1: 1101 G2: 895 (Study included more subjects but this outcome was assessed among only patients with HTN but without DM within each study arm)		Baseline G1: 75 G2: 70  6 months G1: 73 G2: 76 p=NS (adjusted for baseline BP status) Calculated OR: 0.898, 95% CI 0.733 to 1.099, p=0.296

**Table D9. Blood pressure: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1: 25 G2: 26	Mean (SD) SBP (mm Hg) at 6 months	Baseline G1: 151 (21) G2: 145 (19) p: 0.29
				Follow-up G1: 140 (14) G2: 143 (20) Calculated Mean Difference: -9.00 95% CI, -19.451 to 1.451; p=0.09558
			Mean (SD) DBP (mm Hg) at 6 months.	Baseline G1: 82 (9) G2: 80 (9) p: NS
				Follow-up G1: 80 (8) G2: 79 (10) Calculated Mean Difference, -1.00; 95% CI, -5.977 to 3.977; p=0.694
			Percent with blood pressure control	Baseline: G1: 52 G2: 54 Calculated p=0.90
				Follow-up: G1: 68 G2: 58  Calculated OR: 1.558; 95% CI, 0.496 to 4.898; p=0.448

**Table D9. Blood pressure: Summary of results (continued)**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Isetts et al., 2008 <sup>22</sup> Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percent of patients meeting HEDIS measures related to hypertension management at 12 months.	G1: 71 G2: 59  Calculated OR: 1.728; 95% CI, 1.026 to 2.911; p=0.04

Abbreviations: BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; DM = diabetes mellitus; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HTN = hypertension; mm Hg = millimeter mercury; MTM = Medication Therapy Management; NR= not reported; NS = not sufficient; OR = odds ratio; Q = quarter; RCT= randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; SMD = standardized mean difference

**Table D10. Drug therapy problems identified: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Krska et al., 2001 <sup>28</sup> RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems identified for each study arm at 3 months	G1: 1206 G2: 1380
Welch et al., 2009 <sup>56</sup> Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 123	At least 1 potential drug therapy problem during MTM process	G1: 89.8% G2: 83.7%  Calculated p=0.062

Abbreviations: G = group; MTM = Medication Therapy Management; NA = not applicable; RCT= randomized controlled trial.

**Table D11. Drug therapy problems resolved: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001 <sup>28</sup> RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems wholly or partially resolved at 3 months	G1: 998 G2: 569
Bernsten et al., 2001 <sup>1,2</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  6 months G1: 1024 G2: 953  12 months G1: 863 G2: 764  18 months G1: 704 G2: 636	Number of changes in therapy at baseline, 6, 12, and 18 months	Baseline G1: 1.1 (1.3) G2: 0.9 (1.2) p: <0.05  6 months G1: 1.5 (1.8) G2: 1.1 (1.4) p: <0.05  12 months G1: 1.3 (1.6) G2: 1.2 (1.5) p: NS  18 months G1: 1.4 (1.5) G2: 1.4 (1.4) p: NS
Moczygemba et al., 2011 <sup>37</sup> Moczygemba et al., 2008 <sup>38</sup> Cohort/Medium	G1: Opt-in telephone MTM program G2: No-MTM control group	G1: 60 G2: 60	Medication and health-related problems identified at baseline and 6 months	Mean (SD) Baseline G1: 4.8 (2.7) G2: 9.2 (2.9)  6 month G1: 2.5 (2.0) G2: 7.9 (3.0)  Calculated mean difference: -1.0 (95% CI, -1.97 to -0.03), p=0.4

**Table D11. Drug therapy problems resolved: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>35a</sup>  Cohort/Medium	<p>Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR</p> <p>Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR</p> <p>Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR</p> <p>Comparison – congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care</p> <p>Comparison - Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care</p> <p>Comparison - Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care</p>	<p>G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912</p>	<p>Remove drug-drug interaction within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)</p>	<p>Odds (95% CI) Congestive heart failure G1 vs. G13: 0.87 (0.76, 1.00), p&gt;0.05 G3 vs. G14: 1.05 (0.88, 1.26), p&gt;0.05</p> <p>Chronic obstructive pulmonary disease G5 vs. G15: 0.92 (0.79, 1.07), p&gt;0.05 G7 vs G16: 1.11 (0.89, 1.38), p&gt;0.05</p>



**Table D11. Drug therapy problems resolved: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>35a</sup> (continued)			Discontinue use of high risk medications within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Odds (95% CI) Congestive heart failure G1 vs. G13: 1.04 (.97, 1.11), p>0.05 G3 vs. G14: 0.93 (0.86, 1.01), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 1.06 (0.99, 1.13), p>0.05 G7 vs. G16: 1.00 (0.92, 1.09), p>0.05
			Discontinue use of medication contraindicated for congestive heart failure within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Odds ratio (95% CI) G1 vs. G13: 0.63 (0.58, 0.67), p<0.05 G3 vs. G14: 1.16 (1.03, 1.30), p<0.05
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Change in prevalence of high-risk medication use 9 months after becoming eligible for PCM	G1: -10.8 percentage points; p<0.05 G2: -1.4 percentage points; no significant change

<sup>a</sup>Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; CMR = comprehensive medication review; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; PCM = pharmaceutical case management; PDP = Medicare Part D Plan; NS = not significant; RCT = randomized controlled trial; SD = standard deviation.

**Table D12. Medication adherence: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
<b>Adherence Outcome Type 1: Proportion of patients adherent based on a threshold of percent of pills taken</b>				
Pindolia et al., 2009 <sup>44</sup> Cohort study/High	G1: Telephone based MTM Program	G1: 292	Percent of CHF patients who are adherent to at least 75% of ACE/ARB based on 2006 claims data: Measured during 6 months post-MTMP enrollment compared with 6 months pre-enrollment	Pre-test G1: 36 G2: 38.5 OR: 0.9 95% CI (0.7 to 1.2) p: 0.43
	G2: Patients eligible for MTM program who declined enrollment	G2: 1081 (study year 1)		Post-test G1: 40 G2: 38 OR: 1.1 95% CI (0.8 to 1.4) p=0.53
			Percent of CHF patients who are Adherent to at least 75% of Beta Blocker based on 2006 claims data: Measured during 6 months post-MTMP enrollment compared with 6 months pre-enrollment	Pre-test G1: 34.5 G2: 33 OR: 1.1 95% CI (0.8 to 1.4) p=0.63
				Post-test G1: 34 G2: 30.5 OR: 1.2 95% CI (0.9 to 1.5) p: 0.25
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 33 G2: 36	Percentage of patients adherent defined as self-reported taking 80% or more of medications 12 months after baseline	G1: 100 G2: 88.9 p: 0.115  Calculated OR: 9.3; 95% CI, 0.5 to 179.3; p=0.140

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Brummel et al. 2013 <sup>4</sup> , Soliman, 2013 et al. <sup>5</sup> Ramalho de Oliveira et al., 2010 <sup>6</sup> Cohort study/Medium	G1: Opted into clinic-based MTM program G2: Usual medical care (opted out of MTM program)	G1: 121 G2: 103	Percentage of patients adherent to aspirin (from pharmacy claims data) at baseline (before MTM), 12-month (during MTM demonstration project), and 24-month (1 year post-demonstration)	<p>Before MTM G1: 97.52% G2: 93.29% P: 0.11</p> <p>Baseline Calculated OR 2.828, 95% CI 0.710 to 11.259, p=0.14)</p> <p>During MTM Demonstration Project G1: 100% G2: 98.06% P: 0.12</p> <p>12 Month Calculated OR 5.981 (95% CI 0.284 to 126.030, p=0.250)</p> <p>1 Year Post-Demonstration Project G1: 99.17% G2: 99.03% P: 0.9</p> <p>24 Month Calculated OR 1.17 (95% CI 0.072 to 18.903, p=0.912)</p>

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
<b>Adherence Outcome Type 2: Absolute measure of adherence as percent of prescribed doses taken</b>				
Perlroth et al., 2013 <sup>35a</sup>	Congestive heart failure	G1: 12,658	Percentage of patients achieving adherence (> 80% of prescribed pills taken) to various specified medications	<b>CHF</b> Adherent to any evidence-based medicine (EBM) for CHF G1 vs. G13: 1.28 <sup>a</sup> (1.19, 1.37) G3 vs. G14: 1.40 <sup>a</sup> (1.29, 1.52) p<0.05
Cohort/Medium	G1: enrolled in PDP receiving MTM with CMR	G3: 11,260		
	G3: enrolled in MA-PD, receiving MTM with CMR	G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527	365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	
	Chronic obstructive pulmonary disease	G13: 156,441 G14: 51,938		<b>COPD</b> Adherent to long-acting beta agonist (LABA)-only regimen G5 vs. G15: 1.26* (1.14, 1.40) G7 vs. G16: 1.11 (0.95, 1.29) p<0.05
	G5: enrolled in PDP receiving MTM with CMR	G15: 184,350 G16: 73,623		
	G7: enrolled in MA-PD, receiving MTM with CMR	G17: 133,925 G18: 53,912		
	Diabetes			
	G9: enrolled in PDP receiving MTM with CMR			
	G11: enrolled in MA-PD, receiving MTM with CMR			
	Comparison—congestive heart failure			
	G13: enrolled in PDP, usual care			
	G14: enrolled in MA-PD, usual care			Adherent to long-acting anticholinergic (LAAC)-only regimen G5 vs. G15: 1.36* (1.12, 1.65) G7 vs. G16: 1.01 (0.83, 1.24) p<0.05
	Comparison—Chronic obstructive pulmonary disease			
	G15: enrolled in PDP, usual care			
	G16: enrolled in MA-PD, usual care			Adherent to combination regimen G5 vs. G15: 1.43 <sup>a</sup> (1.26, 1.62) G7 vs. G16: 1.20 (1.00, 1.44) p<0.05
	Comparison—Diabetes			
	G17: enrolled in PDP, usual care			<b>Diabetes</b> Adherent to diabetes medication G9 vs. G17: 1.33 <sup>a</sup> (1.25, 1.41) G11 vs. G18: 1.35 <sup>a</sup> (1.27, 1.45) p<0.05 Adherent to biguanides medication G9: 1.27 <sup>a</sup> (1.19, 1.36) G11: 1.20 <sup>a</sup> (1.12, 1.29) p<0.05

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>35a</sup> (continued)	G18: enrolled in MA-PD, usual care			<p>Adherent to DPP-IV inhibitors medication G9 vs. G17: 1.32<sup>a</sup> (1.12, 1.55) G11 vs. G18: 1.19 (.96, 1.48) p&lt;0.05</p> <p>Adherent to sulfonylureas medication G9 vs. G17: 1.22<sup>a</sup> (1.13, 1.31)) G11 vs. G18: 1.28<sup>a</sup> (1.19, 1.38) p&lt;0.05</p> <p>Adherent to Thiazolidinediones medication G9 vs. G17: 1.31<sup>a</sup> (1.19, 1.45) G11 vs. G18: 1.16<sup>a</sup> (1.04, 1.29) p&lt;0.05</p> <p>Use of ACE Inhibitor or ARB medication G9 vs. G17: 0.99 (0.90, 1.08) G11 vs. G18: 1.24<sup>a</sup> (1.12, 1.38) p&lt;0.05</p> <p>Use of statin medication G9 vs. G17: 1.01 (0.91, 1.13) G11 vs. G18: 1.33<sup>a</sup> (1.16, 1.52) p&lt;0.05</p>
Moczygemba, 2011 <sup>37</sup> Moczygemba, 2008 <sup>38</sup> Retrospective cohort/ Medium	G1: Opt-in telephone SWHP MTM program G2: No-MTM control group	G1: 60 G2: 60	Percent prescribed doses taken: Overall average MPR across all medication (medication possession ratio) measured at 6 months before MTM participation (i.e., baseline) and 6 months post-MTM (i.e., follow-up) using pharmacy data	<p>Baseline G1: 0.7 (0.2) G2: 0.7 (0.2) p: 0.73</p> <p>6 months G1: 0.7 (0.2) G2: 0.7 (0.2) p: NR Overall p: 0.79</p> <p>Calculated mean difference: -0.040 95% CI: -0.101 to 0.021 p=0.201</p>

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Planas, et al 2009 <sup>45</sup> RCT/High	G1: Collaborative home-based medication review G2: No medication review received	Participants G1: 25 G2: 15	Percent mean adherence (percent of prescribed doses taken) to antihypertensive medication	9 months before baseline, % (95% CI) G1: 80.5 (74.9 to 86.0) G2: 79.5 (71.0 to 88.1)	
				9 months after baseline, % (95% CI) G1: 87.5 (82.1 to 93.0) G2: 78.8 (69.7 to 87.9) p: 0.0712 Calculated standardized difference in means from Baseline to 9 months: 0.2 95% CI (-0.4 to 0.9) p: 0.46	
Park et al., 1996 <sup>43</sup> RCT/High	G1: Comprehensive pharmaceutical care G2: Usual care	Visit 1 G1: 7 G2: 5	Mean percent compliance (percent of prescribed pills taken) from pharmacist report of pill counts	Baseline/Visit 1 G1: 87.4 (0.9) G2: 87.8 (13.7)	
				Visit 2 G1: 21 G2: 23	4 month timeframe Visit 2 G1: 96.7 (4) G2: 86.0 (20.7) p=0.025
				Visit 3 G1: 23 G2: 20	Visit 3 G1: 97.2 (4.4) G2: 86.7 (23.1) p=0.037
				Visit 4 G1: 21 G2: 22	Visit 4 G1: 86.8 (28.7) G2: 89.1 (21.8)  Calculated standardized difference in means for change from baseline to Visit 4: -0.1 95% CI (-0.7 to 0.5) p=0.77

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Moore, 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Medication possession ratio by medication type from pharmacy data and medical claims data from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	<p>Asthma MPR at baseline [% (SE)] G1: 56.8 (1.544) G2: 53.8 (1.636) p: 0.180</p> <p>mean change in Asthma MPR [% (SE)] G1: 2.33 (1.22) G2: 1.71 (1.38) p: 0.739</p> <p>Asthma MPR (%) Calculated mean difference = 0.62; 95% CI: -2.988 to 4.228; p = 0.736</p> <p>Depression MPR at baseline [% (SE)] G1: 72.0 (1.064) G2: 74.5 (0.946) p: 0.075</p> <p>mean change in Depression MPR [% (SE)] G1: 1.23 (1.06) G2: 0.07 (0.98) p: 0.420</p> <p>Depression MPR (%) Calculated mean difference = 1.16; 95% CI: -1.667 to 3.987; p = 0.421</p> <p>Diabetes MPR at baseline [% (SE)] G1: 76.0 (1.031) G2: 73.7 (0.984) p: 0.108</p> <p>mean change in Diabetes MPR [% (SE)] G1: 1.64 (1.01) G2: -0.73 (1.08) p: 0.112</p>

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Moore, 2013 <sup>40</sup> (continued)				<p>Diabetes MPR (%) Calculated mean difference = 2.37; 95% CI: -0.549 to 5.289; p = 0.112</p> <p>Dyslipidemia MPR at baseline [% (SE)] G1: 80.9 (0.581) G2: 80.0 (0.639) p: 0.263</p> <p>mean change in Dyslipidemia MPR [% (SE)] G1: 2.10 (0.66) G2: -2.61 (0.76) p&lt;0.001</p> <p>Dyslipidemia MPR (%) Calculated mean difference = 4.71; 95% CI: 2.747 to 6.673; p&lt; 0.001</p> <p>Hypertension MPR at baseline [% (SE)] G1: 81.8 (0.448) G2: 80.9 (0.468) p: 0.188</p> <p>mean change in Hypertension MPR [% (SE)] G1: 2.29 (0.46) G2: -2.31 (0.54) p&lt;0.001</p> <p>Hypertension MPR (%) Calculated mean difference = 4.60; 95% CI: 3.211 to 5.989; p&lt; 0.001</p>



**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
<b>Adherence Outcome Type 3: Self-reported Adherence using Morisky Scale</b>				
Bernsten, 2001 <sup>1</sup> ; Sturgess, 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	Pooled sample (excluding The Netherlands because no baseline adherence data collected)  Baseline G1: 867 G2: 748  6 months G1: NR G2: NR  12 months G1: NR G2: NR  18 months G1: 792 G2: 758	Medication adherence: self-reported as assessed by Morisky Scale  (Note: Percent of participants who we adherent defined as patients responded that they “never” experienced any aspects of non-compliance on the 4-item 4-point scale)	Pooled sample (percent adherent) Baseline G1: 33.9 G2: 38.6 OR: 0.8 Calculated 95% CI (0.7 to 1.0) p: 0.049  6 months G1: 38.5 G2: 36.6 p: NR  12 months G1: 43.8 G2: 37.3 p: NR  18 months G1: 38.2 G2: 39.4 OR: 1.1 95% CI (0.9 to 1.3) p=0.440101  Percent changing from nonadherent to adherent over 18 months G1: 15.2 G2: 12.2 p: 0.028

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> (PREP); Kassam et al., 2001 <sup>55</sup> RCT/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	T1: N=363 G1: 159 G2: 204 T2: N=317 T3: N=292	Self-reported adherence using the 4-item 2-point Morisky Scale where summary score is 0-4 with lower scores being better adherence	Mean Adherence Scale Score Baseline: G1: 0.5 (0.8) G2: 0.6 (0.9) p: NS
		Estimated by group based on overall retention G1: 127 G2: 163	Time 1 (Baseline), Time 2 (mid-point, 6 to 7 months after intervention) and Time 3 (12 to 13 months after intervention)	Calculated standardized difference in means: -0.1 95% CI (-0.3 to 0.1) p=0.208957
				6-month followup: G1: 0.5 (0.7) G2: 0.6 (0.8) p: NS
				12-month followup: G1: 0.6 (0.8) G2: 0.5 (0.7) p: NS
				Calculated standardized difference in means: -0.13 95% CI (-0.11 to 0.36) p=0.289285

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup> RCT/High (medium for study overall by high for adherence due to poor measure)	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Self-reported composite "understanding and compliance" 0-12 score at baseline and 6 months (no further information on measure used)	Baseline Means Scale Score (SD not reported) G1: 2.3 G2: 2.3 p: NS
			Change in self-reported composite score over 6 months with negative score representing improvement	6 months G1: 0.6 G2: 2.1 p: NS  G1: -1.6 G2: -0.2 p: NS

**Table D12. Medication adherence: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
<b>Miscellaneous Adherence Outcomes</b>				
Hanlon et al., 1996 <sup>17</sup> RCT/Medium (low for study overall but medium for adherence due to lack of information about and precision of adherence measure)	G1: Usual care, plus clinical pharmacist care.  G2: Usual care in the GMC	G1: 86 G2: 83	Self-report Medication Compliance with 12 month time frame, assessed by determining whether the way patient said they took the medicine (in terms of number of pills and daily frequency) matched how it was prescribed. Compliance was defined as the proportion of medications for which the patients' response agreed with the directions	Baseline: G1: 73% G2: 74% OR: 0.95 95% CI (0.48 to 1.88) p: 0.88  12 Months Follow-up G1: 77.4% G2: 76.1% p: 0.88
Sidel et al., 1990 <sup>50</sup> RCT/Medium	G1: received at least 2 pharmacist visits involving medication review, patient specific education and counseling; follow up patient phone calls and contact of physicians as needed G2: only contacted for to complete the survey.	G1: 92 G2: 104	Medication-taking Behavior Subscore in change from baseline to 6 month follow-up (negative scores indicate improvement= decreased risk)  Change in normative score for Remembering to take Medicine at 6 months	G1: -3.47 G2: -4.38 p< .001 for within group differences p: 0.52 for between group differences  G1: 0.09 G2: -0.19 p: 0.52

<sup>a</sup> Perlroth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: ACE/ARB = Angiotensin-Converting Enzyme/Angiotensin II Receptor Blockers; CMR = comprehensive medication review; CHF = Cardiovascular Heart Failure; CI = confidence interval; G = group; GMC = General Medicine Clinic; MA-PD = Medicare Advantage Part D Plan; MPR = medication possession ratio; MTM = Medication Therapy Management; MTMP = Medication Therapy Management Program; NR = not reported; NS = not sufficient; OR = odds ratio; PDP = Medicare Part D Plan; PREP = Pharmaceutical Care Research and Education Project; RCT= randomized controlled trial; SD = standard deviation; SWHP = Scott & White Health Plan; T = time.

**Table D13. Medication appropriateness scales: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Covariate-adjusted Medication Appropriateness Index Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 17.7 (0.6) G2: 17.6 (0.6)
	G2: Usual care in the GMC			3 months G1: 13.4 (0.6) G2: 16.5 (0.6) 95% CI: NR p:<0.0006 for between group differences, controlling for baseline and other covariates  12 months G1: 12.8 (0.7) G2: 16.7 (0.7) 95% CI: NR p:<0.0006 for between group differences, controlling for baseline and other covariates
		G1: 105 G2: 103	Change in covariate-adjusted Medication Appropriateness Index Assessed at baseline, 3, 12 months by blinded research pharmacist	3 months change in outcome G1: -4.3 G2: -1.1 95% CI: NR  24% improvement in intervention group compared to a 6% improvement in control group p: 0.0006  12 months change in outcome G1: -4.9 G2: -0.9 95% CI: NR 28% improvement in intervention group versus 5% improvement in control group p: 0.0002

**Table D13. Medication appropriateness scales: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1: 25 G2: 26	Appropriateness of BP regimen	BP Regimen Baseline G1: 8.7 (4.7) G2: 10.3 (4.8)
				Follow-up G1: 10.9 (4.5) G2: 10.1 (5.2) p for change scores NR
			Appropriateness of daily dosage	Appropriateness of daily dosage Baseline G1: 11.6 (4.5) G2: 12.6 (4.5)
				Follow-up G1: 13.4 (3.7) G2: 13.2 (4.1) p for change scores NR
			Appropriateness of dosing interval	Appropriateness of dosing interval Baseline G1: 13.8 (4.3) G2: 13.4 (4.6)
				Follow-up G1: 15.1 (2.3) G2: 13.8 (4.1) p for change scores NR

Abbreviations: BP = blood pressure; CI = confidence interval; G = group; GMC = General Medicine Clinic; NR = not reported; RCT = randomized controlled trial

**Table D14. Medication appropriateness for individual medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
McDonough et al., 2005 <sup>36</sup> cluster-randomized RCT/Medium	G1: Pharmaceutical care provided by pharmacist in a community pharmacy G2: Usual care	Baseline	Nine Month Follow-up	Baseline
		G1: 70 G2: 26	Percentage of patients (at risk for glucocorticoid-induced osteoporosis) on bisphosphonate drug therapy	G1: 17.1 G2: 0 p: <0.05 for between group difference at baseline
		Follow-up G1: 61 G2: 19		9 Month Follow-up G1: 26.2 (p <0.05 for within group difference as compared to baseline) G2: 10.5 p: NS for between group difference at follow-up; change in outcome between baseline and follow-up was NS between groups
Percentage of patients (at risk for glucocorticoid-induced osteoporosis) on estrogen drug therapy			Baseline	Baseline G1: 12.9 G2: 0 p: NS for between group difference at baseline
Percentage of patients (at risk for glucocorticoid-induced osteoporosis) taking calcium supplements			Baseline	9 Month Follow-up G1: 16.4 (p <0.05 for within group difference as compared to baseline) G2: 0 p: NS for between group difference at follow-up; change in outcome between baseline and follow-up was NS between groups.
Percentage of patients (at risk for glucocorticoid-induced osteoporosis) taking calcium supplements			Baseline	Baseline G1: 38.6 G2: 38.5 p: Between group differences at baseline presumably not significant, since P was reported for other outcomes if significantly different between groups.
Percentage of patients (at risk for glucocorticoid-induced osteoporosis) taking calcium supplements			9 Month Follow-up	9 Month Follow-up G1: 55.7 (p <0.05 for within group difference as compared to baseline) G2: 31.6 p: <0.05 for change in outcome between groups from baseline to follow-up

**Table D14. Medication appropriateness for individual medications: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Gattis et al., 1999 <sup>15</sup> RCT/Medium	G1: Clinical pharmacist intervention G2: Usual medical care	G1: 90 G2: 91	6 month follow-up	G1: 87 G2: 79 p: 0.18
			Percent receiving an ACEI at follow-up	
			Fraction of target ACEI dose at follow up	G1: 1 (25%: 0.5, 75%: 1) G2: 0.5 (25% 0.188, 75%: 1) 95% CI: NR p: < 0.001
		G1: 12 G2: 19	Of those NOT on an ACEI at follow-up, percentage receiving alternative drug therapy	G1: 75 G2: 26 p: 0.02

Abbreviations: ACEI = Angiotensin-Converting Enzyme Inhibitors; CI = confidence interval; G = group; NR = not reported; NS = not sufficient; RCT = randomized controlled trial



**Table D15. Medication Appropriateness Index Item 1 (Is there an indication for the drug?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanson et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants	Percent Prescriptions Inappropriate	Baseline G1: 10.5 G2: 12.4
		Number of prescriptions: Baseline G1: 798 G2: 846	Assessed at baseline, 3, 12 months by blinded research pharmacist	3 months G1: 8.1 G2: 10.5 p: NR
	12 months G1: 734 G2: 847		12 months G1: 6.0 G2: 9.7 p: NR	
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline G1: 33.3 G2: 46.8
		Number of prescriptions: Baseline G1: 210 G2: 207	Assessed at baseline, 12 months by blinded research pharmacist	12 months G1: 16.1 G2: 48.2
	12 months G1: 155 G2: 224			

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D16. Medication Appropriateness Index Item 2 (Is the medication effective for the condition?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 4.5
		G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 4.9
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 3.6 G2: 4.9 p: NR
12 months G1: 734 G2: 847	12 months G1: 3.4 G2: 4.9 p: NR			
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 29.1
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 44.9
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 13.6 G2: 44.6
12 months G1: 155 G2: 224				

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D17. Medication Appropriateness Index Item 3 (Is the dosage correct?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanson et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 17.4
		G2: 103		G2: 17.3
		Number of prescriptions: Baseline G1: 798 G2: 846	Assessed at baseline, 3, 12 months by blinded research pharmacist	3 months G1: 13.1 G2: 18.2 p: NR
		12 months G1: 734 G2: 847		12 months G1: 15.0 G2: 20.4 p: NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 63.3
		G2: 36		G2: 62.3
		Number of prescriptions: Baseline G1: 210 G2: 207	Assessed at baseline, 12 months by blinded research pharmacist	12 months G1: 12.9 G2: 63.8
		12 months G1: 155 G2: 224		

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D18. Medication Appropriateness Index Item 4 (Are the directions correct?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 32.7
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 32.2
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 28.1 G2: 32.6 p: NR
		12 months G1: 734 G2: 847		12 months G1: 27.5 G2: 29.9 p: NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 70.5
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 64.3
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 29.7 G2: 56.7
		12 months G1: 155 G2: 224		

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D19. Medication Appropriateness Index Item 5 (Are the directions practical?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 20.7
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 20.0
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 15.8 G2: 18.9 p: NR
	12 months G1: 734 G2: 847		12 months G1: 15.3 G2: 21.2 p: NR	
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 61.0
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 57.0
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 29.7 G2: 56.7
	12 months G1: 155 G2: 224			

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D20. Medication Appropriateness Index Item 6 (Are there clinically significant drug-drug interactions?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanson et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 0
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 0
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 0 G2: 0.1 p: NR
		12 months G1: 734 G2: 847		12 months G1: 0 G2: 0.1
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 22.9
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 17.9
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 5.8 G2: 22.8
		12 months G1: 155 G2: 224		

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D21. Medication Appropriateness Index Item 7 (Are there clinically significant drug-disease interactions?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 1.9
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 1.0
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 2.0 G2: 0.7 p: NR
	12 months G1: 734 G2: 847		12 months G1: 1.9 G2: 1.1 p: NR	
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 18.6
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 21.3
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 9.0 G2: 19.6
	12 months G1: 155 G2: 224			

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D22. Medication Appropriateness Index Item 8 (Is there unnecessary duplication with other drugs?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescription Inappropriate	Baseline
		G1: 105		G1: 4.9
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 6.4
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 3.0 G2: 5.9 p: NR
	12 months G1: 734 G2: 847		12 months G1: 4.9 G2: 8.2 p: NR	
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 11.9
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 6.8
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 4.5 G2: 7.6
	12 months G1: 155 G2: 224			

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial



**Table D23. Medication Appropriateness Index Item 9 (Is the duration of therapy acceptable?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 105		G1: 15.4
	G2: Usual care in the GMC	G2: 103	Assessed at baseline, 3, 12 months by blinded research pharmacist	G2: 17.5
		Number of prescriptions: Baseline G1: 798 G2: 846		3 months G1: 11.8 G2: 14.9 p: NR
		12 months G1: 734 G2: 847		12 months G1: 10.1 G2: 14.9 p: NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants	Percent Prescriptions Inappropriate	Baseline
		G1: 33		G1: 35.2
		G2: 36	Assessed at baseline, 12 months by blinded research pharmacist	G2: 48.8
		Number of prescriptions: Baseline G1: 210 G2: 207		12 months G1: 18.1 G2: 49.1
		12 months G1: 155 G2: 224		

Abbreviations: G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial

**Table D24. Medication Appropriateness Index Item 10 (Is this drug the least expensive alternative compared with others of equal utility?): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanson et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Percent Prescriptions Inappropriate	Baseline G1: 29.2 G2: 30.3
	G2: Usual care in the GMC		Assessed at baseline, 3, 12 months by blinded research pharmacist	3 months G1: 25.6 G2: 27.7 p: NR  12 months G1: 25.3 G2: 28.2 p: NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care G2: Standard care	Baseline G1: 210 G2: 207  12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate  Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 50.0 G2: 62.3  12 months G1: 38.7 G2: 60.3

Abbreviations: G = group; GMC = General Medicine Clinic; NR = not reported; RCT = randomized controlled trial

**Table D25. Medication dosing: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup> RCT/Medium	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Change in number of doses per day at 6 months follow up.	G1: - 1.6 G2: 2.2 p: 0.007

Abbreviations: G = group; mg/kg = milligram/kilogram; MTM = Medication Therapy Management; RCT = randomized controlled trial

**Table D26. Adverse events: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low	G1: Basic MTM services (with medication information gleaned through patient interview)	G1: 211	Percent of patients with an ADE between 0 and 3 months and OR	G1: 42.2
		G2: 218		G2: 27.9
	G2: Enhanced MTM services (pharmacist provided with 2 page clinical summary from patient medical record).	G3: 208	Percent of patients with an ADE between 3 and 6 months and OR	G3: 33.7
				G1 vs. G3: OR: 1.6 p=0.078
G3: Usual pharmacy care				G2 vs. G3: OR: 0.7 p=0.278
				G1: 36.1
				G2: 31.1
				G3: 34.4
				G1 vs. G3: OR: 1.1 p=0.717
				G2 vs. G3: OR: 0.9 p=0.672
			Mean number (SD) of ADEs per patient between 0 and 3 months	G1: 0.750 (1.113)
				G2: 0.547 (1.184)
				G3: 0.559 (1.202)
				G1 vs. G3: Calculated Mean Difference, 0.191; 95% CI, -0.031 to 0.413 p=0.091
				G2 vs. G3: Calculated Mean Difference, -0.012; 95% CI, -0.239 to 0.215 p=0.917
			Mean number (SD) of ADEs per patient between 3 and 6 months	G1: 0.814 (1.421)
				G2: 0.530 (0.894)
				G3: 0.468 (0.820)
				G1 vs. G3: Calculated Mean Difference, 0.284; 95% CI, 0.056 to 0.512 p=0.014
				G2 vs. G3: Calculated Mean Difference, -0.062; 95% CI, -0.225 to 0.101 p=0.455

**Table D26. Adverse events: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Medium	G1: Clinical pharmacist care within a general medicine clinic.  G2: Usual care	G1: 86 G2: 83	Percent with an ADE at 12 months	G1: 30.2 G2: 40.0 p=0.19  Calculated OR: 0.6; 95% CI, 0.37 to 1.15 p=0.14
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/High <sup>a</sup>	G1: Pharmaceutical care G2: Standard care	G1: 33 G2: 36	Percent of patients with at least one medication misadventure at 12 months	G1: 2.8 <sup>b</sup> (N=4) G2: 3.0 <sup>b</sup> (N=3) Calculated OR based on reported percent: 0.93; 95% CI, 0.056 to 15.603 p: 0.0961  Calculated OR based on reported N: 1.5 (95% CI, 0.31 to 7.34), p= 0.606
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup> RCT/High <sup>a</sup>	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Change in mean medication side effect score at six months.	G1: -3.7 G2: -1.9 p: NS and unable to calculate.
Fischer et al., 2000 <sup>10</sup> NRCT/High <sup>a</sup>	G1: Comprehensive drug therapy management program G2: Standard community pharmacy practice	G1: 201 G2: 368	OR for likelihood of reporting side effects or problems due to prescription medication (95% CI)	1.8 (1.20 to 2.80)

<sup>a</sup> This study was rated medium risk of bias overall, but due to measurement bias with this specific outcome, it was considered high risk of bias for this outcome.

<sup>b</sup> The percent reported by authors cannot be generated based on the reported N and the reported number of events.

Abbreviations: ADE = adverse drug event; CI = confidence interval; G = group; MTM = Medication Therapy Management; N = number; NRCT = nonrandomized controlled trial; NS = not significant; NS = not sufficient; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; vs. = versus.

**Table D27. Cognitive, affective, and physical functioning: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Williams, 2004 <sup>37</sup> RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	Baseline and 6 weeks Mean (SD)	Baseline 6 weeks
			Timed manual performance (seconds)	G1: 9.8 (4.2) 9.3 (4.0) G2: 9.6 (3.81) 9.0 (4.1) Calculated mean differences at 6 weeks (unadjusted for baseline differences): 0.300; 95% CI, -1.093 to 1.693; p=0.673
			Physical performance test (seconds)	G1: 57.2(28.59) 59.6(31.6) G2: 57.2(28.88) 56.3(27.5) Calculated mean differences at 6 weeks (unadjusted for baseline differences): -3.300; 95% CI, -13.370 to 6.770; p=0.52
			Functional reach (inches)	G1: 11.5(3.0) 11.3(3.3) G2: 11.2(3.1) 11.3(3.0) Calculated mean differences at 6 weeks (unadjusted for baseline differences): 0.00; 95% CI, -1.076 to 1.076; p=1.0
			Digit Span (WAIS)	G1: 12.8(4.72) 13.3(4.3) G2:12.8(3.82) 13.1(4.3) Calculated mean differences at 6 weeks (unadjusted for baseline differences): 0.200; 95% CI, -1.277 to 1.677; p=0.791
			Digit Symbol (WAIS)	G1: 33.9(15.8) 33.1(15.9) G2: 30.4(14.3) 33.1(14.2) Calculated mean differences at 6 weeks (unadjusted for baseline differences): 0.00; 95% CI, -5.134 to 5.134; p=1.0
			Randt Memory Test	G1: 9.7(3.7) 9.6(3.5) G2:10.1(3.75) 9.6(3.4) Calculated mean differences at 6 weeks (unadjusted for baseline differences): 0.00; 95% CI, -1.182 to 1.182; p=1.00

**Table D27. Cognitive, affective, and physical functioning: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Williams, 2004 <sup>37</sup> RCT/Medium (continued)	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care (continued)	G1: 57 G2: 76 (continued)	CES-D score	G1: 12.4(7.4) 11.9(7.9) G2: 11.9(8.3) 10.8(7.9) Calculated mean differences at 6 weeks (unadjusted for baseline differences): -1.10 95% CI -3.813 to 1.613, p=0.427	
			Self-rating Anxiety Scale score	G1: 14.2(7.8) 13.2(6.5) G2: 14.4(6.4) 13.1(6.8) Calculated mean differences at 6 weeks (unadjusted for baseline differences): -0.100 95% CI -2.392 to 2.192, p=0.932	
Marques et al., 2013 <sup>33</sup> RCT/Medium	G1: Dader method pharmacotherapy intervention G2: Usual care	G1: 22 G2: 26	Beck Depression Inventory Score at baseline and three months:	Baseline , 3 months, Mean change G1: 28, 14.5, -13.5 G2: 23, 20.5, -2.5 95% CI: NR p: 0.0275	
			G1: 22 G2: 26	Beck Anxiety Inventory Score at baseline and three months:	Baseline, 3 months , Mean change G1: 29, 16, -13.0 G2: 24, 20,5 -3.0 95% CI: NR p: 0.0194
			G1: 22 G2: 26	Percentage with Depression Remission (defined as BDI < 11)	G1: 30.4 G2: 15.3 Calculated OR, 2.406; 95% CI, 0.601 to 9.632, p=0.215
			G1: 5 G2: 5	Percentage with severe depression improvement	G1: 80.0 G2: 60.0 Calculated OR, 2.667; 95% CI, 0.158 to 45.141, p=0.497
			G1: 13 G2: 13	Percentage with moderate depression improvement	G1: 53.8 G2: 7.7 Calculated OR, 14.00; 95% CI, 1.385 to 141.485, p=0.025

Abbreviations: BDI= Beck Depression Inventory; CES-D= Center for Epidemiological Studies-Depression Scale; CI= confidence interval; G = group; NR = not reported; OR= odds ratio; SD= standard deviation; RCT = randomized controlled trial; WAIS= Wechsler Adult Intelligence Scale

**Table D28. All-cause mortality: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Gattis et al., 1992 <sup>15</sup> RCT/Medium	G1: Clinical pharmacist intervention in addition to usual medical care G2: Usual medical care	G1: 90 G2: 91	Percent died and OR for all-cause mortality within 6 months (95% CI)	G1: 3.3% G2: 5.5% OR: 0.59 (0.12 to 2.49) p=0.48
Welch et al., 2009 <sup>56</sup> Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (opt-out)	G1: 459 G2: 336	Percent died and adjusted OR for all-cause mortality, within 6 months (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	G1: 4.1% G2: 7.4% Adjusted OR: 0.5 (0.3 to 0.9) p=0.044
Yamada et al., 2012 <sup>61</sup> Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Adjusted HR for all-cause mortality within 1 to 4 years (adjusted for age, sex, Charlson, CHF, ESRD)	Adjusted HR: 0.92 95% CI, 0.87 to 0.96 p< 0.001

Abbreviations: CHF=congestive heart failure; CI = confidence interval; DCG=diagnostic cost group (a measure of health care use and comorbidity), ESRD=end-stage renal disease; G = group; HR=hazard ratio; MTM = Medication Therapy Management; OR = odds ratio; RCT = randomized controlled trial;



**Table D29. Gastrointestinal bleeding events: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Pindolia et al., 2009 <sup>44</sup> Cohort study/High	G1: Opted in to a telephone based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR (Was only assessed among patients with arthritis in each study arm and N for this outcome was not reported)	Change in percent of patients gastrointestinal bleeding at 6 months.	G1: -60% G2: 0 % Between-group p: 0.001

Abbreviations: CI = confidence interval; G = group; MTM = Medication Therapy Management.

**Table D30. Self-reported health status: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Physical Functioning Domain (change from baseline)	6-Month Follow-up G1: -4.9 (1.0 SE) G2: -3.4 (0.9 SE)  12-Month Follow-up G1: -5.3 (1.0 SE) G2: -6.1 (1.0 SE)  p=0.412
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Physical Functioning Domain	Baseline G1: 62.0 (29.4) G2: 61.9 (24.3)  12-Month Follow-up G1: 68.6 (24.0) G2: 56.1 (27.5)  p: NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Physical Functioning Domain	Baseline: G1: 48.0 (2.7) G2: 45.3 (2.7)  12-Month Follow-up G1: 44.1 (2.0) G2: 42.2 (2.0)  p= 0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Physical Functioning Domain (Change between Baseline and 18-Month Follow-Up)	G1: -1.0 G2: -0.7  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Physical Functioning Domain	Baseline G1: 61.5 G2: 66.5  6-Month Follow-up G1: 70.7 G2: 67.7  p=NR
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Physical Functioning Domain	Baseline G1: 77.0 (26.1) G2: 66.3 (29.1)  4-Month Follow-up G1: 77.8 (30.4) G2: 70.2 (29.2)  p=NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Physical Functioning Domain	Baseline G1: 55.6 (95% CI, 55.5 to 56.0) G2: 54.2 (95% CI, 48.0 to 54.4)  5-Month Follow-up G1: 55.0 (95% CI, 54.6 to 55.3) G2: 55.0 (95% CI, 54.8 to 55.2)  p: 0.93
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Physical Functioning Domain	G1: NR G2: NR  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Role Physical Domain (change from baseline)	6-Month Follow-up G1: -3.5 (1.8 SE) G2: -4.3 (2.1 SE)  12-Month Follow-up G1: -4.3 (2.0 SE) G2: -8.2 (2.00 SE)  p=0.245
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Role Physical Domain	Baseline G1: 50.8 (42.2) G2: 47.9 (42.8)  12-Month Follow-up G1: 68.2 (42.1) G2: 52.8 (42.2) 95% CI: NR  p=NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Role Physical Domain	Baseline: G1: 38.3 (3.2) G2: 36.5 (3.2)  12-Month Follow-up G1: 38.6 (3.2) G2: 32.3 (3.7)  p=0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Role Physical Domain (Change between Baseline and 18-Month Follow-Up)	G1: -1.1 G2: -0.3  p=NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> , Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Role Physical Domain	Baseline G1: 54.3 G2: 63.5  6-Month Follow-up G1: 74.0 G2: 62.5  p=NR
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Role Physical Domain	Baseline G1: 85.9 (30.0) G2: 77.9 (31.1)  4-Month Follow-up G1: 85.2 (31.5) G2: 73.1 (40.6)  p=NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug- related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Role Physical Domain	Baseline G1: 53.8 (95% CI, 53.1 to 54.6) G2: 55.0 (54.5 to 55.5)  5-Month Follow-up G1: 48.5 (95% CI, 47.8 to 49.3) G2: 52.1 (95% CI, 41.6 to 42.6)  p: 0.65
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Role Physical Domain	G1: NR G2: NR  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Bodily Pain Domain (change from baseline)	6-Month Follow-up G1: -0.8 (1.0 SE) G2: -3.3 (0.9 SE)  12-Month Follow-up G1: -0.3 (1.0 SE) G2: -4.8 (1.0 SE)  p=0.004
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Bodily Pain Domain	Baseline G1: 60.0 (27.0) G2: 65.4 (23.0)  12-Month Follow-up G1: 68.5 (22.3) G2: 63.1 (25.8)  p=NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Bodily Pain Domain	Baseline G1: 45.0 (2.8) G2: 42.2 (2.8)  12-Month Follow-up G1: 43.6 (2.7) G2: 41.7 (2.7)  p=0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Bodily Pain Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.06 G2: +0.53  p=NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997, <sup>7</sup> Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Bodily Pain Domain	Baseline G1: 58.4 G2: 76.7  6-Month Follow-up G1: 71.1 G2: 74.7  p=NR
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Bodily Pain	Baseline G1: 77.4 (19.0) G2: 73.1 (21.3)  4-Month Follow-up G1: 80.5 (22.9) G2: 73.7 (19.0)  p=NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Bodily Pain	Baseline G1: 60.5 (95% CI, 60.2 to 60.8) G2: 60.8 (95% CI, 60.6 to 61.0)  5-Month Follow-up G1: 56.6 (95% CI, 56.4 to 56.8) G2: 59.0 (95% CI, 58.8 to 59.2)  p: 0.65
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Bodily Pain	G1: NR G2: NR  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 General Health Perception Domain (change from baseline)	6-Month Follow-up G1: -1.6 (0.8 SE) G2: -2.2 (0.7 SE)  12-Month Follow-up G1: -2.4 (0.8 SE) G2: -5.3 (0.8 SE) 95% CI: NR p=0.026
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 General Health Perception Domain	Baseline G1: 50.8 (19.5) G2: 49.9 (19.8)  12-Month Follow-up G1: 57.0 (19.6) G2: 50.1 (15.9)  p: NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 General Health Perception Domain	Baseline G1: 34.9 (2.1) G2: 34.2 (2.1)  12-Month Follow-up G1: 37.4 (1.6) G2: 35.2 (1.7)  p=0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup>  RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 General Health Perception Domain (Change between Baseline and 18-Month Follow-Up)	G1: +0.28 G2: -0.66  p: NS



**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 General Health Perception Domain	Baseline G1: 58.2 G2: 61.2  6-Month Follow-up G1: 58.7 G2: 64.0  p=NR
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 General Health Perception Domain	Baseline G1: 67.8 (18.7) G2: 59.5 (15.1)  4-Month Follow-up G1: 72.3 (13.1) G2: 64.7 (19.0)  p: NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 General Health Perception Domain	Baseline G1: 62.2 (95% CI, 61.9 to 62.6) G2: 65.0 (95% CI, 64.8 to 65.2)  5-Month Follow-up G1: 60.5 (95% CI, 60.3 to 60.7) G2: 60.8 (95% CI, 60.6 to 61.0)  p: 0.17
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 General Health Perception Domain	G1: NR G2: NR  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al., 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Social Functioning Domain	Baseline G1: 88.6 (16.8) G2: 81.3 (18.5)  4-Month Follow-up G1: 90.2 (15.5) G2: 81.0 (19.1)  p: NS
Sellers et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Social Functioning Domain	Baseline G1: 79.2 (95% CI, 79.0 to 79.4) G2: 81.9 (95% CI, 81.8 to 82.0)  5-Month Follow-up G1: 75.4 (95% CI, 75.1 to 75.8) G2: 77.5 (95% CI, 77.3 to 77.7)  p: 0.34
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Social Functioning Domain	G1: NR G2: NR  p: NS
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al, 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Role Emotional Domain (change from baseline)	6-Month Follow-up G1: -2.6 (2.2 SE) G2: -3.4 (1.9 SE)  12-Month Follow-up G1: -0.3 (2.3 SE) G2: -7.4 (2.3 SE)  p=0.065

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Role Emotional Domain	Baseline G1: 59.6 (44.7) G2: 69.4 (45.3)  12-Month Follow-up G1: 82.8 (36.4) G2: 65.8 (45.4)  p: NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Role Emotional Domain	Baseline: G1: 73.0 (4.1) G2: 68.1 (4.1)  12-Month Follow-up G1: 66.4 (1.8) G2: 67.0 (3.9)  p=0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Role Emotional Domain (Change between Baseline and 18-Month Follow-Up)	G1: +0.2 G2: -2.9  p: NS
Carter et al., 1997 <sup>7</sup> , Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Role Emotional Domain	Baseline G1: 50.0 G2: 69.4  6-Month Follow-up G1: 63.9 G2: 65.3  p=NR

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Role Emotional Domain	Baseline G1: 88.4 (25.8) G2: 88.5 (28.2)  4-Month Follow-up G1: 92.8 (24.5) G2: 78.2 (29.7)  p: NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Role Emotional Domain	Baseline G1: 71.8 (95% CI, 70.9 to 72.7) G2: 74.9 (95% CI, 74.5 to 75.2)  5-Month Follow-up G1: 66.4 (95% CI, 65.7 to 67.0) G2: 72.7 (95% CI, 72.1 to 73.2)  p: 0.80
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Role Emotional Domain	G1: NR G2: NR  p: NS
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al, 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Mental Health Domain (change from baseline)	6-Month Follow-Up G1: -0.5 (0.8 SE) G2: -1.4 (0.7 SE)  12-Month Follow-up G1: 0.1 (0.8 SE) G2: -2.3 (0.8 SE)  p=0.029

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Mental Health Domain	Baseline G1: 72.0 (17.4) G2: 69.0 (18.6)  12-Month Follow-up G1: 73.1 (21.2) G2: 72.3 (17.1)  p=NS
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Mental Health Domain	Baseline: G1: 61.0 (2.5) G2: 63.5 (2.5)  12-Month Follow-up G1: 61.1 (1.8) G2: 60.4 (1.8)  p=0.99
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Mental Health Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.8 G2: -1.3  p=NS
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Mental Health Domain	Baseline G1: 73.4 G2: 75.5  6-Month Follow-up G1: 71.0 G2: 75.7  p: NR

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Mental Health Domain	Baseline G1: 77.0 (14.6) G2: 73.1 (21.3)  4-Month Follow-Up G1: 80.2 (14.6) G2: 73.7 (19.0)  p=NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Health Domain	Baseline G1: 75.2 (95% CI, 75.1 to 75.3) G2: 76.7 (95% CI, 75.8 to 77.6)  5 Month Follow-Up G1: 74.2 (95% CI, 74.0 to 74.3) G2: 74.7 (95% CI: 74.7 to 74.8)  p: 0.49
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Mental Health Domain	Baseline and 3-Month Follow-Up G1: NR G2: NR  p: NS
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  18 months G1: 704 G2: 636	SF-36 Mental Health Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.8 G2: -1.3  p=NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Mental Health Domain	Baseline G1: 73.4 G2: 75.5  6-Month Follow-Up G1: 71.0 G2: 75.7  p:NR
Park et al, 1996 <sup>43</sup> RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Mental Health Domain	Baseline G1: 77.0 (14.6) G2: 73.1 (21.3)  4-Month Follow-Up G1: 80.2 (14.6) G2: 73.7 (19.0)  p=NS
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Health Domain	Baseline G1: 75.2 (95% CI, 75.1 to 75.3) G2: 76.7 (95% CI, 75.8 to 77.6)  5 Month Follow-Up G1: 74.2 (95% CI, 74.0 to 74.3) G2: 74.7 95% CI, (74.7 to 74.8)  p: 0.49
Krska et al, 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Mental Health Domain	G1: NR G2: NR  p: NS

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Change in Health (change from baseline)	6-Month Follow-Up G1: -1.1 (1.3) G2: -4.8 (1.3)  12-Month Follow-Up G1: -2.4 (1.5 SE) G2: -6.3 (1.3 SE) 95% CI: NR p=0.004
Triller and Hamilton, 2007 <sup>62</sup> RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: 77 G2: 77	SF -12 assessed at 30, 90, and 180 day follow ups	Values not reported, but results state that values did not significantly differ between the two groups.
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Question 1: Overall Health Rating	Baseline G1: 3.3 (95% CI, 3.3 to 3.3) G2: 3.4 (95% CI, 3.3 to 3.4)  5-Month Follow-Up G1: 3.2 (95% CI, 3.2 to 3.3) G2: 3.2 (95% CI, 3.2 to 3.3)  p: 0.35
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Physical Component	Baseline G1: 39.1 (95% CI, 37.2 to 41.0) G2: 38.9 (95% CI, 37.7 to 40.1)  5-Month Follow-Up G1: 37.9 (95% CI, 36.6 to 39.2) G2: 38.4 (95% CI, 37.2 to 39.7)  p: 0.30



**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001, <sup>54,55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline N = 363 G1: 159 G2: 204  6 Month Follow-Up N = 317 G1: NR G2: NR  12 Month Follow-Up N = 292 G1: NR G2: NR	SF-36 Physical Component	Baseline G1: 38.4 (12.7) G2: 40.1 (11.9)  6 Month Follow-Up G1: 38.0 (11.9) G2: 39.2 (11.6)  12 Month Follow-Up G1: 36.9 (11.6) G2: 38.4 (11.4)  p= NS (Between group comparisons at follow-up assessments)
Sellors et al., 2003 <sup>47</sup> RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Component	Baseline G1: 52.2 (95% CI, 50.8 to 53.5) G2: 53.4 (95% CI, 52.6 to 54.3)  5-Month Follow-Up G1: 51.0 (95% CI, 49.7 to 52.4) G2: 52.2 (95% CI, 51.2 to 53.2)  p: 0.65

**Table D30. Self-reported health status: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54, 54,55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline N = 363 G1: 159 G2: 204	SF-36 Mental Component	Baseline G1: 55.1 (8.7) G2: 53.2 (9.3)
		6 Month Follow-Up N = 317 G1: NR G2: NR		6 Month Follow-Up G1: 55.9 (9.1) G2: 54.4 (9.3)
		12 Month Follow-Up N = 292 G1: NR G2: NR		12 Month Follow-Up G1: 56.1 (8.3) G2: 54.6 (8.7) p= NS (Between group comparisons at follow-up assessments)
Williams et al., 2004 <sup>57</sup> RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary team in addition to usual care and "Bound for Health" booklet. G2: Usual care plus provision of "Bound for Health" booklet	G1: 57 G2: 76	SF-36 Overall Score	Baseline: G1: 61.8 (17.8) G2: 63.3 (16.5)  6-Week Follow-Up: G1: 65.5 (18.9) G2: 65.7 (17.0)  p=NS

Abbreviations: CI = confidence interval; G = group; N = number; NR = not reported; NS = not sufficient; PCIs = pharmaceutical care issues; RCT= randomized controlled trial; SE = standard error; SF-36 = multi-purpose, short-form health survey with only 36 questions; VA = Veteran's Administration

**Table D31. Condition-specific quality of life: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup> RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44  Year 1: G1: 44 G2: 36  Year 2: G1: 24 G2: 32	Renal Quality of Life Profile (Increased score indicates worsening of HRQOL, maximum score=172)	Total Score Baseline G1: 71.9 (40) G2: 74.5 (33.5)  Year 1 G1: 71.4 (33.6) G2: 87.5 (30.4)  Year 2 G1: 56.5 (32.6) G2: 68.8 (35.8)  p<0.05 for G1 vs. G2 for Y1;
Clifford et al., 2002 <sup>11</sup> RCT/Medium	G1: Collaborative pharmaceutical care program for diabetes G2: Standard outpatient care for diabetes	G1: 48 G2: 25	Diabetes Quality of Life instrument  Scale of 1-5, with higher scores indicating greater dissatisfaction, worry, or impact of diabetes	Baseline G1: 2.0 (0.6) G2: 1.9 (0.5) p: NS 6-Month Follow-Up G1: 1.9 (0.5) G2: 1.9 (0.4)  p>0.15

Abbreviations: G = group; HRQOL = health related quality of life; RCT= randomized controlled trial; vs. = versus

**Table D32. Patient satisfaction: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	General health care satisfaction at 12-Month Follow Up (Higher scores indicate greater dissatisfaction)	G1: 1.5 (0.7) G2: 1.6 (0.8) p=0.70
Hanlon et al., 1996 <sup>17</sup> RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	Pharmacy-related health care satisfaction at 12-month Follow-Up (Higher scores indicate greater dissatisfaction)	G1: 5.2 (1.5) G2: 5.4 (1.7) p=0.52
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al, 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	Patient satisfaction with primary health care provider (Higher scores indicate greater satisfaction)	G1: Baseline 51.9 (7.5) Time 2: 51.7 (7.3) G2: Baseline 51.9 (7.5) Time 2: NR  p=NS
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup> RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164  6 months G1: 1024 G2: 953  12 months G1: 863 G2: 764  18 months G1: 704 G2: 636	% rating pharmacy services provided as "excellent"	Baseline G1: 66.2 G2: 68.2 p: NR  6 months G1: 72.8 G2: 63.7 p: <0.05  12 months G1: 73.4 G2: 71.2 p: NR  18 months G1: 73.8 G2: 64.6 p: <0.05

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am very satisfied with the pharmacy services I receive," collected at 6 months	6-Month Follow-Up G1: 100 G2: 96 p: 0.065
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "Overall, the program provided a valuable service to me," collected at 6 months	6-Month Follow-Up G1: 100 G2: 80 p: 0.0018
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "The quality of information provided to me by the pharmacist was excellent," collected at 6 months	6-Month Follow-Up G1: 100 G2: 88 p: 0.012
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "My participation in this program helped me to understand high blood pressure better," collected at 6 months	6-Month Follow-Up G1: 100 G2: 83 p: 0.011
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "The area was private enough for me to feel comfortable talking about my high blood pressure," collected at 6 months	6-Month Follow-Up G1: 96 G2: 96 p: 0.036
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I felt comfortable talking with the pharmacist about my health problems," collected at 6 months	6-Month Follow-Up G1: 100 G2: 96 p: 0.052

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am confident the pharmacist is able to help me control my high blood pressure," collected at 6 months	6-Month Follow-Up G1: 100 G2: 92 p: 0.340
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am confident the information provided by the pharmacist to the physician improved my health care," collected at 6 months	6-Month Follow-Up G1: 87 G2: 83 p: 0.325
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "There are things about the high blood pressure program that could be better," collected at 6 months	6-Month Follow-Up G1: 9 G2: 0 p: 0.157
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am very willing to continue to see the pharmacist for help with my high blood pressure control," collected at 6 months	6-Month Follow-Up G1: 95 G2: 88 p: 0.459
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I think the pharmacist should provide this type of service for everyone," collected at 6 months	6-Month Follow-Up G1: 77 G2: 75 p: 0.890
Carter et al.,1997 <sup>7</sup> ; Barnette, Murphy, and Carter, 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I think the pharmacist should be paid for this type of service," collected at 6 months	6-Month Follow-Up G1: 91 G2: 82 p: 0.379

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	General satisfaction (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 1.59 (0.77)
		G1: 159		G2: 1.56 (0.73)
		G2: 204		
		6 Month Follow-Up N = 317		6 Month Follow-Up G1: 1.51 (0.84) G2: 1.57 (0.72)
		G1: NR		
		G2: NR		
		12 Month Follow-Up N = 292		12 Month Follow-Up G1: 1.53 (0.77) G2: 1.62 (0.88)
		G1: NR		
		G2: NR		p= NS for all between-group differences
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Interpersonal skills (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 1.36 (0.48)
		G1: 159		G2: 1.37 (0.53)
		G2: 204		
		6 Month Follow-Up N = 317		6 Month Follow-Up G1: 1.37 (0.59) G2: 1.35 (0.57)
		G1: NR		
		G2: NR		
		12 Month Follow-Up N = 292		12 Month Follow-Up G1: 1.31 (0.50) G2: 1.45 (0.72)
		G1: NR		
		G2: NR		p= NS for all between-group differences

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Evaluation and goal setting (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 2.58 (1.12)
		G1: 159		G2: 2.74 (1.09)
		G2: 204		
		6-Month Follow-Up N = 317		6-Month Follow-Up G1: 2.46 (0.98) G2: 2.98 (1.24)
		G1: NR		
		G2: NR		
		12-Month Follow-Up N = 292		12-Month Follow-Up G1: 2.49 (1.10) G2: 2.90 (1.08)
		G1: NR		p<0.05 for between-group differences in score changes from Time 1 to Time 2 and Time 1 to Time 3
		G2: NR		
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Trust (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 1.62 (0.66)
		G1: 159		G2: 1.46 (0.57)
		G2: 204		
		6-Month Follow-Up N = 317		6-Month Follow-Up G1: 1.40 (0.54) G2: 1.39 (0.58)
		G1: NR		
		G2: NR		
		12-Month Follow-Up N = 292		12-Month Follow-Up G1: 1.43 (0.58) G2: 1.51 (0.75)
		G1: NR		p<0.05 for between-group differences in score changes from Time 1 to Time 2
		G2: NR		p<0.05 for group x measure interaction over all three time periods



**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Helping patients (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 2.25 (1.31)
		G1: 159		G2: 2.22 (1.14)
		G2: 204		
		6-Month Follow-Up		6-Month Follow-Up
		N = 317		G1: 1.98 (1.17)
		G1: NR		G2: 2.23 (1.15)
		G2: NR		
		12-Month Follow-Up		12-Month Follow-Up
		N = 292		G1: 2.07 (1.22)
		G1: NR		G2: 2.37 (1.21)
		G2: NR		p= NS for all between-group differences
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Explanation (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 1.34 (0.55)
		G1: 159		G2: 1.34 (0.63)
		G2: 204		
		6-Month Follow-Up		6-Month Follow-Up
		N = 317		G1: 1.39 (0.67)
		G1: NR		G2: 1.30 (0.56)
		G2: NR		
		12-Month Follow-Up		12-Month Follow-Up
		N = 292		G1: 1.38 (0.73)
		G1: NR		G2: 1.35 (0.61)
		G2: NR		p= NS for all between-group differences

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Pharmacy finances (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 3.08 (1.82)
		G1: 159		G2: 2.85 (1.80)
		G2: 204		
		6-Month Follow-Up N = 317		6-Month Follow-Up G1: 2.89 (1.89) G2: 2.86 (1.75)
		G1: NR		
		G2: NR		
		12-Month Follow-Up N = 292		12-Month Follow-Up G1: 3.08 (1.80) G2: 3.16 (1.88)
		G1: NR		
		G2: NR		p= NS for all between-group differences
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline	Drug plan finances (Higher numbers reflect greater dissatisfaction)	Baseline
		N = 363		G1: 3.31 (1.70)
		G1: 159		G2: 3.41 (1.75)
		G2: 204		
		6-Month Follow-Up N = 317		6-Month Follow-Up G1: 3.45 (1.96) G2: 3.39 (1.83)
		G1: NR		
		G2: NR		
		12-Month Follow-Up N = 292		12-Month Follow-Up G1: 3.65 (1.67) G2: 3.56 (1.83)
		G1: NR		
		G2: NR		p= NS for all between-group differences

**Table D32. Patient satisfaction: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 <sup>54</sup> ; Kassam et al., 2001 <sup>55</sup> RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Baseline N = 363 G1: 159 G2: 204  6-Month Follow-Up N = 317 G1: NR G2: NR  12-Month Follow-Up N = 292 G1: NR G2: NR	Communicates with doctor (Higher numbers reflect greater dissatisfaction)	Baseline G1: 1.50 (0.77) G2: 1.60 (0.89) 6-Month Follow-Up G1: 1.36 (0.63) G2: 1.72 (1.00) 12-Month Follow-Up G1: 1.36 (0.65) G2: 1.74 (0.97)  p<0.05 for between-group differences in score changes from Time 1 to Time 3

Abbreviations: G = group; N = study sample size; NRCT=Non-randomized controlled trial; NR = not reported; NS = not significant; RCT= randomized controlled trial

**Table D33. Use of generic medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Perlroth et al., 2013 <sup>35a</sup>  Cohort/Medium	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR	G1: 12,658 G3: 11,260 G5: 16,372	Generic substitution ratio within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Odds (95% CI) For CHF/COPD/diabetes drugs Congestive heart failure G1 vs. G13: 0.001 (-0.000, 0.002), p>0.05 G3 vs. G14: 0.005 (0.003, 0.006), p<0.05	
	G3: enrolled in MA-PD, receiving MTM with CMR	G7: 10,575 G9: 16,545 G11: 13,527			
	Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR	G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623			Chronic obstructive pulmonary disease G5 vs. G15: -0.001 (-0.003, 0.000), p>0.05 G7 vs. G16: 0.000 (-0.002, 0.002), p>0.05
	G7: enrolled in MA-PD, receiving MTM with CMR	G17: 133,925 G18: 53,912			Diabetes G9 vs. G17: -0.000 (-0.000, 0.000), p>0.05 G11 vs. G18: 0.000 (-0.000, 0.000), p>0.05
	Diabetes G9: enrolled in PDP receiving MTM with CMR				
	G11: enrolled in MA-PD, receiving MTM with CMR				For non-CHF/COPD/diabetes drugs Congestive heart failure G1 vs., G13: 0.000 (-.002, 0.002), p>0.05 G3 vs., G14: -0.010 (-0.013, -0.008), p<0.05
	Comparison—congestive heart failure G13: enrolled in PDP, usual care				
	G14: enrolled in MA-PD, usual care				Chronic obstructive pulmonary disease G5 vs., G15: 0.000 (-0.001, 0.003), p>0.05 G7 vs., G16: 0.006 (0.003, 0.009), p<0.05
	Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care				
	G16: enrolled in MA-PD, usual care				Diabetes G9 vs., G17: -0.001 (-0.002, 0.000), p>0.05 G11 vs., G18: -0.002 (-0.003, -0.001), p<0.05
	Comparison—Diabetes G17: enrolled in PDP, usual care				
	G18: enrolled in MA-PD, usual care				

**Table D33. Use of generic medications: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Pindolia et al., 2009 <sup>44</sup> Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1,081	Increase in the overall use of generic drugs	G1: 6% G2: 3%  p not calculated because baseline percentages not provided
Winston and Lin, 2009 <sup>58</sup> Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Weighted generic substitution ratio: 30-day equivalent claims divided by total number of claims	Pre-MTM (Jan 1 2007-April 30, 2007) G1: 60.1 (29.8) G2: 58.6 (25.7) G3: 58.7 (27.6) p: NR  Post-MTM (Jan 1 2008-April 30, 2008) G1: 65.7 (32.5) G2: 64.6 (30.5) G3: 63.5 (32.2) p: NR  Calculated SMD for G1 vs. G3: -0.04 (95% CI, -0.06 to -0.02; p<0.001)  Calculated SMD for G2 vs. G3: -0.03 (95% CI, -0.06 to 0.01; p=0.134)

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; G = group; CMR = comprehensive medication review; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; N = number; PDP = Medicare Part D Plan

**Table D34. Patient co-payments: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Shimp et al., 2012 <sup>49</sup> RCT/Medium	G1: MTM program for University of Michigan beneficiaries, entitled Focus on Medicines G2: Usual care (not described)	G1: NR G2: NR	Annualized prescription drug costs for patient-paid amount	12 months before first visit G1: 1,334 ± 593 G2: 1,293 ± 680 95% CI: NR p: NR at baseline  12 months after second visit G1: 1,100 ± 645 G2: 1,123 ± 643 95% CI: NR p: NR at followup  Mean difference with variance between arms not calculable without N, reported P for G1 from baseline to followup: 0.004 p for G2 from baseline to followup: 0.062
Christensen et al., 2007 <sup>10</sup> NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in patient co-payment for prescriptions over 6 months in \$ (SD)	G1: 34.3 (263.6) G2: -54.3 (253.9) Calculated SMD for G1 vs. G2, assuming correlation between baseline and followup of 0.5 = -0.3; 95% CI, -0.5 to -0.04 (p=0.025)  G3: -46.1 (282.9) Calculated SMD for G1 vs. G3, assuming correlation between baseline and followup of 0.5 = -0.2; 95% CI, -0.6 to -0.1 (p=0.007)
Pindolia et al., 2009 <sup>44</sup> Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1081	Mean out-of-pocket prescription costs per health plan member in \$ (assumed per year, as NR in study) (SD)	2006 G1: 1513 (1171) G2: 1183 (1084)  2007 G1: 1571 (1163) G2: 1164 (1201)  Calculated SMD, assuming correlation between baseline and followup of 0.5 = -0.1; 95% CI, -0.2 to 0.1 (p=0.328)

**Table D34. Patient co-payments: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Prescription Costs to Patients</b>	<b>Results</b>
Fox et al., 2009 <sup>14</sup> Cohort/High	G1: MTM program (acceptors)	G1: 247	Mean difference in Medicare Part D medication copayment costs per patient per month	G1: 7.4 (76.0) G2: 11.3 (43.8) p: 0.62
	G2: Opt-out from MTM program	G2: 50	Mean difference in all medication copayments (Medicare Part D and not Part D) costs per patient per month	G1: 5.2 (80.5) G2: 6.9 (37.5) p: 0.82

Abbreviations: CI: confidence interval; G = group; MTM = Medication Therapy Management; NR = not reported; NRCT = nonrandomized controlled trial; RCT= randomized controlled trial; SD = standard deviation; SMD: standardized mean difference; vs. = versus

**Table D35. Total expenditures on medications by health plans: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup> RCT/Medium	G1: Pharmacotherapy consultation G2: Usual care	G1: 27 G2: 29	Change in cost (USD) of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	G1: -130 G2: 163 Calculated mean difference: -293, 95% CI, -501.5 to -84.5 p< 0.01
Sellers et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient to the Ontario Drug Benefit Program (assumed CAD) at 5 months	G1: 3.6 G2: 3.8 Calculated mean difference: 0.19, 95% CI, -1.5 to 1.1 p: 0.78
Sellers et al., 2001 <sup>48</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 61 G2: 60	Mean daily medication costs to the Ontario Drug Benefit Program (assumed CAD) at 6 months	G1: 3.28, 95% CI: 2.64 to 3.92 G2: 3.76, 95% CI: 3.76 to 4.45 Calculated mean difference in CAD (95% CI) = -0.48 (-1.44 to 0.48) p=0.33  Calculated mean difference over 6 months=-0.48*30*6=-86.4
Christensen et al., 2007 <sup>10</sup> NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in amount insurer paid for prescriptions over 6 months in USD (SD)	G1: -90.1 (793.0) G2: -35.4 (939.5) G3: -97.3 (907.4)  Calculated mean difference for G1 vs. G2, assuming correlation between baseline and followup of 0.5= -54.7, 95% CI, -287.6 to 178.2 (p=0.645)  Calculated mean difference for G1 vs. G3, assuming correlation between baseline and followup of 0.5 = -7.2; 95% CI, -230.8 to 216.4 (p=0.950)



**Table D35. Total expenditures on medications by health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Moczygemba et al., 2011 <sup>37</sup> Moczygemba et al., 2008 <sup>38</sup> Moczygemba et al., 2008 <sup>38</sup> Cohort/Medium	G1: MTM-eligible patients who opting-in to a telephone MTM program (acceptors) G2: MTM- eligible patients who did not opt-in to the MTM program (opt-out)	G1: 60 G2: 60	Mean Part D drug costs in USD (based on prescription claim records, excludes non-Part D drug costs) (SD) at baseline and 6 months and 12 months	Baseline G1: \$2289 (\$887) G2: \$2131 (\$1273) p: NR Follow up at 6 months G1: \$2311 (\$1148) G2: \$2429 (\$1697) Adjusted p: 0.80  Calculated mean difference: -276.0, 95% CI, -751.3 to 199.3, p: 0.26  12 months G1: \$3,938 (\$1,022) G2: \$4,842 (\$3,405) Unadjusted P= 0.03 Adjusted p: NS  Reported mean difference: -USD 800 95% CI NR, p=0.03 for t-test, but no significant predictors when sociodemographic, health-related, and use variables were controlled for in the multiple regression analysis
Moore et al., 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Total plan-paid costs for all dispensed medications in pre- and post-periods 1 year before invitation to MTM program and 1 year after	Baseline G1: \$4,853 (122.77) G2: \$5,081 (151.77) p: 0.242  mean change in total plan-paid pharmacy costs [Mean (SE)] G1: \$327 (85.65) G2: -\$98 (86.69) p< 0.001  Calculated mean difference in USD (95% CI): 425 (109.79 to 12,054.24) p: < 0.001

**Table D35. Total expenditures on medications by health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Perlroth et al., 2013 <sup>35a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658	Total payments recorded on Part D claims for all prescription medications not used for treatment of condition specific to MTM eligibility (CHF, COPD, or diabetes) within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators)	Adjusted costs in USD (95% CI) Congestive heart failure cohort G1 vs. G13: 87.05 (7.33, 166.78), p<0.05 G3 vs. 14: 140.52 (55.79, 225.25), p<0.05  Chronic obstructive pulmonary disease cohort G5 vs. 15: 42.55 (-28.12, 113.22), p>0.05 G7 vs. G16: 95.45 (18.88, 172.02), p<0.05  Diabetes G9 vs. G17: 109.70 (50.16, 169.25), p<0.05 G11 vs. G18: 173.79 (118.35, 229.22), p<0.05
	G1: enrolled in PDP receiving MTM with CMR	G3: 11,260		
	G3: enrolled in MA-PD, receiving MTM with CMR	G5: 16,372		
		G7: 10,575		
		G9: 16,545		
		G11: 13,527		
	Chronic obstructive pulmonary disease	G13: 156,441		
	G5: enrolled in PDP receiving MTM with CMR	G14: 51,938		
	G7: enrolled in MA-PD, receiving MTM with CMR	G15: 184,350		
		G16: 73,623		
		G17: 133,925		
		G18: 53,912		
	Diabetes	G9: enrolled in PDP receiving MTM with CMR		
	G11: enrolled in MA-PD, receiving MTM with CMR			
Comparison—congestive heart failure	G13: enrolled in PDP, usual care			
	G14: enrolled in MA-PD, usual care			
Comparison—Chronic obstructive pulmonary disease	G15: enrolled in PDP, usual care			
	G16: enrolled in MA-PD, usual care			
Comparison—Diabetes	G17: enrolled in PDP, usual care			
	G18: enrolled in MA-PD, usual care			

**Table D35. Total expenditures on medications by health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Wittayanukorn et al., 2013 <sup>60</sup> Cohort/Medium	G1: Pharmacist provided face-to-face MTM services for 30–60 minutes per encounter, not always including a followup visit G2: Patients who did not receive MTM services	G1: 63 G2: 62	Mean pharmacy expenditures, during the 6 months prior to the initial MTM visit and costs during the 6 months after the initial MTM visit, in USD	<p>6 months pre-MTM G1: IG: 126.8 (20.3) G2: CG: 133.7 (23.8) 95% CI: NR : &lt;0.0001</p> <p>6 months post-MTM G1: IG: 104.8 (17.8) G2: CG: 144.4 (24.6) 95% CI: NR : &lt;0.0001</p> <p>Within group cost difference G1: IG: -22.0 (19.1) G2: CG: 10.7 (24.2) 95% CI: NR : &lt;0.0001</p> <p>Mean between-group cost difference in USD (SD): -31.9 (25.1) p&lt;0.001</p>
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Mean amount billed per patient for active drugs in USD (based on Medicaid claims) (SD) at baseline and at 9 months	<p>Baseline G1: 488.4 (20.8) G2: 441.9 (14.5) Followup G1: 525.0 (22.1) G2: 477.6 (15.5)</p> <p>Calculated mean difference: -0.95, 95% CI, -58.7 to 56.8, p: 0.974</p>

**Table D35. Total expenditures on medications by health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Hirsch et al., 2011 <sup>19</sup> Hirsch et al., 2009 <sup>20</sup> Cohort/High	G1: Patients served at pilot pharmacies	2005 G1: 439	Paid claims amount for all prescription medications, ART medications, and non-ART medications (total cost-cost of ART medications)	Mean USD (SE) 2005 G1: 26,797 (703)
	G2: Patients served at nonpilot pharmacies	G2: 1,795		G2: 22,544 (290)
		2006 G1: 617 G2: 1,617		p<0.001  2006 G1: 27,671 (613) G2: 23,190 (315)
		2007 G1: 628 G2: 1,606		p<0.001  2007 G1: 29,955 (679) G2: 25,690 (362) p<0.001

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: ART = antiretroviral therapy; CAD = Canadian dollars; CI = confidence interval; G = group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; N = number; PCM = pharmaceutical case management; PDP = Medicare Part D Plan; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SMD = standardized mean difference; USD = United States dollars.

**Table D36. Total expenditures on medications by patients and health plans: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Price to the VA for the agent, plus the average cost of filling prescriptions (time period NR) (25th-75th percentile)	Mean cost in USD G1: 1,006 (574–1,285) G2: 1,096 (566–1,456) 95% CI: NR p: NS at 0.05 level, specifics NR
Krska et al., 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Average monthly costs of prescribed medication per patient in British? pounds (SD) at 3 months (calculated using information from patient on actual use)	Baseline: G1: 39.3 (29.1) G2: 42.8 (33.5) Followup G1: 38.8 (29.6) G2: 42.6 (31.8)  Calculated mean difference: -0.2, 95% CI, -6.7 to 6.5) p=0.956
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual drug costs in USD (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	G1: +203 G2: +140  Calculated mean difference: 63, 95% CI, -5.1 to 131.1; p: 0.07
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient at 5 months (assumed CAD)	G1: 5.01 G2: 4.82  Calculated mean difference: 0.2, 95% CI, -0.8 to 1.2; p=0.72
Sellors et al., 2001 <sup>48</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 61 G2: 60	Mean daily medication costs (assumed CAD) at 6 months	G1: CAD 3.85 (2.77) G2: CAD 4.26 (2.78) 95% CI: NR P: 0.43 Calculated mean difference: -0.41 CAD (-1.40 to 0.58) p: 0.42

**Table D36. Total expenditures on medications by patients and health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Williams et al., 2004 <sup>57</sup> RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	Average monthly wholesale price (USD) of prescription and non-prescription drugs in USD	G1: -26.92 G2: -0.68  Reported mean difference: -20.2, 95% CI, 5.8 to 34.5 p: 0.006
Jeong et al., 2009 <sup>25</sup>  Cohort/Medium	G1: Participants in Part D Medicare MTM program (opted in to MTM program) G2: Control subjects without Part D Medicare as their primary drug benefit but otherwise similar to intervention subjects.	G1: 2,780 G2: 2,251	Full retail cost of medication had the patient not had insurance coverage at 6 months before and 6 months after enrollment in USD	Pre G1: \$3572 (3464) G2: \$3438(2840) 95% CI: P: Post: G1: \$3458 (3968) G2: \$3888 (3388)  Change: G1: -\$114 (2893) G2: +449(3340) p< 0.001  Calculated mean difference in USD (95% CI): -563 (-735.33 to -390.67) p<0.001
Yamada et al., 2012 <sup>61</sup> Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Change in annual prescription costs	Mean change adjusted for age, sex, Charlson, CHF, ESRD: +\$310 (271 to 350) p<0.001  2010 subgroup only (different unspecified criterion for MTM): -\$46 (-\$107 to \$15) p NS adjusted for age, sex, Charlson, CHF, ESRD

**Table D36. Total expenditures on medications by patients and health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup> RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean drug costs in USD (calculated from average wholesale price) over 2 years	Baseline: G1: 430 (197) G2: 451 (267)  Followup: Pharmaceutical care reduced mean drug costs by \$6.21 compared with the standard of care group, p=NS, no absolute costs or other details reported
Fox et al., 2009 <sup>14</sup> Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (opt-out)	G1: 247 G2: 50	Mean difference in annual Medicare Part D drug cost in USD (patient copay + insurance plan medication costs + dispensing fee)	G1: -76.7 (350.8) G2: -49.0 (92.8) Calculated mean difference: -27.8, 95% CI, -125.8 to 26.6 p: 0.57
Pindolia et al., 2009 <sup>44</sup> Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1081	Total annual prescription drug cost per health plan member in USD	Pre-enrollment (\$) (January-June 2006) G1: 576.3 (394.3) G2: 468.1 (335.9)  Post-enrollment (\$) (July-December 2006) G1: 480.7 (404.3) G2: 434.7 (421.4)  Calculated mean difference: -62.2, 95% CI, -112.5 to -12.0; p=0.015
Staresinic et al., 2007 <sup>51</sup> Cohort/High	G1: MTP program (acceptors) G2: Usual care (opt-out)	G1: 282 G2: 1544	Total prescription cost per MTMP beneficiary per month in USD (gross drug cost=ingredient cost paid + dispensing fee + sales tax/member months in part D contract)	Participants spent less on prescription medications on average (described as per member per month drug spending) than non-participants. Figure provided suggests a decrease spend of between 100 and 150 in the intervention group, but exact numbers not reported.

**Table D36. Total expenditures on medications by patients and health plans: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Welch et al., 2009 <sup>56</sup> Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Mean change in medication costs per day in USD at 6 months. No SD reported. (from data on study beneficiaries' purchases of ambulatory prescription medications)  Mean percent increase in medication costs per day in USD at 6 months (no SD reported)	G1: 0.3 G2: -3.3 Adjusted p: 0.203 NOTE: Age, sex, chronic disease score, and preperiod drug cost included in multivariate regression modeling for adjusted P  G1: 49.7 G2: 39.9 p: 0.006 Adjusted OR (95% CI): 1.4 (1.1 to 1.9) NOTE: Model adjusted for age, sex, chronic disease score, and baseline medication cost
Winston and Lin, 2009 <sup>58</sup> Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Mean (SD) drug cost per patient per month in USD after 8 months of services (based drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, prior to subtracting any patient cost-sharing amounts)	Pre-MTM period (Jan 1 2007-April 30, 2007) G1: 669 (461) G2: 676 (463) G3: 698 (513)  Post-MTM period (Jan 1 2008-April 30, 2008) G1: 634 (512) G2: 661 (494) G3: 698 (556)  Calculated mean difference for G1 vs. G3: -35.0, 95% CI, -43.4 to -26.6; p<0.001  Calculated mean difference for G2 vs. G3: -15.0, 95% CI, -33.4 to 3.4; p=0.11

Abbreviations: CAD = Canadian dollar; CI = confidence interval; G = group; MTM = Medication Therapy Management; MTMP= Medication Therapy Management Program; NR = not reported; NS = not sufficient; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation; USD= US dollar; VA = Veterans Administration; VAMC = Veterans Affairs Medical Center; vs. = versus.



**Table D37. Medication and other costs: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.  G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Total cost = drug outlays + average per diem cost of inpatient care based on annual output and expenditure data for bed sections in the cost distribution report + costs of surgery based on relative value weights, and VA costs per relative value weight + health services valued using 1991 estimates of VAMC unit costs; costs for non-VA hospital care were imputed using logic underlying VA cost methodology (time period NR) (25th-75th percentile)	Mean cost in USD G1: 7,873 (1,622–6,649) G2: 5,926 (1,608–7,036) 95% CI: NR p: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost (SE) of health care resources per patient, including all hospital stays at 5 months (CAD assumed)	G1: 1894.1 (200.7) G2: 1644.7 (220.8) p=0.83  Calculated mean difference: 249.4, 95% CI, -338.4 to 837.2
			Mean cost (SE) of health care resources per patient, including only drug-related hospital stays at 5 months (CAD assumed)	G1: 1281.3 (101.4) G2: 1299.4 (154.7) p=0.45  Calculated mean difference: -18.1, 95% CI, -386.7 to 350.5

**Table D37. Medication and other costs: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Bernsten et al., 2001 <sup>1,2</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748  6 months G1: NR G2: NR  12 months G1: NR G2: NR  18 months G1: NR G2: NR	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs	Cost data not pooled and analyzed for costs because of differing health care systems between countries. However, no significant between-group differences in any country (p=NS)
Fischer et al., 2002 <sup>13</sup> NRCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Change in total charges (in USD) for inpatient care, outpatient care, and pharmacy	G1: -900 G2: -2000 95% CI: NR p: NS, no details reported Calculated mean difference: 1100.
Moore et al., 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2250 G2: 2250	Total plan-paid costs for all dispensed medications + total plan-paid costs for all covered medical services 1 year before invitation to MTM program and 1 year after	Total plan-paid health care costs at baseline (SE) G1: \$9,456 (372.05) G2: \$9,499 (375.26) P: 0.935  Mean change in total plan-paid health care costs [Mean (SE)] G1: -\$977 (357.16) G2: \$62 (396.45) P: 0.048  Calculated mean difference in USD (95% CI): -1,039 (-2,084.85 to 6.849) p=0.052

**Table D37. Medication and other costs: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Wittayanukorn et al., 2013 <sup>60</sup> Cohort/Medium	G1: Pharmacist provided face-to-face MTM services for 30-60 minutes per encounter, not always including a followup visit G2: Patients who did not receive MTM services	G1: 63 G2: 62	Mean total expenditures (pharmacy+medical), during the 6 months prior to the initial MTM visit and costs during the 6 months after the initial MTM visit, in USD	6 months pre-MTM G1: IG: 481.2 (137.0) G2: CG: 291.3 (49.0) 95% CI: NR P: <0.0001  6 months post-MTM G1: IG: 406.1 (135.3) G2: CG: 580.3 (309.9) 95% CI: NR P: <0.0001  Within group cost difference G1: IG: -75.1 (136.2) G2: CG: 289.0 (269.5) 95% CI: NR P: <0.0001  Mean between-group cost difference in USD (SD): -359.3 (219.2) p<0.001
Hirsch et al., 2011 <sup>19</sup> Hirsch et al., 2009 <sup>20</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606	Paid claims amounts for inpatient, hospital outpatient (includes emergency department), outpatient, mental health, laboratory/X-ray, and AIDS Waiver Programc	Mean USD (SE) 2005 G1: 35,546 (1,093) G2: 33,501 (505) p=0.079  2006 G1: 36,806 (980) G2: 35,230 (575) p= 0.157  2007 G1: 38,983 (1,023) G2: 38,856 (633) p= 0.915

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; GP = general practitioner; MTM = medication therapy management; NR = not reported, NS = not significant; RCT = randomized controlled trial; SE = standard error; USD = United States dollars

**Table D38. Number of outpatient visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Mean general medicine clinic visits (time period NR) (25th–75th percentile)	G1: 5.5 (3–6) G2: 5.8 (3–7) 95% CI: NR p: NS at 0.05 level, specifics NR
	G2: Usual care in the General Medicine Clinic			Mean other clinic visits (time period NR) (25th–75th percentile)
Krska et al., 2001 <sup>28</sup> RCT/Medium	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: NR G2: NR	Hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist review	No differences, details NR
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of clinic visits (including visits with the pharmacists in the intervention arm)	G1: +4.8 G2: +2.8 p: 0.003
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Number of clinic visits (SE)	G1: 0.3 (0.15) G2: 0.3 (0.6) p: 0.40
	G1: received at least 2 pharmacist visits involving medication review, patient specific education and counseling; follow up patient phone calls and contact of physicians as needed G2: only contacted for to complete the survey.	G1: 92 G2: 104	Change in number of ambulatory visits over 3 months	G1: -1.2 G2: 0.3 p: 0.08

**Table D38. Number of outpatient visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sidel, 1990 <sup>50</sup> RCT/Medium	G1: Patients received at least 2 pharmacist visits involving medication review, patient-specific education and counseling; followup patient telephone calls and contact of physicians as needed G2: Patients contacted only to complete the survey.	G1: 92 G2: 104	Change in number of ambulatory visits over past 3 months, measured at baseline and again at 36 months	G1: -1.16 G2: 0.25 95% CI: NR P: 0.08  Calculated mean difference: -1.41, 95% CI: -2.98 to 0.160, p=0.078
Touchette et al., 2012 <sup>53</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	0-3 months G1: 180 G2: 190 G3: 193 3-6 months G1: 183 G2: 190 G3: 183	0-3 months G1: 2.6 (2.2) G2: 2.7 (2.3) G3: 2.6 (2.2) G1 vs. G3: (p=0.646) G2 vs. G3: (p=0.816)  3-6 months G1: 2.2 (2.1) G2: 2.1 (2.1) G3: 2.2 (2.2) G1 vs. G3: (p=0.760) G2 vs. G3: (p=0.458)

**Table D38. Number of outpatient visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Bernsten et al., 2001 <sup>1,2</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 6 months G1: 1024 G2: 953 12 months G1: 863 G2: 764 18 months G1: 704 G2: 636	Mean number of contacts with primary care providers, including home visits and office appointments (SD)	Baseline G1: 4.8 (8.4) G2: 4.3 (6.2) p: NS 6 months G1: 4.0 (5.7) G2: 3.6 (4.6) p: NS 12 months G1: 4.0 (7.0) G2: 3.5 (5.5) p: NS 18 months G1: 4.3 (8.0) G2: 3.2 (4.0) p: NS
Moore et al., 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of physician visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Number of physician visits at baseline (SE) G1: 27.7 (0.344) G2: 27.2 (0.379) P: 0.325  mean change in number of physician visits G1: -0.70 (0.27) G2: -3.18 (0.31) p< 0.001 Calculated mean difference (95% CI): 2.48 (1.674 to 3.286, p<0.001)
Fischer et al., 2002 <sup>13</sup> NRCT/High	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Changes in number of clinic visits over 1 year	Intention-to-treat analysis Adjusted between-group difference not significant, details NR
Carter et al., 1997 <sup>7,8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Number of distinct dates of service over 6 months	G1: 2.2 (2.4) G2: 1.0 (1.0) p=0.07
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	No. of outpatient facility claims at 12 months	Results NR, p=0.121

Abbreviations: DRP = drug-related problems; G = group; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; NS = not sufficient; PCM = pharmaceutical case management; QOL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; vs. = versus

**Table D39. Costs of outpatient visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Annual health care costs in USD for general medicine clinic care at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients(time period NR) (25th–75th percentile)	G1: 334 USD (200–366) G2: 356 USD (183–427) 95% CI: NR p: NS at 0.05 level, specifics NR
	G2: Usual care in the General Medicine Clinic			Annual health care costs for other clinic care in USD at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients(time period NR) (25th–75th percentile) G1: 422 (67–500) G2: 565 (23–923) 95% CI: NR p: NS at 0.05 level, specifics NR
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual cost of clinic visits in US \$	G1: +231 G2: +333 95% CI: NR p: 0.02
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of physician visits in in \$ (assumed CAD) (SE) at 5 months	G1: 204.0 (11.1) G2: 198.3 (10.4) 95% CI (calculated for standardized difference in means): -0.11 to 0.12 p (calculated for standardized difference in means): 0.71
			Mean cost of clinic visits in in \$ (assumed CAD) (SE) at 5 months	G1: 18.8 (8.1) G2: 20.9 (5.0) 95% CI (calculated for standardized difference in means): -0.16 to 0.12 p (calculated for standardized difference in means): 0.82
			Mean cost of other health care services/visits to health care professionals in in \$ (assumed CAD) (SE) at 5 months	G1: 288.30 (40.02) G2: 293.00 (55.25) 95% CI (calculated for standardized difference in means): -0.145 to 0.135 p (calculated for standardized difference in means): 0.97

**Table D39. Costs of outpatient visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Outpatient facility claims at 12 months	Results NR  p: 0.107
Carter et al., 1997 <sup>7,8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Hypertension-related charges in \$ (SD) at 6 months  Mean visit charges in \$ (SD) at 6 months	G1: 122 (124) G2: 52 (65) p=0.03  G1: 823 (1,123) G2: 336 (246) p=0.02
Hirsch et al., 2011 <sup>19</sup> Hirsch et al., 2009 <sup>20</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606	Outpatient costs (not defined)	Mean USD (SE) 2005 G1: 112 (11) G2: 44 (2) p<0.001  2006 G1: 82 (7) G2: 43 (2) p<0.001  2007 G1: 83 (7) G2: 40 (2) p<0.001

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; NR = not reported; PCM = pharmaceutical care management; RCT = randomized controlled trial; SD = standard deviation; USD = United States dollars.



**Table D40. Number of laboratory tests: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Sellers et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of laboratory tests and imaging procedures at 5 months	G1: 8.7 (0.6) G2: 8.6 (0.1) 95% CI (calculated for standardized difference in means): -0.12 to 0.16 p (calculated for standardized difference in means): 0.791
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual number of laboratory tests	G1: +3.1 G2: +4.7 95% CI: NR p: 0.001

Abbreviations: CI = confidence interval; G = group; NR = not reported; QOL = quality of life; RCT = randomized controlled trial.

**Table D41. Costs of laboratory tests: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for diagnostic tests at 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients, (25th–75th percentile)	G1: 214 (52–318) G2: 354 (55–473) 95% CI: NR P: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all lab and imaging procedures at 5 months \$ (assumed CAD) (SE)	G1: 249.3 (20.8) G2: 243.1 (17.2) 95% CI (calculated for standardized difference in means): -0.12 to 0.16 p (calculated for standardized difference in means): 0.816
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual costs for laboratory tests in US \$	G1: +\$43 G2: +\$76 95% CI, NR p: 0.05
Hirsch et al., 2011 <sup>19</sup> Hirsch et al., 2009 <sup>20</sup> Cohort/High	G1: Patients served at pilot pharmacies G2: Patients served at nonpilot pharmacies	2005 G1: 439 G2: 1,795  2006 G1: 617 G2: 1,617  2007 G1: 628 G2: 1,606	Costs of laboratory/x-ray services	Mean USD (SE) 2005 G1: 389 (34) G2: 402 (17) p=0.736  2006 G1: 387 (28) G2: 407 (18) p=0.530  2007 G1: 401 (29) G2: 402 (18) p=0.974

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; N = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; SE = standard error; USD = United States dollars.

**Table D42. ED visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Mean emergency room visits (time period NR) (25th-75th percentile)	G1: 1.6 (0–2) G2: 2.3 (0–3) 95% CI: NR p: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of ED/urgent care visits and ambulance use (SE) at 5 months	G1: 0.2 (0.03) G2: 0.2 (0.03)
Touchette et al., 2012 <sup>53</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 211 G2: 218 G3: 208	Mean number of ED visits per participant	0 to 3 months G1: 0.3 (0.6) G2: 0.2 (0.6) G3: 0.2 (0.5) G1 vs. G3: (p=0.735) G2 vs. G3: (p=0.963)  3 to 6 months G1: 0.2 (0.5) G2: 0.2 (0.6) G3: 0.4 (0.8) G1 vs. G3: (p=0.077) G2 vs. G3: (p=0.057)
Taylor, Byrd, and Krueger, 2003 <sup>52</sup> RCT/High	G1: Pharmaceutical care group G2: Standard care	G1: 33 G2: 36	Change in no. of ED visits from 12 months before baseline through 12 months after	G1: -12 G2: 0 p=0.044
Moore et al., 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of ED visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Number of ER visits at baseline (SE) G1: 0.7 (0.027) G2: 0.8 (0.032) P: 0.016  mean change in number of ER visits G1: -0.04 (0.03) G2: -0.08 (0.03) P: 0.399  Calculated mean difference (95% CI): 0.04 (-0.043 to 0.123, p=0.346)

**Table D42. ED visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perlroth et al., 2013 <sup>35a</sup>  Cohort/Medium	<p>Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR</p> <p>Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR</p> <p>Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR</p> <p>Comparison—congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care</p> <p>Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care</p> <p>Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care</p>	<p>G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912</p>	<p>Odds of any all-cause emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators) (95% CI)</p>	<p>For PDP Congestive heart failure G1 vs. G13: 0.94 (0.90, 0.98), p&lt;0.05</p> <p>Chronic obstructive pulmonary disease G5 vs. G15: 0.89 (0.86, 0.93), p&lt;0.05</p> <p>Diabetes G9 vs. G17: 0.96 (0.92, 1.00), p&gt;0.05</p>

**Table D42. ED visits: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>35a</sup> (continued)			Odds of condition-specific emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly-assigned date in 2010 (for comparators) (95% CI)	For PDP Congestive heart failure G1 vs. G13: 1.01 (0.95, 1.07), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 1.09 (1.04, 1.15), p<0.05  Diabetes G9 vs. G17: 1.00 (0.96, 1.05), p>0.05
Welch et al., 2009 <sup>56</sup> Retrospective cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (opt-out)	G1: 459 G2: 336	Adjusted OR of ED visit from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	Adjusted OR: 0.9 (0.6 to 1.3)
Jeong, <sup>26</sup> ; Jeong, 2012 <sup>27</sup>  Cohort/High	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	G1: 23,638 G2: 14,232 G3: 1,810	Percentage with ED visits within 12 months of CMR	G1: 47.95 G2: 51.52 G3: 52.15 p<0.001  Calculated OR G1 vs. G2: 0.867 (0.832–0.904, p<0.001); calculated OR for G1 vs. G3: 0.845 (0.768–0.930, p=0.001)

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CI = confidence interval; CMR = comprehensive medication review; DRP = drug related problems; ED = emergency department; G =group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; OR = odds ratio; PCP = primary care physician; RCT = randomized controlled trial.

**Table D43. Costs of emergency department visits: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.  G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for emergency room visits (25th-75th percentile) in USD (95% CI)	G1: 119 (0–146) G2: 171 (0–219) 95% CI: NR p = NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of ED/urgent care visits and ambulance use at 5 months in \$ (assumed CAD) (SE)	G1: 0.2 (0.03) G2: 0.2 (0.03) 95% CI (calculated for standardized difference in means): -0.19 to 0.10 p (calculated for standardized difference in means): 0.53
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges of ED claims at 12 months	Results NR  p: 0.513
Perlroth et al., 2013 <sup>35a</sup>  Cohort/Medium	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR  Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR  Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR  Comparison—congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	Change in costs of any all-cause emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) in USD (95% CI)  Change in costs of condition-specific emergency room visits within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	For PDP Congestive heart failure G1 vs. G13: -12.66 (-33.61, 8.30), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: -16.21 (-35.37, 2.96), p>0.05  Diabetes G9 vs. G17: -8.76 (-23.65, 6.12), p>0.05 For PDP Congestive heart failure G1 vs. G13: -3.17 (-14.59, 8.25), p>0.05  Chronic obstructive pulmonary disease G5 vs. G15: 12.81 USD (-.14, 25.76), p>0.05 Diabetes G9 vs. G17: -3.27 (-15.37, 8.84), p>0.05

**Table D43. Costs of emergency department visits: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Perloth et al., 2013 <sup>35a</sup> (continued)	Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care  Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care			

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

<sup>a</sup>Abbreviations: CAD = Canadian dollars, CI = confidence interval; CMR = comprehensive medication review; ED = Emergency department; G = group; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; PCM = pharmaceutical care management; PDP = Medicare Part D Plan; SE = standard error; USD = United States dollars.

**Table D44. Number of hospitalizations: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.	G1: 105 G2: 103	Mean hospital admission (time period NR) (25th–75th percentile)	G1: 0.7 (0–1) G2: 0.8 (0–1) 95% CI: NR p= NS at 0.05 level, specifics NR
	G2: Usual care in the General Medicine Clinic			
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> (interventions); Malone et al., 2001 <sup>31</sup> (detailed QOL outcomes); Ellis et al., 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care	G1: 523	Mean change in number of hospitalizations	G1: +0.1 G2: +0.2 p: 0.29
	G2: Usual care	G2: 531		
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean all-cause hospitalizations (SE)	G1: 0.1 (0.02) G2: 0.1 (0.02) p: 0.77
			Mean drug-related hospitalizations (SE)	G1: 0.04 (0.01) G2: 0.04 (0.01) p: 0.08
Touchette et al., 2012 <sup>53</sup> RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	Time One G1: 180 G2: 190 G3: 193	Percent of participants with at least one hospital visit	Time One G1: 13.9 G2: 7.9 G3: 10.4  G1 vs. G3: 1.6 (p=0.350) G2 vs. G3: 0.6 (p=0.370) G2 vs. G1: 0.4 (p=0.080)
		Time Two G1: 183 G2: 190 G3: 183		Time Two G1: 17.6 G2: 12.1 G3: 9.3  G1 vs. G3: 2.6 (p=0.049) G2 vs. G3: 1.4 (p=0.484) G2 vs. G1: 0.3 (p=0.214)



**Table D44. Number of hospitalizations: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>33</sup> RCT/Medium (continued)			Mean number of hospital visits per participant	Time One G1: 0.2 (0.5) G2: 0.1 (0.4) G3: 0.1 (0.4)  G1 vs. G3: (p=0.265) G2 vs. G3: (p=0.619) G2 vs. G1: (p=0.109)  Time Two G1: 0.2 (0.5) G2: 0.1 (0.4) G3: 0.1 (0.4)  G1 vs. G3: (p=0.056) G2 vs. G3: (p=0.547) G2 vs. G1: (p=0.174)
Moore et al., 2013 <sup>40</sup> Cohort/Medium	G1: MTM program (opt-in) G2: control group (refusers)	G1: 2,250 G2: 2,250	Change in number of inpatient visits from 365 days preceding the patient's program invitation date to 365 days following patient's program invitation date	Number of inpatient visits at baseline (SE) G1: 0.5 (0.018) G2: 0.5 (0.016) P: 0.853  mean change in number of inpatient visits G1: -0.09 (0.02) G2: 0.12 (0.02) p< 0.001 Calculated mean difference (95% CI): -0.21(-0.265 to -0.155, p<0.001)

**Table D44. Number of hospitalizations: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results	
Perloth et al., 2013 <sup>35a</sup>  Cohort/Medium	Congestive heart failure	G1: 12,658	Odds of any all-cause hospitalization within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	Congestive heart failure	
	G1: enrolled in PDP receiving MTM with CMR	G3: 11,260		G1 vs. G13: 0.90 (0.86, 0.94), p<0.05	
	G3: enrolled in MA-PD, receiving MTM with CMR	G5: 16,372		G3 vs. G14: 0.96 (0.91, 1.02), p>0.05	
	G7: enrolled in MA-PD, receiving MTM with CMR	G7: 10,575		Chronic obstructive pulmonary disease	
	G9: 16,545	G9 vs. G15: 0.90 (0.87, 0.94), p<0.05			
	G11: 13,527	G7 vs. G16: 0.96 (0.91, 1.01), p>0.05			
	G13: 156,441	Diabetes			
	G14: 51,938				G9 vs. G17: 0.91 (0.87, 0.95), p<0.05
	G15: 184,350				G11 vs. G18: 0.93 (0.88, 0.98), p<0.05
	G7: enrolled in MA-PD, receiving MTM with CMR	G17: 133,925		Odds of any CHF/COPD/diabetes-related hospitalization within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators) (95% CI)	Congestive heart failure
	G18: 53,912	G1 vs. G13: 0.95 (0.90, 1.0), p<0.05			
	Diabetes	G3 vs. G14: 1.03, (0.97, 1.09), p>0.05			
G9: enrolled in PDP receiving MTM with CMR	Chronic obstructive pulmonary disease				
G11: enrolled in MA-PD, receiving MTM with CMR	G5 vs. G15: 1.04 (0.99, 1.08), p>0.05				
G7 vs. G16: 0.91 (0.86, 0.97), p<0.05					
Comparison—congestive heart failure	G13: enrolled in PDP, usual care	Diabetes	G9 vs. G17: 0.91 (0.87, 0.96), p<0.05		
G14: enrolled in MA-PD, usual care	G11 vs. G18: 0.92 (0.87, 0.97), p<0.05				
Comparison—Chronic obstructive pulmonary disease	G15: enrolled in PDP, usual care				
G16: enrolled in MA-PD, usual care					
Comparison—Diabetes	G17: enrolled in PDP, usual care				
G18: enrolled in MA-PD, usual care					

**Table D44. Number of hospitalizations: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Yamada et al., 2012 <sup>61</sup> Cohort study/Medium	G1: MTM enrolled patients G2: Eligible MTM patients not enrolled but matched on age, gender, region and DCG risk	G1: 34,352 G2: 138,182	Odds of hospital admission between 1 to 4 years depending on when patient was enrolled	0.91 (0.88 to 0.93) p< 0.001  Note: adjusted for age, sex, Charlson, CHF, and ESRD (95% CI)
Bernsten et al., 2001 <sup>1,2</sup> RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748  6 months G1: NR G2: NR  12 months G1: NR G2: NR  18 months G1: NR G2: NR	Percent with ≥1 hospitalization in the prior 18 months	Pooled sample Baseline (during 18 months prior to study) Overall: NR G1: 41.7 G2: 41.3 p=NS  18 months Overall: NR G1: 35.6 G2: 40.4 p=NS
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup> RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	All-cause hospitalizations  Cumulative hospitalized time (days)	G1: 1.8 (2.4) G2: 3.1 (3.0) p: 0.02  G1: 9.7 (14.7) G2: 15.5 (16.3) p: 0.06
Jeong, <sup>26</sup> ; Jeong, 2012 <sup>27</sup> Cohort/High	G1: Kaiser-Permanente MTM program participants (2010) G2: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser-Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	G1: 23,638 G2: 14,232 G3: 1,810	Percentage hospitalized within 12 months of CMR	G1: 30.82 G2: 35.94 G3: 42.38 p<0.001  Calculated OR G1 vs. G2: 0.794 (0.760–0.830); calculated OR for G1 vs. G3: 0.606 (0.550–0.668)

**Table D44. Number of hospitalizations: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Roughead et al., 2009 <sup>46</sup> Cohort/Medium	G1: Collaborative home-based medication review G2: No medication review received	G1: 273 G2: 5444	Rate of hospitalization for HF at any time during study	Adjusted HR (95% CI): 0.6 (0.4 to 0.8) p: NR  NOTE: Model adjusted for age, sex, comorbidity, SES, season, region of residence, and Ns of prescriptions, prescribers, pharmacies, changes in medications, hospitalizations, occupational therapy visits, and speech therapy visits
Welch et al., 2009 <sup>56</sup> Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of hospitalization from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	Adjusted OR (95% CI): 1.4 (1.1 to 2.0)  NOTE: Model adjusted for age, sex, Chronic Disease Score, specific baseline utilization

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CHF = congestive heart failure; CI = confidence interval; CMR = comprehensive medication review; DCG = diagnostic cost group (a measure of health care use and comorbidity); DRP = drug-related problems; ESRD = end-stage renal disease; G = group; HR = hazard ratio; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management, N = number; NR = not reported; NS = not significant; OR = odds ratio; PCP = primary care physician; QOL = quality of life; RCT = randomized controlled trials; RR = relative risk; SES = socioeconomic status.

**Table D45. Costs of hospitalization: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Annual health care costs for inpatients 1-year closeout or adjusted to a 1-year followup and weighted by actual time for censored patients	Mean USD (25th–75th percentile) G1: 5751 (0–3780) G2: 3349 (0–4824) 95% CI: NR p: NS at 0.05 level, specifics NR
Sellors et al., 2003 <sup>47</sup> RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all admissions to hospital \$ (assumed CAD) (SE)	G1: 753.7 (183.1) G2: 594.9 (135.2) 95% CI (calculated for standardized difference in means), -0.09 to 0.20 p (calculated for standardized difference in means): 0.479
Malone, 2000 <sup>29</sup> ; Ellis, 2000 <sup>30</sup> (interventions); Malone, 2001 <sup>31</sup> (detailed QOL outcomes); Ellis, 2000 <sup>32</sup> RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual hospitalization costs in US \$	G1: +542 G2: +763 Variance not reported 95% CI, NR p: 0.21
Perlroth et al., 2013 <sup>35 a</sup> Cohort/Medium	Congestive heart failure G1: enrolled in PDP receiving MTM with CMR G3: enrolled in MA-PD, receiving MTM with CMR  Chronic obstructive pulmonary disease G5: enrolled in PDP receiving MTM with CMR G7: enrolled in MA-PD, receiving MTM with CMR  Diabetes G9: enrolled in PDP receiving MTM with CMR G11: enrolled in MA-PD, receiving MTM with CMR	G1: 12,658 G3: 11,260 G5: 16,372 G7: 10,575 G9: 16,545 G11: 13,527 G13: 156,441 G14: 51,938 G15: 184,350 G16: 73,623 G17: 133,925 G18: 53,912	All hospitalization costs: Generic substitution ratio within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators)	Risk adjusted costs in USD for PDP (95% CI) G1 vs. G13: -526.19 (-.919.71, -132.66), p<0.05 G5 vs. G15: -249.70 (-574.03, 74.62), p>0.05 G9 vs. G17: -398.98 (-651.21, -146.75), p<0.05

**Table D45. Costs of hospitalization: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Perloth et al., 2013 <sup>35</sup> <sup>a</sup> (continued)	<p>Comparison—Congestive heart failure G13: enrolled in PDP, usual care G14: enrolled in MA-PD, usual care</p> <p>Comparison—Chronic obstructive pulmonary disease G15: enrolled in PDP, usual care G16: enrolled in MA-PD, usual care</p> <p>Comparison—Diabetes G17: enrolled in PDP, usual care G18: enrolled in MA-PD, usual care</p>		Any CHF/COPD/diabetes-related hospitalization costs within 365 days after date of MTM enrollment (for interventions) or randomly assigned date in 2010 (for comparators)	Risk adjusted costs in USD for PDP (95% CI) G1 vs. G13: -222.08 (-525.99, 81.82), p>0.05 G5 vs. G15: 200.21 (-55.81, 456.23), p>0.05 G9 vs. G17: -363.45 (-562.00, -164.91), p<0.05
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges of inpatient claims	Results NR  p: 0.937

<sup>a</sup> Perloth et al. included MTM arms without CMR; these results were not eligible for our review because of our requirement for CMR. We have excluded groups 2, 4, 6, 8, 10, and 12 from our summary tables.

Abbreviations: CAD = Canadian dollars; CHF = congestive heart failure; CMR = comprehensive medication review; COPD = chronic obstructive pulmonary disease; MA-PD = Medicare Advantage Part D Plan; MTM = medication therapy management; NR = not reported; PCM = pharmaceutical care management; PDP = Medicare Part D Plan; RCT = randomized controlled trial; USD = United States dollars.

**Table D46. Length of hospital stay: summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996 <sup>17,18</sup> RCT/Low	G1: Usual care, plus clinical pharmacist care.  G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Hospitalized days (time period NR)	Mean (25th–75th percentile) G1: 6.7 (0–5) G2: 4.9 (0–6) 95% CI: NR p: NS at 0.05 level, specifics NR
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup> RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44  Year 1: G1: 44 G2: 36  Year 2: G1: 24 G2: 32	Cumulative hospital time (days) over 2 years	Cumulative hospital time G1: 9.7 days (14.7) G2: 15.5 days (16.3) p: 0.06  Pharmaceutical care reduced length of stay by 21% compared with the standard of care group. p=NS

Abbreviations: G = group; NR = not reported; NS = not significant; RCT= randomized controlled trial.

**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low	G1: Basic MTM services (with medication information from patient interview)  G2: Enhanced MTM services (pharmacist provided with 2-page clinical summary from patient medical record)  G3: Usual pharmacy care	G1: 211 G2: 218 G3: 208	Percentage with ≥ 1 ADE at 0 and 3 months	Time One G1: 42.2% G2: 27.9% G3: 33.7 % G1 vs G3: 1.629 (p = 0.078) G2 vs G3: 0.726 (p = 0.278) G2 vs G1: 0.444 (p= 0.005) Time Two G1: 36.1% G2: 31.1% G3: 34.4 % G1 vs G3: 1.107 (p = 0.717) G2 vs G3: 0.889 (p = 0.672) G2 vs G1: 0.803 (0.432)  Calculated OR: 1.294, 95% CI: 0.768 to 2.180, p=0.333



**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low (continued)			Percentage with ≥ 1 emergency department visit at 0 and 0 and 3 months	<p>Time One            G1: 0.750 ± 1.113            G2: 0.547 ± 1.184            G3: 0.559 ± 1.202            G1 vs G3:            (p = 0.110)            G2 vs G3:            (p = 0.916)            G2 vs G1:            (p= 0.900)</p> <p>Time Two            G1: 0.814 ± 1.421            G2: 0.468 ± 0.820            G3: 0.530 ± 0.894            G1 vs G3:            (p = 0.041)            G2 vs G3:            (p = 0.479)            G2 vs G1:            (p= 0.003)</p> <p>Time One            G1: 20.3%            G2: 20.0%            G3: 20.0%            G1 vs G3: 0.938            (p= 0.825)</p> <p>G2 vs G3: 0.989            (p = 0.970)            G2 vs G1: 1.055            (p = 0.854)</p>

**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low (continued)				Time Two G1: 23.6% G2: 20.8% G3: 16.8% G1 vs G3: 0.780 (p=0.380) G2 vs G3: 0.578 (p=0.064) G2 vs G1: 0.743 (p=0.317)
				Calculated OR: 1.222, 95% CI: 0.795 to 1.878, p=0.360
			Percentage with ≥ 1 hospitalization at 3 months	Time One G1: 13.9% G2: 7.9% G3: 10.4 %  G1 vs G3: 1.557 (p=0.350) G2 vs G3: 0.626 (p=0.370) G2 vs G1: 0.402 (p=0.080)
				Time Two G1: 17.6% G2: 12.1% G3: 9.3% G1 vs G3: 2.550 (p=0.049) G2 vs G3: 1.404 (p=0.484) G2 vs G1: 0.293 (p=0.214)
				Calculated OR: 1.539, 95% CI: 0.862 to 2.746, p=0.145
			Mean number of ADEs at 0 and 3 months	Calculated mean difference: 0.346, 95% CI: 0.112 to 0.580, p=0.004

**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low (continued)			Mean number of emergency department visits at 0 and 3 months	<p>Time One</p> <p>G1: 0.261 ± 0.573            G2: 0.242 ± 0.558            G3: 0.229 ± 0.480            G1 vs G3:            (p = 0.735)            G2 vs G3:            (p = 0.963)            G2 vs G1:            (p= 0.769)</p> <p>Time Two</p> <p>G1: 0.246 ± 0.512            G2: 0.247 ± 0.6404            G3: 0.352 ± 0.806            G1 vs G3:            (p = 0.077)            G2 vs G3:            (p = 0.057)            G2 vs G1:            (p= 0.900)</p> <p>Calculated mean difference: -0.001            , 95% CI:            -0.119 to 0.117, p=0.987</p>

**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low (continued)			Mean number of hospitalizations at 0 and 3 months	<p>Time One</p> <p>G1: 0.172 ± 0.458                      G2: 0.111 ± 0.440                      G3: 0.119 ± 0.370</p> <p>G1 vs G3:                      (p = 0.265)                      G2 vs G3:                      (p = 0.619)                      G2 vs G1:                      (p= 0.109)</p> <p>Time Two</p> <p>G1: 0.202 ± 0.477                      G2: 0.147 ± 0.435                      G3: 0.110 ± 0.362</p> <p>G1 vs G3:                      (p = 0.056)                      G2 vs G3:                      (p = 0.547)                      G2 vs G1:                      (p= 0.174)</p> <p>Calculated mean difference: 0.055 ,                      95% CI:                      -0.038 to 0.148, p=0.244</p>

**Table D47. Access to patient records (basic MTM versus enhanced MTM): Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012 <sup>53</sup> RCT/Low (continued)			Mean number of physician visits at 0 and 3 months	<p>Time One</p> <p>G1: 2.57 ± 2.218 G2: 2.73 ± 2.31 G3: 2.57 ± 2.24 G1 vs G3: (p = 0.646) G2 vs G3: (p = 0.816) G2 vs G1: (p= 0.490)</p> <p>Time Two</p> <p>G1: 2.24 ± 2.08 G2: 2.14 ± 2.08 G3: 2.19 ± 2.19 G1 vs G3: (p = 0.760) G2 vs G3: (p = 0.458) G2 vs G1: (p= 0.664)</p> <p>Calculated mean difference: 0.100 , 95% CI: -0.322 to 0.522 , p=0.643</p>

Abbreviations: ADE = adverse drug event; CI = confidence interval; OR = odds ratio.

**Table D48. Intensity of care coordination and followup following comprehensive medication review: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Grymonpre, 2001 <sup>16</sup> Cohort/High	G1: Comprehensive drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensive drug therapy review only with referral to usual pharmacist.	G1: 56 G2: 58	Non-prescribed drugs discontinued	Mean (SD) non-prescribed drugs Baseline G1: 7.2(4.1) G2: 5.9(3.8) 6 months G1: 6.8 (3.4) G2: 5.8 (3.2) 95% CI: NR p: 0.130  Calculated OR: 1.08, 95% CI (0.52–2.27); p=0.830
			Taking home remedies	Mean home remedies Baseline G1: 1.0(0.2) G2: 1.4(0.6) 6 months G1: 1.1(0.3) G2: 1.1(0.4) 95% CI: NR p: 0.160  Calculated OR: 1.00, 95% CI (0.07–13.77); p=1.000
			Hoarding drugs	Mean hoarded drugs Baseline G1: 3.0 (2.9) G2: 2.7(2.2), 95% CI: NR 6 months G1: 1.8 (1.2) G2: 2.0 (2.0) p: 0.018 Calculated OR: 1.48, 95% CI (0.65–3.34); p=0.348

**Table D48. Intensity of care coordination and followup following comprehensive medication review: Summary of results**

Study	Study Arms	N Analyzed	Outcome and Time Period	Results
Grymonpre, 2001 <sup>16</sup> Cohort/High (continued)			Mean symptoms reported	Baseline G1: 7.2(3.7) G2: 7.5(3.5) 95% CI: NR p: NR
				6 months G1:7.9 (4.1) G2: 7.2 (3.7) 95% CI: NR p: NR
				Between group p-value: 0.089 Calculated mean: 0.70, 95% CI (-0.73--2.13); p=0.34
			Mean medication adherence	Baseline G1: 95.0 (79.4) G2: 95.5 (56.7) 95% CI: NR p:
				6 months G1: 86.7(46.0) G2: 85.1(41.1) 95% CI: NR p:
				Overall p-value: 0.895 Calculated mean: 1.60, 95% CI (-14.40--17.60); p=0.84

**Table D48. Intensity of care coordination and followup following comprehensive medication review: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Grymonpre, 2001 <sup>16</sup> Cohort/High (continued)			Estimated annual prescription costs in USD per client	Baseline G1: 881 (650) G2: 944 (687) 95% CI: NR 95% CI: NR p: NR 6 months G1:809 (578) G2:874 (754)  Between group P= 0.971 Calculated mean: -65.00, 95% CI (-305.67–175.67); p=0.60

Abbreviations: CI = confidence interval; OR = odds ratio; USD = United States dollars.



**Table D49. Pharmacy intensity of adoption: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chrischilles et al., 2004 <sup>9</sup> Cohort/High	Groups 1 and 2 were combined in these analyses. Thus, all PCM-eligible people were grouped together, regardless of whether they received services. The subgroup analyses involved stratifying the combined group by level of pharmacy intensity. SG1: High intensity SG2: Moderate intensity	G1: NR G2: NR	Number of emergency department claims	Findings NR, p=0.330
			Number of inpatient institutional claims	Findings NR, p=0.839
			Number of outpatient facility claims	Findings NR, p=0.112
			Number of pharmacy, institutional, and medical services	Findings NR, p=0.616
			Emergency department claims	Findings NR, p=0.652
			Inpatient institutional claims	Findings NR, p=0.862
			Outpatient facility claims	Findings NR, p=0.212
			Pharmacy, institutional, and medical services	Findings NR, p=0.166

Abbreviation: NR = not reported; SG = subgroup.

**Table D50. Community pharmacy versus call center: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Winston et al., 2009 <sup>58</sup> Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Drug cost per patient per month (USD)	Pre-MTM (Jan 1 2007-April 30, 2007) G1: 669 (461) G2: 676 (463) G3: 698 (513) p: NR Post-MTM (Jan 1 2008-April 30, 2008) G1: 634 (512) G2: 661 (494) G3: 698 (556) p: NR  Difference (% change) G1: -35 ± 353 (-5.2) G2: -15 ± 374 (-2.2) G3: 0 ± 406 (0) 95% CI: NR p: NR  Calculated mean difference: -20.0, 95% CI: -32.826 to -7.174, p=0.002
			Drug use per patient per month	Pre-MTM (Jan 1 2007-April 30, 2007) G1: 9.79 (3.17 ) G2: 9.76 (2.93) G3: 9.70 (2.94) p: NR Post-MTM (Jan 1 2008-April 30, 2008) G1: 9.29 (3.60) G2: 9.63 (3.47) G3: 9.53 (3.61) p: NR Difference (% change) G1: -0.50 ± 3.01 (-5.0) G2: -0.13 ± 2.78 (-1.3) G3: -0.18 ± 2.88 (-1.8) 95% CI: NR p: NR Calculated mean difference: -0.370, 95% CI: -0.477 to -0.263, p<0.001

**Table D50. Community pharmacy versus call center: Summary of results (continued)**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Winston et al., 2009 <sup>58</sup> Cohort/High (continued)			Weighted generic dispensing ratio	Pre-MTM (Jan 1 2007-April 30, 2007) G1: 60.1 (29.8) G2: 58.6 (25.7) G3: 58.7 (27.6) p: NR Post-MTM (Jan 1 2008-April 30, 2008) G1: 65.7 (32.5) G2: 64.6 (30.5) G3: 63.5 (32.2) p: NR Difference (% change) G1: 5.6 ± 26.2 (9.4) G2: 6.0 ± 23.1 (10.2) G3: 4.8 ± 23.8 (8.1) 95% CI: NR p: NR  Calculated mean difference: 9.710, 95% CI: 9.583 to 9.837, p<0.001

Abbreviations: CI = confidence interval; USD = United States dollars.

**Table D51. Type of payer: Summary of results**

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Witry et al., 2011 <sup>59</sup> Cohort/High	G1: Iowa Medicaid Pharmaceutical Case Management (PCM), which pays for pharmacists to collaborate with patients and their physicians. Pharmacists conducted CMR, looked for DRPs and untreated conditions, provided pt education as needed, followed up with pt as needed, and coordinated care with physicians and pts. G2: PCM provided to patients with private individual-group insurance	G1: 45	Per-patient Medication Appropriateness Index at followup	Baseline Overall: NR G1: 9.4 (7.7) G2: 1.53 (1.64) P: NR Final Overall: NR G1: 8.3 (7.1) G2: 1.24 (1.22) P: NR  Calculated mean difference: 0.81, 95% CI: -1.303 to 2.923, p=0.452
		G2: 469		
		G1: 45 G2: 474	Proportion of patients for whom cost was a problem at followup	Baseline Overall: NR G1: 67.1 G2: 60.0 P: NR Final Overall: NR G1: 65.2 G2: 55.6 P: 0.198  Calculated OR: 1.498, 95% CI: 0.807 to 2.778, p=0.20
		G1: 91 G2: 524	Drug therapy problems identified	2.6 in both arms, p=1.0

Abbreviations: CI = confidence interval; OR = odds ratio.

**Table D52. Confusion: Summary of results**

<b>Study Design/Risk of Bias</b>	<b>Study Arms</b>	<b>N Analyzed</b>	<b>Outcome and Time Period</b>	<b>Results</b>
Carter et al., 1997 <sup>7</sup> , Barnette et al., 1996 <sup>8</sup> Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percentage that agree or strongly agree with the statement that they were inconvenienced by monthly appointments with the pharmacists	G1: 40 percent G2: 69 percent Calculated OR: 0.278, 95% CI: 0.088 to 0.875; p=0.029

Abbreviations: CI = confidence interval; OR = odds ratio.

**Table D53. Applicability**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)</b>	<b>Intervention broadly applicable? (e.g., design of interventions reflected in current practice)</b>	<b>Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)</b>	<b>Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)</b>
Bernsten et al., 2001 <sup>1</sup> ; Sturgess et al., 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	Yes	Yes	Yes	Yes
Carter et al., 1997 <sup>7</sup> , Barnette et al., 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	No Rural population	Yes	Yes	Yes

**Table D53. Applicability (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)</b>	<b>Intervention broadly applicable? (e.g., design of interventions reflected in current practice)</b>	<b>Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)</b>	<b>Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)</b>
Chrischilles et al., 2004 <sup>9</sup>	G1: PCM provided by pharmacists G2: Did not receive PCM services	Yes	Yes	Yes	Yes
Christensen et al., 2007 <sup>10</sup>	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	Yes	Yes	Yes	Yes

**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Clifford et al., 2002 <sup>11</sup>	G1: Pharmaceutical care provided by a clinical pharmacist, which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	Yes	Yes	Yes	Yes
Fischer et al., 2000 <sup>12</sup>	G1: Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists. G2: Standard Community Pharmacy Practice G3: A set of refusers surveyed and included in some analyses among those who were at eligible clinics but initially declined to participate.	Yes	Yes	Yes	No  The outcomes are very intermediate (receipt of information, use of reminders to take medication, and awareness of side effects)
Fischer et al., 2002 <sup>13</sup>	Pharmaceutical care based on the Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care with no additional interventions.	Yes	Unclear or NR  Pharmacies volunteered to participate in the intervention group. Not clear how representative they are of community pharmacies in general.	Yes	Yes



**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Fox et al., 2009 <sup>14</sup>	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	Yes	Yes	Yes	Yes
Gattis et al., 1999 <sup>15</sup>	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	No Study population limited to patients with moderate to severe heart failure.	Yes	Yes	Yes
Hanlon et al., 1996 <sup>17</sup>	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	No All male VA patients.	Yes	Yes	Yes

**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Isetts et al., 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	Yes	Yes	Yes	Yes
Jameson, VanNoord, and Vanderwoud, 1995 <sup>23</sup>	Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	Yes	Yes	Yes	Yes
Jeong et al., 2007 <sup>24</sup>	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff G2: Eligible for Part D MTMP but declined enrollment G3: Patients without Part D as their primary drug benefit	Yes	No  MTM intervention itself may be applicable, but it was delivered within Kaiser Permanente's integrated healthcare system, which does not reflect organization of most healthcare systems in the US.	Yes	Yes
Krska et al., 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	No  Older adults	Yes	Yes	Yes

**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup>	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	Yes	No	Yes	No
IMPROVE			VA is a large integrated health system with on- site pharmacy and highly trained clinical pharmacists who are embedded within ambulatory care clinics. This is not typical of most primary care practices.		Unclear how applicable VA costing methods and systems are to the rest of the healthcare system.
McDonough et al., 2005 <sup>36</sup>	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of doses, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	Yes	Yes	Yes	Yes
Moczygemba et al., 2011 <sup>37</sup> Moczygemba et al., 2008 <sup>38</sup>	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	Yes	Yes	Yes	Yes

**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	No  Narrow eligibility - Adults with ESRD who were undergoing a stable hemodialysis.	Yes	Yes	Yes
Park et al., 1996 <sup>43</sup>	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	Yes	Yes	Yes	Yes
Pindolia et al., 2009 <sup>44</sup>	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists. G2: Usual medical care	Yes	Yes	Yes	Yes
Planas et al., 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	Yes	Yes	Yes	Yes
Roughead et al., 2009 <sup>46</sup>	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	Yes	Unclear or NR Australia's health care system is different than the U.S. health care system, so it is unclear how generalizable these results are to the US.	Yes	Yes

**Table D53. Applicability (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)</b>	<b>Intervention broadly applicable? (e.g., design of interventions reflected in current practice)</b>	<b>Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)</b>	<b>Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)</b>
Sellors et al., 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	Yes and No  Yes for Canada, but may not be for US.	Yes	Yes	Yes
Sidel et al., 1990 <sup>50</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	Unclear or NR  Narrow eligibility based on excluding low and medium risk patients and those considered to be "difficult".	Yes	Yes	No  Short-term, most subjective and not broadly applicable, most surrogate outcomes.
Staresinic et al., 2007 <sup>51</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	Yes	Yes	Yes	Unclear or NR
Taylor, Byrd, and Krueger, 2003 <sup>52</sup>	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	Yes	Yes	Yes	Yes
Touchette et al., 2012 <sup>53</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	Yes	Yes	Yes	Yes

**Table D53. Applicability (continued)**

Author, Year Trial Name	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Volume et al., 2001 <sup>54</sup> , Kassam et al., 2001 <sup>55</sup> PREP	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	Yes	Yes	Yes	Yes
Welch et al., 2009 <sup>56</sup>	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	Yes	Yes  KPCO's level of integration not widespread, but intervention itself is applicable	Yes	Yes
Williams et al., 2004 <sup>57</sup>	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	Yes	Yes	Yes	Yes

**Table D53. Applicability (continued)**

<b>Author, Year Trial Name</b>	<b>Interventions and Comparator Descriptions</b>	<b>Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)</b>	<b>Intervention broadly applicable? (e.g., design of interventions reflected in current practice)</b>	<b>Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)</b>	<b>Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)</b>
Winston and Lin, 2009 <sup>58</sup>	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Yes	Yes	Yes	Yes
Witry, Doucette, and Gainer, 2011 <sup>59</sup>	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	Yes	Yes	Yes	Yes

Abbreviations: BP = blood pressure; G = group; HMR = home medication review; KPCO = Kaiser Permanente Colorado; MTM = medication therapy management; MTMP = medication therapy management program; NR = not reported; PA = physician assistant; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; US = United States; VA = Veterans Affairs

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## Appendix E. Risk of Bias Evaluations and Rationale

**Table E1. Risk of bias domains and ratings: Part 1**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Bernsten et al., 2001 <sup>1</sup> ; Sturgess, 2003 <sup>2</sup>	G1: Structured community pharmacy- based pharmaceutical care program G2: Usual community pharmacy services	RCT: cluster- rando- mized	Unclear or NR	Unclear or NR	No	Yes	Yes	Unclear or NR	Yes	Yes	Yes
Blakey and Hixson- Wallace, 2000 <sup>3</sup>	G1: Pharmacist evaluation plus usual medical care G2: Usual medical care	NRCT	NA	NA	Yes	No	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Brummel et al., 2013 <sup>4</sup> ; Soliman et al., 2013 <sup>5</sup> ; Ramalho de Oliveira, , Brummel, and Miller, 2010 <sup>6</sup>	G1: Fairview Pharmacy Services' MTM program (opt-in) G2: control group (did not opt-in)	Cohort	NA	NA	Yes	No	NA	No	Unclear or NR	NA	NA
Carter et al., 1997 <sup>7</sup> ; Barnette et al., 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within interdisciplinary practice model. Standardized patient education (lifestyle, risk factor modifications, and drug therapy). G2: Usual care	Cohort	NA	NA	Yes	No	Yes	Unclear or NR	Unclear or NR	No	NA

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Chrischilles et al., 2004 <sup>9</sup>	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	Cohort	NA	NA	Yes	No	Unclear or NR	Unclear or NR	NA	No	No
Christensen et al., 2007 <sup>10</sup>	G1: MTM services designed by a health plan for beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention. G3: Patients from a different county than G1 who did not receive intervention.	NRCT for G1 vs. G3, Cohort for G1 vs. G2	NA	NA	Yes	Yes	Unclear or NR	No	Yes	Yes	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Clifford et al., 2002 <sup>11</sup>	G1: Pharmaceutica l care provided by a clinical pharmacist, including a comprehensiv e review relating to pharma- cotherapy and diabetes, use of proprietary and non- proprietary medications, such as complementar y medicines, and identification of DTPs. G2: Standard outpatient care for diabetes	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., $\geq 20\%$ ) or differential characteristics? (i.e., $\geq 15\%$ ) attrition	Did attrition result in differences in group charac- teristics?
Fischer et al., 2000 <sup>12</sup>	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists (acceptors). G2: Standard Community Pharmacy Practice. G3: A set of those at eligible clinics who initially declined to participate (opt-out).	NRCT	NA	NA	No	Yes	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes



**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Fischer et al., 2002 <sup>13</sup>	G1: Pharmaceutical care based on Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care.	NRCT	NA	NA	Yes	Yes	Unclear or No NR	Unclear or No NR	Unclear or NR	Unclear or NR	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Fox et al., 2009 <sup>14</sup>	G1: Florida Health Care Plans MTM program, consisting of medication therapy review and evaluation by a clinical pharmacist that was documented and sent to patient's physician through health plan review (acceptors) G2: Opt-out from MTM program	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	No	No

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Gattis et al., 1999 <sup>15</sup>	G1: Clinical pharmacy services, including assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about purpose of each drug and reinforcing adherence. Detailed written information also provided to patients. G2: Usual medical care	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	No	No	Unclear or NR	Unclear or NR	No

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Grymonpre, Williamson, and Montgomery, 2001 <sup>16</sup>	G1: Comprehensiv e drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensiv e drug therapy review only with referral to usual pharmacist.	RCT: parallel, not clustered	Yes	Unclear or NR	Yes	No	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR
Hanlon et al., 1996 <sup>17</sup> ; Cowper et al., 1998 <sup>18</sup>	G1: Pharmaceutica l care provided by clinical pharmacist. G2: Usual care in the General Medicine Clinic	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Isetts et al., 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM.	Cohort	NA	NA	Yes	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR
Jameson et al., 1995 <sup>23</sup>	G1: Pharmaco- therapy consultation and follow-up provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	No	No	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Jeong et al., 2007 <sup>24</sup> ; Jeong et al., 2009 <sup>25</sup>	G1: Pharmacist- managed MTMP provided by ambulatory care pharmacists and healthcare support staff (acceptors) G2: Eligible for Part D MTMP but declined enrollment (refusers) G3: Patients without Part D as their primary drug benefit	Cohort	NA	NA	Yes	No	Unclear or No NR	Unclear or No NR	Unclear or NR	Unclear, only included subjects with available data.	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., $\geq 20\%$ ) or differential characteristics? (i.e., $\geq 15\%$ ) attrition	Did attrition result in differences in group charac- teristics?
Jeong et al. <sup>26</sup> ; Jeong et al., 2012 <sup>27</sup>	G1: Kaiser- Permanente MTM program participants (2010) G2: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	Cohort	NA	NA	Yes	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear, only included subjects with available data.	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Krska et al., 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities G2: Usual care without pharmaceutical care	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Unclear or NR	Yes	Unclear or NR	No	Unclear or NR



**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Marques et al., 2013 <sup>33</sup>	G1: Intervention group: Dader method pharma- cotherapy follow-up intervention monthly over 3-month follow-up period G2: Control group: monthly pharmacist visits without pharmaco- therapy follow- up intervention	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Marrufo et al., 2013 <sup>34</sup> , Perlroth et al., 2013 <sup>35</sup>	<b>CHF</b> G1: enrolled in Medicare PDP receiving MTM with a CMR G2: enrolled in PDP receiving MTM, no CMR G3: enrolled in MA-PD receiving MTM with CMR G4: enrolled in MA-PD, receiving MTM, no CMR <b>COPD</b> G5: enrolled in Medicare PDP receiving MTM with a CMR G6: enrolled in PDP receiving MTM, no CMR G7: enrolled in MA-PD receiving MTM with CMR G8: enrolled in MA-PD, receiving MTM, no CMR	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	No	NA

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
McDonough et al., 2005 <sup>36</sup>	G1: Pharmaceutica l care provided by community pharmacists. Drug therapy monitoring focused on 5 DTPs: appropriatenes s of dose, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster- rando- mized	Unclear or NR	Unclear or NR	No	No	Unclear or NR	No	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Moczygemba et al., 2011 <sup>37</sup> ; Moczygemba et al., 2008 <sup>38</sup> ; Moczygemba, Barner, and Gabrillo, 2012 <sup>39</sup>	G1: Opt-in telephone- based MTM program, in which MTM services provided by clinical pharmacists or managed care pharmacy resident based on American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework (acceptors) G2: No-MTM control group (opt-out)	Cohort	NA	NA	Yes	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR
Moore et al., 2013 <sup>40</sup>	G1: MTM program (opt- in) G2: control group (refusers)	Cohort	NA	NA	Yes	Yes	NA	Unclear or NR	NA	NA	NA

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>	G1: Pharmaceutica l care including drug therapy reviews conducted by nephrology- trained clinical pharmacist with patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by nurse	RCT: cluster- rando- mized	No	Yes	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Yes	No

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., $\geq 20\%$ ) or differential characteristics? (i.e., $\geq 15\%$ ) attrition	Did attrition result in differences in group charac- teristics?
Park et al., 1996 <sup>43</sup>	G1: Compre- hensive pharmaceuti- cal services, including drug therapy monitoring and patient education provided by community pharmacy resident. G2: Usual care	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	No	No	Unclear or NR	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., $\geq 20\%$ ) or differential characteristics? (i.e., $\geq 15\%$ ) attrition	Did attrition result in differences in group charac- teristics?
Pindolia et al., 2009 <sup>44</sup>	G1: Telephone- based MTM services provided as part of Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors) G2: Usual medical care (opt-out)	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	Unclear or NR	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., $\geq 20\%$ ) or differential characteristics? (i.e., $\geq 15\%$ ) attrition	Did attrition result in differences in group charac- teristics?
Planas et al., 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clustered	Yes	Yes	No	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR



**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocatio n conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Roughead et al., 2009 <sup>46</sup>	G1: HMRs conducted by accredited pharmacists G2: No medication review received	Cohort	NA	NA	Unclear or NR	No	Unclear or NR	Unclear or NR	NA	Unclear or NR	Unclear or NR
Sellors et al., 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: cluster-randomized	Yes	Yes	No	Yes	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR
Sellors et al., 2003 <sup>47</sup>	G1: Pharmaceutical consultation G2: Usual care	RCT: parallel, not clustered	Yes	Yes	No	Unclear or NR	Yes	Unclear or NR	Unclear or NR	No	NA

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Shimp et al., 2012 <sup>48</sup>	G1: MTM program for University of Michigan beneficiaries, entitled FOM G2: Usual care	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR
Sidel et al., 1990 <sup>49</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Staresinic et al., 2007 <sup>50</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by MTM Coordinator (non-clinical staff) and pharmacist (acceptors) G2: Usual care provided to MTM-eligible enrollees who chose not to participate (opt-out)	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	Yes	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Taylor, Byrd, and Krueger, 2003 <sup>51</sup>	G1: Pharmaceutica l care provided not by pharmacists clustered G2: Standard care without advice or recom- mendations given to patients or physicians	RCT: parallel, clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Touchette et al., 2012 <sup>52</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clustered	Yes	Yes	No	Yes	Yes	Unclear or NR	No	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Volume et al., 2001 <sup>53</sup> , Kassam et al., 2001 <sup>54</sup>  PREP (Pharmaceutic al Care Research and Education Project)	G1: Compre- hensive pharma- ceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists G2: Traditional pharmacy care	RCT	Unclear or NR	Yes	Unclear or NR	Yes	No	Unclear or NR	Unclear or NR	Yes	Unclear or NR
Welch et al., 2009 <sup>55</sup>	G1: MTM program provided to home-based beneficiaries as part of Medicare Part D MTM program (acceptors) G2: No-MTM control group (voluntary opt- out)	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	No	No

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Williams et al., 2004 <sup>56</sup>	G1: Modification of patient's medication regimen conducted by interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Winston and Lin, 2009 <sup>57</sup>	G1: MTM provided in community pharmacy (i.e., care in face-to- face meetings or by telephone) as part of Medicare Part D MTM program G2: MTM provided by pharmacist- staffed call centers as part of Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	NA	NA	Yes	Yes	NA	Unclear or NR	Unclear or NR	NA	NA



**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Witry, Doucette, and Gainer, 2011 <sup>58</sup>	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided to patients with private individual- group insurance	Cohort	NA	NA	Yes	No	Unclear or NR	Unclear or NR	NA	Unclear or NR	Unclear or NR
Wittayanukorn et al., 2013 <sup>59</sup>	G1: Intervention group: Pharmacist provided face- to-face MTM services for 30-60 minutes per encounter, not always including a follow-up visit G2: Control group: Patients who did not receive MTM services (economic analyses only)	Cohort	NA	NA	Yes	Yes	Unclear or NR	No	NA	NA	NA

**Table E1. Risk of bias domains and ratings: Part 1 (continued)**

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi- zation method adequate? (RCTs only)	Allocation conceal- ment ad- equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or difference s adjusted for in analysis?	Outcome asse- ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions ? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential characteristics? (i.e., ≥15%) attrition	Did attrition result in differences in group charac- teristics?
Yamada, 2012 <sup>60</sup>	G1: Kaiser- Permanente MTM enrolled patients G2: Kaiser patients enrolled in Medicare part D, but not in MTM program matched to control on age, gender, region and DCG risk	Cohort	NA	NA	Yes	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear, only included subjects with available data.	Unclear or NR

Abbreviations: CHF = chronic heart failure; CMR = comprehensive medication review; COPD = chronic obstructive pulmonary disease; DTP = drug therapy problem; FOM = Focus on Medicines; G = group; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; MA-PD = Medicare Advantage Part D; MTM = medication therapy management; MTMP = medication therapy management program; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; PCM = pharmaceutical case management; PCP = primary care provider; PDP = Medicare Part D Plan; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; VNA = visiting nurse association.

**Table E2. Risk of bias domains and ratings: Part 2**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Bernsten et al., 2001 <sup>1</sup> ; Sturgess, 2003 <sup>2</sup>	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	RCT: cluster- rando- mized	No	Yes	Yes	Yes	Yes	Unclear or NR	Partial (some variables were taken in to account)	Medium (country- specific) High (pooled data)
Blakey and Hixson- Wallace, 2000 <sup>3</sup>	G1: Pharmacist evaluation plus usual medical care G2: Usual medical care	NRCT	Unclear or NR	No	Yes	NA	NA	Yes	No (Not accounted for or not identified)	High
Brummel et al., 2013 <sup>4</sup> ; Soliman et al., 2013 <sup>5</sup> ; Ramalho de Oliveira, , Brummel, and Miller, 2010 <sup>6</sup>	G1: Fairview Pharmacy Services' MTM program (opt-in) G2: control group (did not opt-in)	Cohort	NA	Yes	Yes	NA	NA	Yes	Partial (some variables were taken in to account)	Medium ROB for main analysis, high ROB for subgroup analysis because intensity of service is completely confounded with potential outcomes

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Carter et al., 1997 <sup>7</sup> ; Barnette et al., 1996 <sup>8</sup>	G1: Pharmaceutical care provided by pharmacists within interdisciplinary practice model. Standardized patient education (lifestyle, risk factor modifications, and drug therapy). G2: Usual care	Cohort	No	Yes	No	Yes	Yes	Yes	No (Not accounted for or not identified)	High
Chrischilles et al., 2004 <sup>9</sup>	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	Cohort	No	Yes	Yes	NA	Yes	Yes	No (Not accounted for or not identified)	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Christensen et al., 2007 <sup>10</sup>	G1: MTM services designed by a health plan for beneficiaries and provided by either community pharmacists or medical clinic- based pharmacists. G2: Patients from same counties as G1 who did not receive intervention. G3: Patients from a different county than G1 who did not receive intervention.	NRCT for G1 vs. G3, observa tional (cohort) for G1 vs. G2	Un- clear or NR	Unclear or NR	Yes	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Clifford et al., 2002 <sup>11</sup>	G1: Pharmaceutical care provided by a clinical pharmacist , including a comprehensive review relating to pharmaco- therapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of DTPs. G2: Standard outpatient care for diabetes	RCT: parallel, not clus- tered	Yes	Yes	Yes	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fischer et al., 2000 <sup>12</sup>	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists (acceptors). G2: Standard Community Pharmacy Practice. G3: A set of those at eligible clinics who initially declined to participate (opt-out).	NRCT	Un- clear or NR	Yes	No	No	NA	Unclear or NR	Yes	Medium for most outcomes, high for adverse drug events

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fischer et al., 2002 <sup>13</sup>	G1: Pharmaceutical care based on Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care.	NRCT	No	Yes	NA	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium



**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fox et al., 2009 <sup>14</sup>	G1: Florida Health Care Plans MTM program, consisting of medication therapy review and evaluation by a clinical pharmacist that was documented and sent to patient's physician through health plan review (acceptors) G2: Opt-out from MTM program	Cohort	NA	Yes	Unclear or NR	NA	Yes	Yes	No (Not accounted for or not identified)	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Gattis et al., 1999 <sup>15</sup>	G1: Clinical pharmacy services, including assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about purpose of each drug and reinforcing adherence. Detailed written information also provided to patients. G2: Usual medical care	RCT: parallel, not clus- tered	Yes	Yes	Yes	No	NA	Yes	NA	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures ?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Grymonpre, Williamson, and Montgomery, 2001 <sup>16</sup>	G1: Comprehensive drug therapy review, then issues addressed with the client and/or the client's physician, with follow-up as required. G2: Comprehensive drug therapy review only with referral to usual pharmacist.	RCT: parallel, not clus- tered	No	Yes	Yes	Yes	Yes	Yes	No (Not accounted for or not identified)	High
Hanlon et al., 1996 <sup>17</sup> ; Cowper et al., 1998 <sup>18</sup>	G1: Pharmaceutical care provided by clinical pharmacist. G2: Usual care in the General Medicine Clinic	RCT: parallel, not clus- tered	Yes for MAI and health utilizat- ion, no for SF- 36	Yes	Yes	Yes	Yes	Yes	Yes	Low for MAI outcomes and health utilization (ITT), medium for SF-36

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Hirsch et al., 2011 <sup>19</sup> ; Hirsch et al., 2009 <sup>20</sup> ; Rosenquist et al., 2010 <sup>21</sup>	G1: Patients served at nonpilot pharmacies G2: Patients served at pilot pharmacies	Cohort	No	Yes	Yes	NA	Yes	Yes	Partial (some variables were taken in to account)	High
Isetts et al., 2008 <sup>22</sup>	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM.	Cohort	Un- clear or NR	Unclear or NR	Yes	NA	NA	Unclear or NR	No (Not accounted for or not identified)	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Jameson et al., 1995 <sup>23</sup>	G1: Pharmaco- therapy consultation and follow-up provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clus- tered	No	Yes	Yes	NA	Yes	Yes	No (Not accounted for or not identified)	Medium for most outcomes, high for adverse drug events
Jeong et al., 2007 <sup>24</sup> ; Jeong et al., 2009 <sup>25</sup>	G1: Pharmacist- managed MTMP provided by ambulatory care pharmacists and healthcare support staff (acceptors) G2: Eligible for Part D MTMP but declined enrollment (refusers) G3: Patients without Part D as their primary drug benefit	Cohort	NA	Yes	Yes	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Jeong et al. <sup>26</sup> ; Jeong et al., 2012 <sup>27</sup>	G1: Kaiser- Permanente MTM program participants (2010) G2: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled with a PCP visit during first half of 2010 G3: Kaiser- Permanente patients eligible for MTM, but who declined enrollment or disenrolled without a PCP visit during first half of 2010	Cohort	NA	Yes	NA	NA	Unclear or NR	Yes	Unclear or NR	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Krska et al., 2001 <sup>28</sup>	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	No	Yes	Yes	Yes	Unclear or NR	Yes	No (Not accounted for or not identified)	Medium
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup>  IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities G2: Usual care without pharmaceutical care	RCT: parallel, not clustered	Yes	Yes	Yes	Yes	Yes	Unclear or NR	Yes	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Marques et al., 2013 <sup>33</sup>	G1: Intervention group: Dader method pharmacotherap y follow-up intervention monthly over 3- month follow-up period G2: Control group: monthly pharmacist visits without pharmacotherap y follow-up intervention	RCT: parallel, not clustere d	No	Yes	NA	Yes	NA	Yes	No (Not accounted for or not identified)	Medium



**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Marrufo et al., 2013 <sup>34</sup> ; Perlroth et al., 2013 <sup>35</sup>	<b>CHF</b> G1: enrolled in Medicare PDP receiving MTM with a CMR G2: enrolled in PDP receiving MTM, no CMR G3: enrolled in MA-PD receiving MTM with CMR G4: enrolled in MA-PD, receiving MTM, no CMR <b>COPD</b> G5: enrolled in Medicare PDP receiving MTM with a CMR G6: enrolled in PDP receiving MTM, no CMR G7: enrolled in MA-PD receiving MTM with CMR G8: enrolled in MA-PD, receiving MTM, no CMR	Cohort	Yes	Yes	Yes	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
McDonough et al., 2005 <sup>36</sup>	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 DTPs: appropriateness of dose, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster- rando- mized	Yes	Yes	Yes	NA	NA	Unclear or NR	No (Not accounted for or not identified)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Moczygemba et al., 2011 <sup>37</sup> ; Moczygemba et al., 2008 <sup>38</sup> ; Moczygemba, Barner, and Gabrillo, 2012 <sup>39</sup>	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or managed care pharmacy resident based on American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework (acceptors) G2: No-MTM control group (opt-out)	Cohort	Un- clear or NR	NA	Yes	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Moore et al., 2013 <sup>40</sup>	G1: MTM program (opt-in) G2: control group (refusers)	Cohort	NA	Yes	NA	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>	G1: Pharmaceutical care including drug therapy reviews conducted by nephrology- trained clinical pharmacist with patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by nurse	RCT:	No	Yes	Yes	NA	Yes	Yes	Yes	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Park et al., 1996 <sup>43</sup>	G1: Comprehensive pharmaceutical services, including drug therapy monitoring and patient education provided by community pharmacy resident. G2: Usual care	RCT: parallel, not clus- tered	Yes	Yes	Yes	Yes	NA	Unclear or NR	No (Not accounted for or not identified)	High
Pindolia et al., 2009 <sup>44</sup>	G1: Telephone- based MTM services provided as part of Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors) G2: Usual medical care (opt-out)	Cohort	Yes	Yes	Unclear or NR	Unclear or NR	Yes	Yes	No (Not accounted for or not identified)	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Planas et al., 2009 <sup>45</sup>	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clus- tered	No	Yes	Unclear or NR	NA	NA	Yes	No (Not accounted for or not identified)	High
Roughead et al., 2009 <sup>46</sup>	G1: HMRs conducted by accredited pharmacists G2: No medication review received	Cohort	Un- clear or NR	Yes	NA	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Sellors et al., 2003 <sup>47</sup>	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: Un- cluster- randomi zed	clear or NR	Yes	NA	No	Yes	Yes	Yes	Medium risk of bias for other outcomes; high risk of bias for quality of life measures.
Sellors et al., 2003 <sup>47</sup>	G1: Pharmaceutical consultation G2: Usual care	RCT: parallel, not clustered	No	Yes	NA	NA	Unclear or NR	Unclear or NR	No (Not accounted for or not identified)	Medium
Shimp et al., 2012 <sup>48</sup>	G1: MTM program for University of Michigan beneficiaries, entitled FOM G2: Usual care	RCT: parallel, not clustered	No	Unclear or NR	NA	NA	Unclear or NR	Unclear or NR	No (Not accounted for or not identified)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Sidel et al., 1990 <sup>49</sup>	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clus- tered	No	No	Yes	NA	Yes	Yes	No (Not accounted for or not identified)	High



**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Staresinic et al., 2007 <sup>50</sup>	G1: MTM services provided as part of a Medicare Part D MTM program by MTM Coordinator (non-clinical staff) and pharmacist (acceptors) G2: Usual care provided to MTM-eligible enrollees who chose not to participate (opt-out)	Cohort	Yes	Yes	NA	NA	Yes	Unclear or NR	No (Not accounted for or not identified)	High
Taylor, Byrd, and Krueger, 2003 <sup>51</sup>	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	RCT: parallel,	No	Yes	Yes	Yes	Yes	Yes	No (Not accounted for or not identified)	Medium for most outcomes, high for adverse drug events

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Touchette et al., 2012 <sup>52</sup>	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clus- tered	Yes	Yes	No	Yes	Yes	Yes	Yes	Low

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Volume et al., 2001 <sup>53</sup> ; Kassam et al., 2001 <sup>54</sup>	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists G2: Traditional pharmacy care	RCT: cluster- rando- mized	No	Yes	Yes	Yes	NA	Yes	No (Not accounted for or not identified)	Medium
PREP (Pharmaceutic al Care Research and Education Project)										
Welch et al., 2009 <sup>55</sup>	G1: MTM program provided to home-based beneficiaries as part of Medicare Part D MTM program (acceptors) G2: No-MTM control group (voluntary opt- out)	Cohort	NA	Yes	Unclear or NR	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium for outcomes reported as adjusted ORs, high for outcomes reported without adjustments for confounding

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Williams et al., 2004 <sup>56</sup>	G1: Modification of patient's medication regimen conducted by interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clus- tered	No	Yes	Yes	Yes	No	Yes	No (Not accounted for or not identified)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Winston and Lin, 2009 <sup>57</sup>	G1: MTM provided in community pharmacy (i.e., care in face-to- face meetings or by telephone) as part of Medicare Part D MTM program G2: MTM provided by pharmacist- staffed call centers as part of Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	NA	Yes	NA	NA	Yes	Yes	No (Not accounted for or not identified)	High

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Witry, Doucette, and Gainer, 2011 <sup>58</sup>	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided to patients with private individual-group insurance	Cohort	Un- clear or NR	Yes	Unclear or NR	NA	NA	Yes	No (Not accounted for or not identified)	High
Wittayanukorn et al., 2013 <sup>59</sup>	G1: Intervention group: Pharmacist provided face-to- face MTM services for 30- 60 minutes per encounter, not always including a follow-up visit G2: Control group: Patients who did not receive MTM services (economic analyses only)	Cohort	Yes	Yes	NA	NA	Yes	Yes	Partial (some variables were taken into account)	Medium

**Table E2. Risk of bias domains and ratings: Part 2 (continued)**

Author, Year Trial Name	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre- specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Yamada, 2012 <sup>60</sup>	G1: Kaiser- Permanente MTM enrolled patients G2: Kaiser patients enrolled in Medicare part D, but not in MTM program matched to control on age, gender, region and DCG risk	Cohort	NA	Yes	NA	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

Abbreviations: BP = blood pressure; CHF = chronic heart failure; CMR = comprehensive medication review; COPD = chronic obstructive pulmonary disease; DTP = drug therapy problem; FOM = Focus on Medicines; G = group; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; ITT = intention-to-treat; MA-PD = Medicare Advantage Part D; MTM = medication therapy management; MTMP = medication therapy management program; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; PA = physician assistant; PCM = pharmaceutical case management; PCP = primary care provider; PDP = Medicare Part D Plan; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; VNA = visiting nurse association.

**Table E3. Rationale for high and medium risk of bias ratings**

Author, Year Trial Name	Risk of Bias  Rationale for Rating
Bernsten et al., 2001 <sup>1</sup> ; Sturgess, 2003 <sup>2</sup>	Medium (country-specific) High (pooled data)  Potential for performance and selective outcome reporting bias: <ul style="list-style-type: none"><li>• Issues concerning site and country-specific variation in pooled analyses</li><li>• Some selective reporting of country-specific outcomes when statistically significant</li></ul> Potential for attrition bias: <ul style="list-style-type: none"><li>• High overall attrition and no strategies used to take into account baseline differences between patients LTFU and study completers</li></ul> Potential for selection bias: <ul style="list-style-type: none"><li>• Some important potential confounders not measured at baseline, like baseline disease severity and co-morbidity</li></ul>
Blakey and Hixson-Wallace, 2000 <sup>3</sup>	High  Potential for selection bias <ul style="list-style-type: none"><li>• Groups were not at all similar at baseline. Patients were targeted for interventions because of characteristics that were deemed by the pharmacists or referring providers to put them at high risk for ADEs. No attempts were made in the analysis to mitigate for this.</li></ul> Potential for detection bias <ul style="list-style-type: none"><li>• Outcome assessment was done by the same individuals providing the intervention.</li><li>• Study has some issues with respect to the timing of outcome measurement.</li></ul> Potential for attrition bias <ul style="list-style-type: none"><li>• Study has some issues with respect to how the number of patients in each group are reported.</li></ul>
Brummel et al., 2013 <sup>4</sup> ; Soliman et al., 2013 <sup>5</sup> ; Ramalho de Oliveira, Brummel, and Miller, 2010 <sup>6</sup>	Medium for main analysis High for subgroup analysis  Potential for selection and measurement bias <ul style="list-style-type: none"><li>• Confounders not controlled for through matching</li><li>• Groups had significant differences at baseline</li><li>• Analysis controls for differences but does not clarify whether there was unmeasured or residual confounding</li><li>• Levels of intensity appear to be a function of need (rather than randomly assigned) and are completely confounded with potential outcomes, leading to high risk of bias for subgroup analysis</li></ul>
Carter et al., 1997 <sup>7</sup> ; Barnette et al., 1996 <sup>8</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• No accounting for differences in recruitment strategies or for baseline differences</li></ul>



**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias  Rationale for Rating</b>
Chrischilles et al., 2004 <sup>9</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• High risk of confounding from the pharmacist potentially selecting patients for the intervention who were on high risk medications</li><li>• Differences in the prevalence of high risk medications at baseline not controlled for the analysis.</li></ul>
Christensen et al., 2007 <sup>10</sup>	Medium  Potential for selection bias: <ul style="list-style-type: none"><li>• Group assignment not randomized; both arms have different risks of bias</li></ul>
Clifford et al., 2002 <sup>11</sup>	Medium  Potential for selection bias: <ul style="list-style-type: none"><li>• Not clear how groups compare in terms of comorbidity or number of medications at baseline.</li></ul> However, measures taken to reduce bias in other domains, such having the same pharmacist provide the intervention to all patients.
Fischer et al., 2000 <sup>12</sup>	Medium for most outcomes, high for adverse drug events  Potential for selection bias: <ul style="list-style-type: none"><li>• Unclear reporting of N's in outcome analyses makes fully determining selection bias difficult</li></ul> Potential for measurement bias: <ul style="list-style-type: none"><li>• Outcome measures, although piloted and assessed for face validity prior to study, were not validated and relied on self-report.</li><li>• While authors claim research questions a priori included assessment of "awareness of side effects", they apparently found it paradoxical that intervention arm reported more side effects and so post hoc decided to interpret this as "increased awareness" making it very difficult to draw a valid conclusion.</li></ul>
Fischer et al., 2002 <sup>13</sup>	Medium  Potential for selection bias: <ul style="list-style-type: none"><li>• Lack of randomization</li><li>• Intention-to-treat analysis excluded those who died, disenrolled, or discontinued pharmacy benefits before the end of the study period</li></ul>
Fox et al., 2009 <sup>14</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• No baseline clinical data provided about patients, in particular number of diagnosed conditions, number of medications prescribed, and healthcare utilization</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias</b>
Gattis et al., 1999 <sup>15</sup>	Medium  Rationale for Rating  Potential for measurement bias: <ul style="list-style-type: none"><li>• Lack of blinded outcome assessment</li><li>• Additional potential source of bias because intervention pharmacist was responsible for assessing control group's outcomes</li><li>• Reliability of self-report for capturing events that occurred outside of Duke questionable</li></ul> Missing information <ul style="list-style-type: none"><li>• Unclear to what extent included patients had care outside of Duke</li></ul>
Grymonpre, Williamson, and Montgomery, 2001 <sup>16</sup>	High  Potential for selection and attrition bias <ul style="list-style-type: none"><li>• Those at risk of life-threatening events were excluded from the intervention arm but not the control arm; no ITT was conducted to account for these exclusions. The two groups were statistically different at baseline on at least two variables: the number of home remedies and living alone. There did not appear to be a multivariate analysis that could have controlled for such variables</li></ul> Missing Information <ul style="list-style-type: none"><li>• Allocation concealment and other study details were unclear or NR</li><li>• Control group received a comprehensive review and referral to usual pharmacist, but it is not clear whether further interventions were provided</li></ul>
Hanlon et al., 1996 <sup>17</sup> ; Cowper et al., 1998 <sup>18</sup>	Low for MAI outcomes and health utilization (ITT) Medium for SF-36 and adverse drug events  Potential for attrition bias <ul style="list-style-type: none"><li>• Although regression analyses were conducted, no ITT analysis were performed to account for their loss to followup for quality of life outcomes</li></ul> Potential for measurement bias for some outcomes
Hirsch et al., 2011 <sup>19</sup> ; Hirsch et al., 2009 <sup>20</sup> ; Rosenquist et al., 2010 <sup>21</sup>	High  Potential for contamination <ul style="list-style-type: none"><li>• Patients switched between groups throughout the study, making it difficult to determine the long-term effects of the intervention on outcomes</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias  Rationale for Rating</b>
Isetts et al., 2008 <sup>22</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Differences in recruitment methods, but no evidence that any methods used to adjust for these differences</li><li>• Unclear how clinics with MTM differed from clinics without MTM in terms of patient populations served and other services available that might also influence outcomes</li><li>• Unclear how HEDIS comparison group was identified</li></ul> Potential for measurement bias: <ul style="list-style-type: none"><li>• Did not take into account different confounding and modifying variables into a multivariate analysis</li><li>• Unclear whether HEDIS comparisons controlled for differences between groups</li></ul> Missing information <ul style="list-style-type: none"><li>• Data on baseline covariates between intervention and HEDIS control group not presented</li></ul>
Jameson et al., 1995 <sup>23</sup>	Medium for most outcomes High for adverse drug events  Potential for detection and attrition bias: <ul style="list-style-type: none"><li>• Outcome assessment not blinded and no ITT analysis conducted</li></ul>
Jeong et al., 2007 <sup>24</sup> ; Jeong et al., 2009 <sup>25</sup>	Medium  Potential for selection bias: <ul style="list-style-type: none"><li>• Cohort study in which patients self-selected group assignment and appropriate statistical controls for selection bias not in place</li><li>• Baseline characteristics did not capture important variables that could potentially bias results, such as burden of co-morbidity, number of prescriptions, and multiple demographic variables</li></ul>
Jeong et al. <sup>26</sup> ; Jeong et al., 2012 <sup>27</sup>	High  Potential for selection bias <ul style="list-style-type: none"><li>• Study comparing patients who receive MTM to those who either declined enrollment or requested disenrollment.</li><li>• Age is the only baseline characteristic presented</li></ul> Missing information <ul style="list-style-type: none"><li>• Not clear how similar the groups were to each other at baseline.</li><li>• Not clear to what extent differences in baseline characteristics were accounted for in the analysis.</li></ul>
Krska et al., 2001 <sup>28</sup>	Medium  Potential for selection and measurement bias: <ul style="list-style-type: none"><li>• Insufficient detail on randomization or allocation concealment</li><li>• No details about blinding.</li><li>• Statistically significant differences at baseline in hospitalizations not controlled for in analysis.</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

Author, Year Trial Name	Risk of Bias Rationale for Rating
Malone et al., 2000 <sup>29</sup> ; Ellis et al., 2000 <sup>30</sup> ; Malone et al., 2001 <sup>31</sup> ; Ellis et al., 2000 <sup>32</sup> IMPROVE	Medium Potential for selection bias: <ul style="list-style-type: none"><li>• Lack of information about allocation concealment</li><li>• Impact of attrition on randomization unclear</li></ul> Potential for detection bias: <ul style="list-style-type: none"><li>• Blinding of outcome assessors unclear.</li></ul> Potential for performance bias: <ul style="list-style-type: none"><li>• Numerous concurrent changes within the VA clinical setting may have impacted either the intervention patients, control patients, or both</li></ul>
Marques et al., 2013 <sup>33</sup>	Medium Potential for selection and detection bias <ul style="list-style-type: none"><li>• Despite stratified random sampling, groups had five-point differences in baseline BDI and Anxiety scores, leaving the intervention group with more room to improve from.</li></ul> Missing information <ul style="list-style-type: none"><li>• Many study details not reported</li><li>• Allocation concealment not addressed</li><li>• Unclear if outcome assessors were blinded or were also the interventionists</li></ul>
Marrufo et al., 2013 <sup>34</sup> ; Perlroth et al., 2013 <sup>35</sup>	Medium Potential for selection and performance bias <ul style="list-style-type: none"><li>• Healthy user effect was not fully accounted for, potentially confounding the results</li></ul>
McDonough et al., 2005 <sup>36</sup>	Medium Potential for selection and detection bias: <ul style="list-style-type: none"><li>• Differences in outcome at baseline not adjusted for in analysis</li><li>• Uncertain whether outcome assessors blinded</li><li>• Outcome measurement based on self-report only</li></ul> Potential for attrition bias <ul style="list-style-type: none"><li>• Differential attrition between groups, although study used ITT analysis</li></ul>
Moczygemba et al., 2011 <sup>37</sup> ; Moczygemba et al., 2008 <sup>38</sup> ; Moczygemba, Barner, and Gabrillo, 2012 <sup>39</sup>	Medium Potential for selection bias: <ul style="list-style-type: none"><li>• 16.7% of patients allocated to the intervention group withdrew, and attrition not fully accounted for in design</li><li>• Opt-in observational design</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias  Rationale for Rating</b>
Moore et al., 2013 <sup>40</sup>	Medium  Potential selection bias <ul style="list-style-type: none"><li>• Confounding addressed by design (matching), but cohorts were significantly different at baseline on some characteristics.</li><li>• Confounding was also addressed by analysis through regression, but unmeasured or residual confounding remains unclear</li></ul>
Pai et al., 2009 <sup>41</sup> ; Pai et al., 2009 <sup>42</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Inadequate sequence generation</li><li>• &gt;50% attrition</li></ul>
Park et al., 1996 <sup>43</sup>	High  Potential for selection bias and contamination: <ul style="list-style-type: none"><li>• Lack of cluster randomization increasing likelihood of contamination of the usual care arm at each site</li><li>• Method of randomization and whether allocation concealment used NR</li><li>• Differences in important factors at baseline despite randomization, with no statistical adjustment</li></ul> Potential for performance bias: <ul style="list-style-type: none"><li>• Potential for secular effects or uncontrolled confounding from other interventions or exposures because the intervention was conducted at separate time points at the two separate sites, using two different interventionists</li></ul> Potential for detection bias: <ul style="list-style-type: none"><li>• Lack of outcome assessor blinding</li></ul>
Pindolia et al., 2009 <sup>44</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Neither baseline differences in health utilization characteristics nor important confounders (e.g., polypharmacy, number of conditions) accounted for in statistical analysis</li></ul> Potential for detection bias: <ul style="list-style-type: none"><li>• Not clear that outcome assessors were blinded</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias  Rationale for Rating</b>
Planas et al., 2009 <sup>45</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• No steps taken to control for baseline differences in demographic characteristics and BMI that were measured, and other important potential confounders not measured at all</li></ul> Potential for detection bias: <ul style="list-style-type: none"><li>• Not clear that outcome assessors were blinded</li></ul> Potential for attrition bias <ul style="list-style-type: none"><li>• High rates of attrition in both arms, no ITT analysis</li></ul>
Roughead et al., 2009 <sup>46</sup>	Medium  Potential for selection and performance bias <ul style="list-style-type: none"><li>• Failure to fully control for potential confounding</li></ul> Missing information: <ul style="list-style-type: none"><li>• Lack of clarity on various risk of bias criteria</li></ul>
Sellers et al., 2003 <sup>47</sup>	Medium risk of bias for other outcomes; high risk of bias for quality of life measures.  Potential for selection bias and contamination: <ul style="list-style-type: none"><li>• Unclear if ITT analysis used or if investigators controlled for potential co-interventions</li></ul> Potential for reporting bias <ul style="list-style-type: none"><li>• Although the quality of life measure (SF-36) is valid and reliable, errors in the reporting (e.g., mean not contained within confidence intervals) cast doubt on the accuracy of the results</li></ul>
Sellers et al., 2003 <sup>47</sup>	Medium  Missing information <ul style="list-style-type: none"><li>• Lack of reporting about how costs were measured</li></ul>
Shimp et al., 2012 <sup>48</sup>	Medium  Missing information <ul style="list-style-type: none"><li>• Lack of reporting about major aspects of study design</li></ul>
Sidel et al., 1990 <sup>49</sup>	High Potential for selection and detection bias: <ul style="list-style-type: none"><li>• High attrition</li><li>• Outcomes all self-reported and not validated</li><li>• Unclear if or how researchers blinded when obtaining questionnaires</li><li>• No confounders taken into account in analysis</li><li>• No ITT analysis</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

Author, Year Trial Name	Risk of Bias  Rationale for Rating
Staresinic et al., 2007 <sup>50</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Group assignment based on self-selection, since intervention group formed from those who returned a survey</li></ul>
Taylor, Byrd, and Krueger, 2003 <sup>51</sup>	Medium for most outcomes, high for adverse drug events  Potential for detection bias: <ul style="list-style-type: none"><li>• Lack of blinded outcome assessment</li></ul> Missing information: <ul style="list-style-type: none"><li>• No other major issues with study methods, but little detail reported for key aspects related to study execution (i.e., method of randomization, allocation concealment, outcome assessment)</li></ul>
Volume et al., 2001 <sup>53</sup> ; Kassam et al., 2001 <sup>54</sup>  PREP (Pharmaceutical Care Research and Education Project)	Medium  Potential for performance bias: <ul style="list-style-type: none"><li>• Intervention provided at different pharmacy sites by different interventionists with no mention of measures used to ensure fidelity of intervention</li></ul> Potential for selection bias: <ul style="list-style-type: none"><li>• Lack of adjustment for differences at baseline</li><li>• Borderline high attrition and possibility of selection bias due to pharmacist control over patient recruitment</li></ul>
Welch et al., 2009 <sup>55</sup>	Medium for outcomes reported as adjusted ORs High for outcomes reported without adjustments for confounding  Potential for detection bias: <ul style="list-style-type: none"><li>• Adjusted ORs most reliable outcomes to use because other non-OR outcomes not adjusted for baseline differences with exception of medication cost/day</li><li>• Validity and reliability of sources for outcome data unclear.</li></ul>
Williams et al., 2004 <sup>56</sup>	Medium  Potential for selection bias: <ul style="list-style-type: none"><li>• Although randomized design used, method of randomization and allocation concealment not reported</li><li>• Unclear whether outcome assessors blinded</li></ul> Potential for measurement bias: <ul style="list-style-type: none"><li>• Questionable methods used for calculating costs of drugs, particularly if intervention only 6 weeks long</li></ul>
Winston and Lin, 2009 <sup>57</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Study does not control underlying confounders leading to patients' selection of pharmacies</li><li>• Pharmacies' inability to provide MTM leading to other modalities and outcomes</li></ul>

**Table E3. Rationale for high and medium risk of bias ratings (continued)**

<b>Author, Year Trial Name</b>	<b>Risk of Bias  Rationale for Rating</b>
Witry, Doucette, and Gainer, 2011 <sup>58</sup>	High  Potential for selection bias: <ul style="list-style-type: none"><li>• Use of historical control group with much larger N, not addressed in design</li><li>• No attempts to adjust for potential and actual differences in confounders and baseline characteristics, including baseline comorbidities, age, and sex</li><li>• No reporting of attrition</li></ul> Missing information: <ul style="list-style-type: none"><li>• Lack of reporting about major aspects of study design</li></ul>
Wittayanukorn et al., 2013 <sup>59</sup>	Medium  Potential for selection bias <ul style="list-style-type: none"><li>• Selection bias due to observational design, matching was used to control for baseline differences, but did not include clinical or other factors that might have influenced economic outcomes.</li></ul>
Yamada, 2012 <sup>60</sup>	Medium  Potential for selection bias <ul style="list-style-type: none"><li>• Baseline differences in comorbidity score, conditions, hospitalization rates, and drug costs are all statistically and clinically meaningful. Design attempts to mitigate through matching and presentation of adjusted findings attempts to mitigate this issue through analysis.</li></ul>

Abbreviations: HEDIS = Healthcare Effectiveness Data and Information Set; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; ITT = intention-to-treat; MTM = medication therapy management; N = sample or group size; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; VA = Veterans Affairs.



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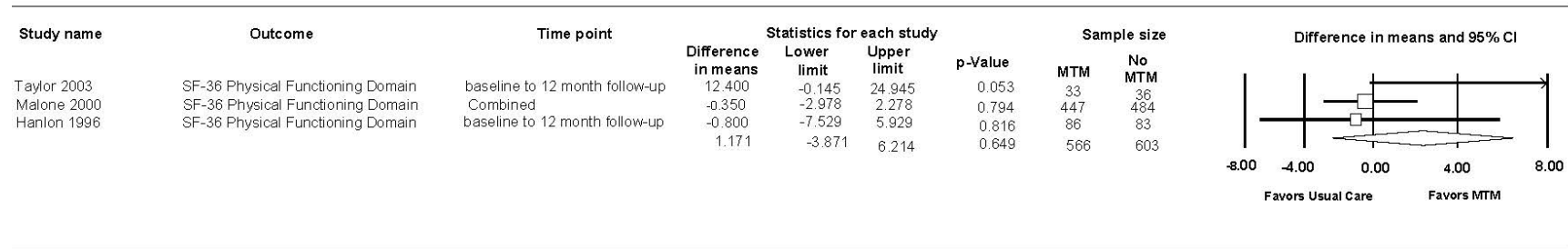
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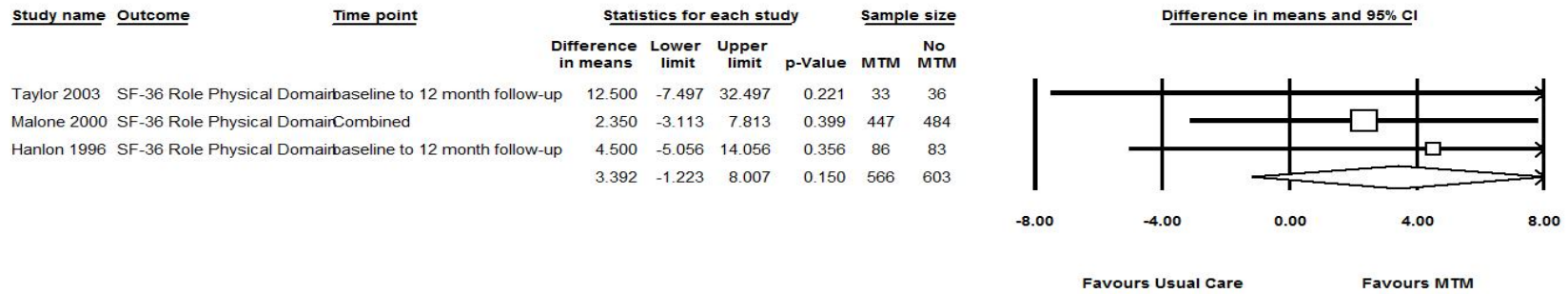
# Appendix F. Meta-Analyses

Figure F1. Effect of MTM on SF-36 physical functioning domain



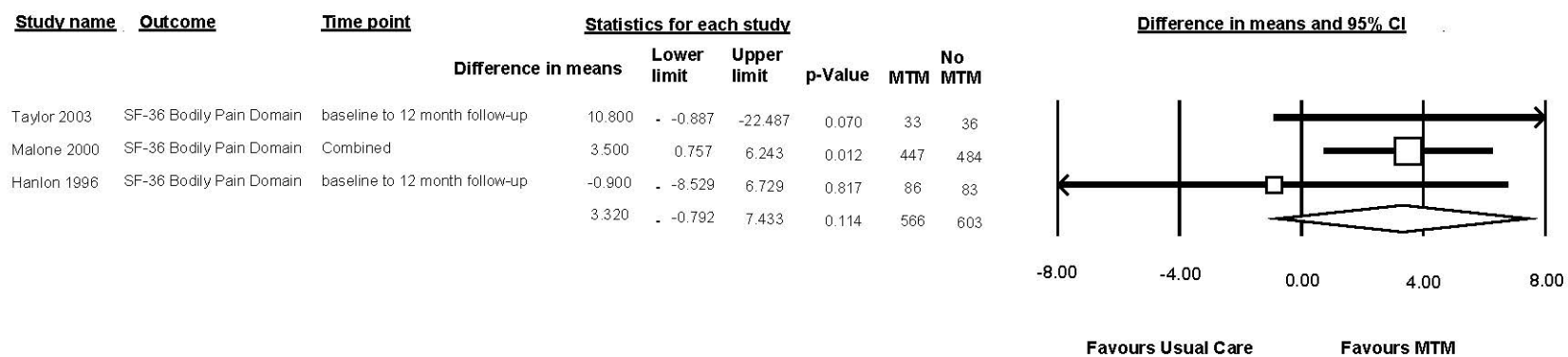
Low or medium risk-of-bias RCTs

**Figure F2. Effect of MTM on SF-36 role physical domain**



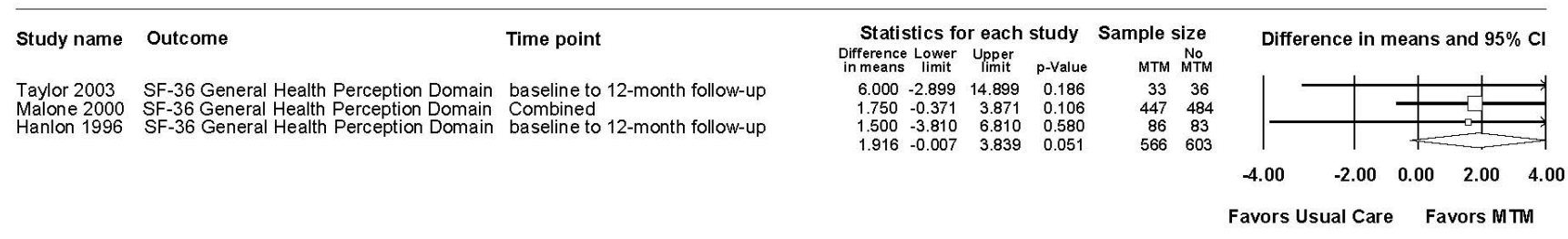
Low or medium risk-of-bias RCTs

**Figure F3. Effect of MTM on SF-36 bodily pain domain**



Low or medium risk-of-bias RCTs

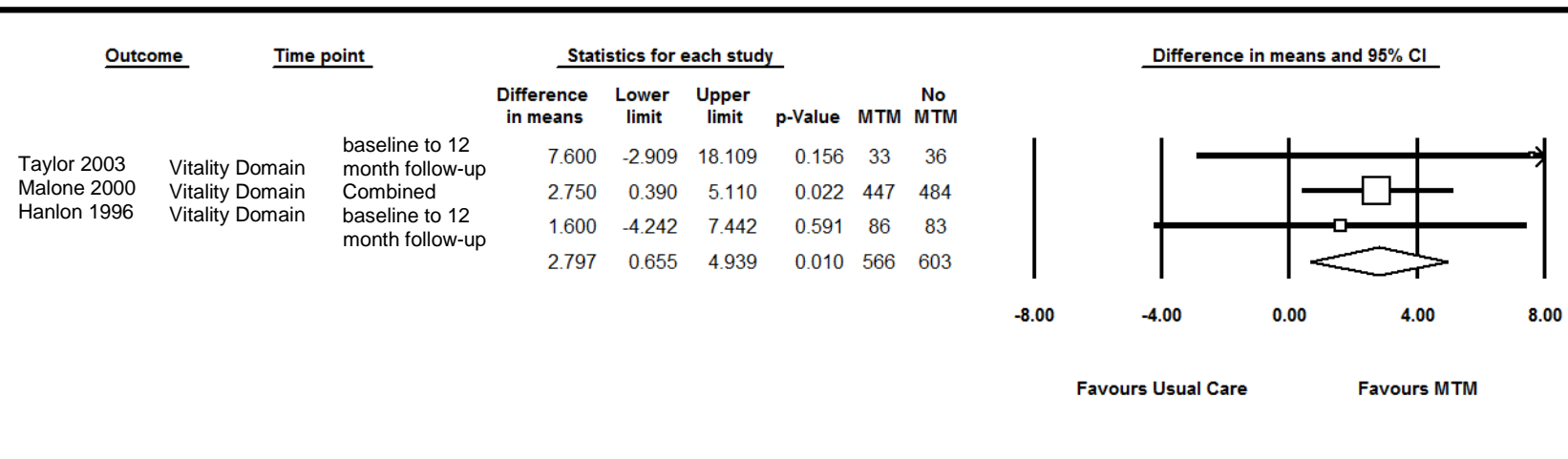
**Figure F4. Effect of MTM on SF-36 general health perception domain**



Low or medium risk-of-bias RCTs

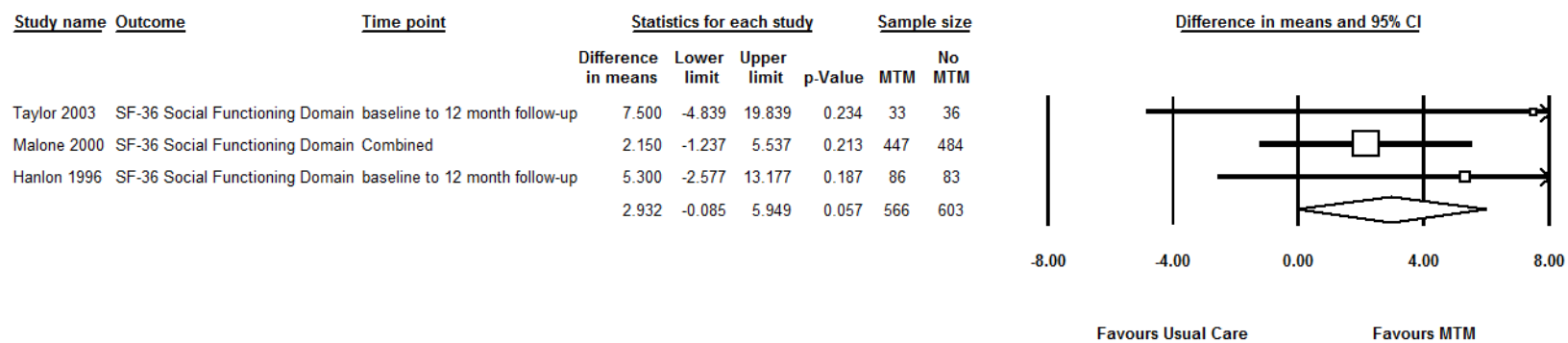


**Figure F5. Effect of MTM on SF-36 vitality domain**



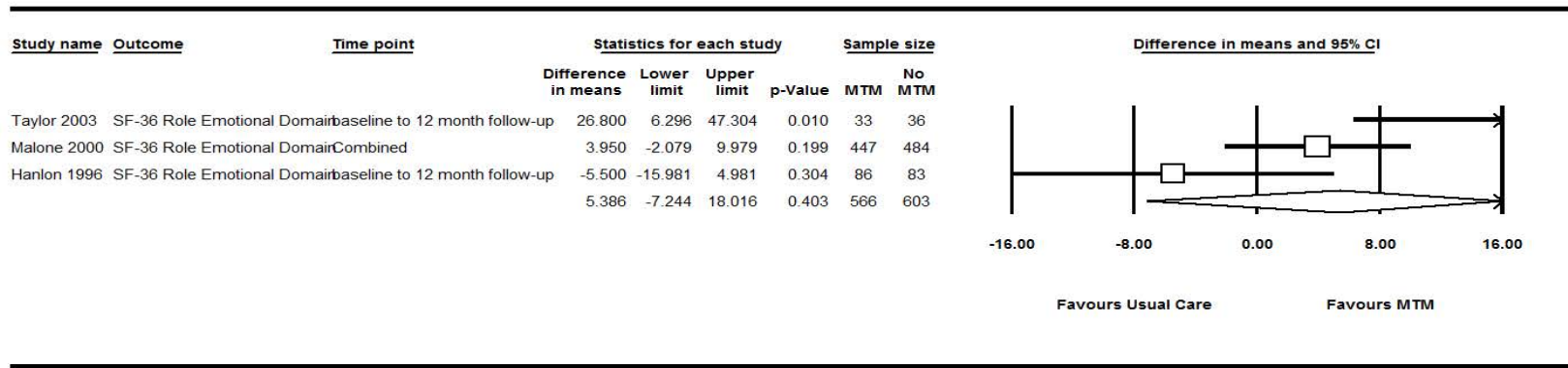
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**Figure F6. Effect of MTM on SF-36 social functioning domain**



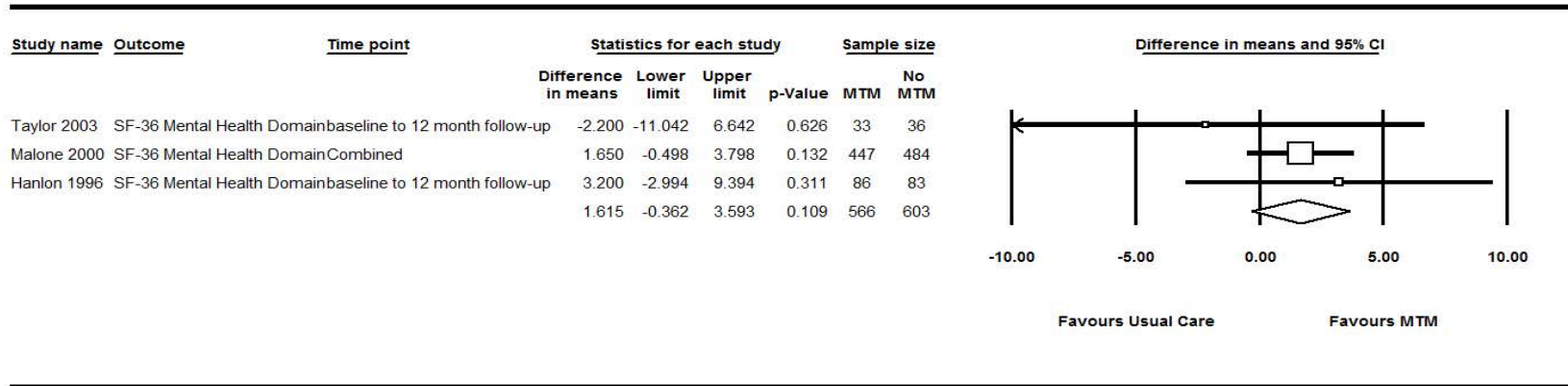
Low or medium risk-of-bias RCTs

**Figure F7. Effect of MTM on SF-36 role emotional domain**



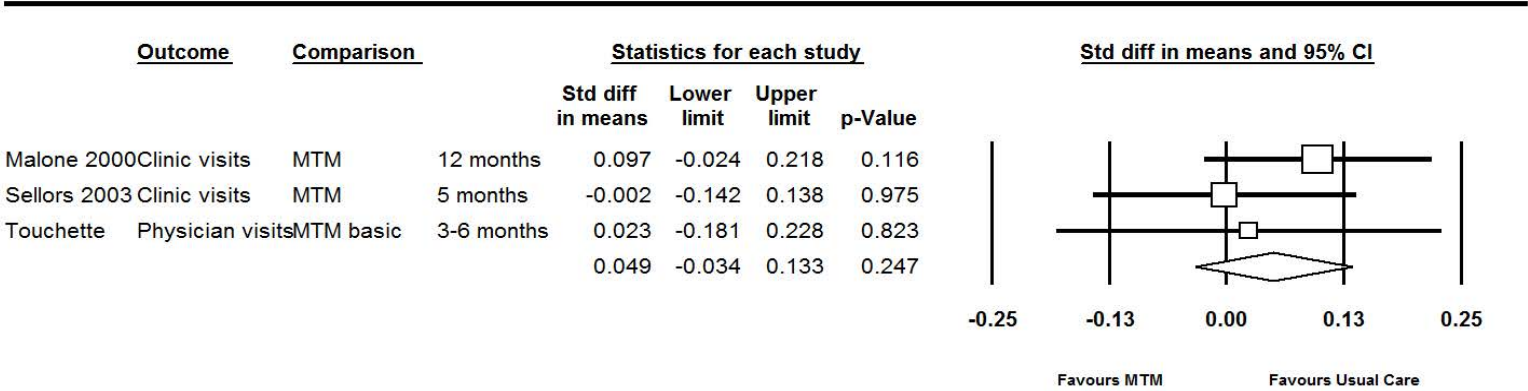
Low or medium risk-of-bias RCTs

**Figure F8. Effect of MTM on SF-36 mental health domain**



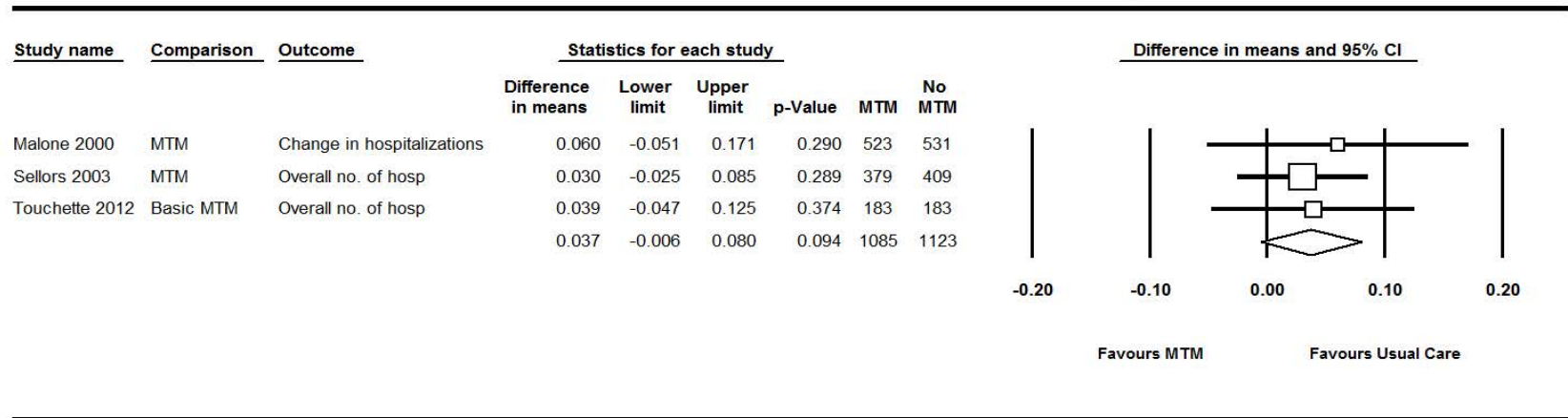
Low or medium risk-of-bias RCTs

**Figure F9. Effect of MTM on outpatient visits**



Low or medium risk-of-bias RCTs

Figure F10. Effect of MTM on mean number of hospitalizations



Low or medium risk-of-bias RCTs