Economic analysis for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Introduction – objective of economic modelling

The choice of initial treatment for adults with a new depressive episode was identified by the committee and the guideline health economist as an area with potentially major resource implications. Although existing economic evidence in this area is quite extensive, no study has currently assessed the relative cost effectiveness of the whole range of available interventions for adults with a new episode of depression in the UK. An economic model was therefore developed to assess the relative cost effectiveness of effective pharmacological, psychological, physical and combined interventions for the treatment of adults with a new episode of depression in the UK. Network meta-analyses (NMAs) were conducted to synthesise available evidence and inform the economic model.

The purpose of the economic model was to assess the best approach for treatment of a new episode of depression up to its (potential) resolution; the model included a two-year follow-up period, in order to incorporate cost-effective maintenance therapy aiming at preventing relapse, where appropriate, in people who remitted following acute treatment. However, people with depression may experience multiple recurrent episodes in the future, following treatment of the new episode, which have not been incorporated in the acute treatment model structure. The consequences (costs and impact on health-related quality of life [HRQoL]) of recurrent depressive episodes in the longer term have been considered in a separate model that was developed to assess the cost effectiveness of interventions for depression aiming at preventing relapse in adults with depression that is in remission. The economic analysis of interventions for relapse prevention is described in Evidence report C, appendix J.

Economic modelling methods

Population

The study population of the economic model comprised adults with depression initiating treatment for a new episode in primary care. This was decided because the majority of adults with a new episode of depression are treated in primary care in routine UK practice. Two populations were considered: adults with a new episode of less severe depression and adults with a new episode of more severe depression. The definition of less severe and more severe depression was the same as that used to classify RCTs in the two respective NMAs undertaken to estimate the acceptability and effectiveness of interventions for the treatment of a new episode of depression, which informed the economic analysis. The definition of less severe and more severe depression is provided in the review protocol shown in appendix A. Generally, according to the criteria used to classify RCTs, less severe depression corresponds to subthreshold and mild depression, while more severe depression corresponds to moderate and severe depression. The study population had no physical comorbidities, psychotic symptoms, complex or chronic depressive symptoms in accordance with the inclusion criteria of the systematic review of RCTs that informed the NMAs.

People in the economic analysis were assumed to be experiencing their first depressive episode if they had less severe depression and their third depressive episode if they had more severe depression, to cover a range of presentations of adults with a new episode of depression in routine clinical practice. The number of previous episodes determined the

study population's risk of relapse following remission of the current episode but had no impact on the effectiveness of interventions in treating their current episode.

The age of the cohorts considered in the economic model was determined by the mean age of onset of depression in adults and the number of the current new episode for which treatment was received.

Kessler 2005 reported the results of a national comorbidity household survey in the US, according to which the median age-of-onset of depression was 32 years (interquartile range 19-44 years). In a Swedish longitudinal cohort study of 3,563 people followed up for 30-49 years, the median age at first onset of depression was reported to be around 35 years (Mattisson 2007). A large (n=20,198) Scottish family-based population study designed to identify the genetic determinants of common diseases, including major depression disorder, reported a mean age of onset of major depressive disorder of 31.7 years (SD 12.3 years) among 2,726 participants that met DSM-IV criteria for current and/or past major depression disorder (Fernandez 2015). On the other hand, Andrade 2003 did a review of results of community epidemiological surveys on major depressive episodes that were carried out in 10 countries in America, Europe and Asia (the UK was not included in these countries); the authors reported a median age of onset of major depression in the early to mid-twenties in all countries other than Japan (late twenties) and the Czech Republic (early thirties). Based on this evidence and following committee's expert advice, the age of onset of major depression in the study population was set at 32 years.

According to the committee's expert opinion, the mean interval between 2 consecutive depressive episodes in people who experience relapses is about 2 years. Therefore, for modelling purposes, adults with a new episode of less severe depression were assumed to be 32 years of age (as this was their first episode) and adults with more severe depression were assumed to be 36 years of age (as this was their third episode).

The percentage of women in each cohort were estimated to be 56%, based on weighted epidemiological data on depressive episodes reported in the most recent adult psychiatric morbidity household survey conducted in England (McManus 2016).

Determining the age and gender mix of the cohorts was necessary in order to estimate mortality risks in the model.

Interventions assessed

The range of interventions assessed in the economic analysis was determined by the availability of relevant clinical data synthesised in the NMA. The selection of classes of interventions was made based on the following criteria:

- The economic analysis on each population (adults with less severe depression and adults with more severe depression) assessed only classes of interventions that were included in the respective (in terms of study population) NMAs.

For each population, only classes of interventions that had been tested on at least 50 participants (across RCTs) in the NMA of standardised mean difference (SMD), which was the main clinical outcome, as well as in the NMAs of discontinuation (for any reason), response in completers and remission in completers (relevant only to the analysis of treatments for more severe depression) were included in the economic analysis, as these outcomes were essential in order to populate the economic model. This followed the committee's decision to consider only treatment classes that had been tested on at least 50 participants across the RCTs included in the respective NMA, after looking at the total size of the evidence base on treatments for a new episode of less severe depression and the large volume of evidence for some treatment classes relative to others.

- The NMA outcomes considered in the economic analysis are described in the 'Summary of methods', under 'Evidence Synthesis'. An exception to this rule was made for classes of interventions that are routinely available in the NHS, that is, such classes were included

in the analysis even if they had been tested on fewer than 50 participants in the NMAs mentioned above. For some treatment classes, inclusion in the economic model was not possible as no data were available on one or more NMA outcomes that informed economic modelling. For such classes, additional relevant data were sought by contacting authors of studies already included in the guideline systematic review, so as to enable inclusion of the classes in the respective NMAs and, subsequently, in the economic modelling.

- In addition, only classes with a higher mean effect on the SMD outcome compared with the selected reference treatment (treatment as usual [TAU] in less severe depression and placebo in more severe depression) were considered in the economic analysis.

Once the classes of interventions for inclusion in the economic analysis were determined, one intervention was used as exemplar within each class, so that the model utilised individual intervention (rather than class) effects and costs. The selection of interventions from each class was based on judgement, using a number of criteria:

- the size (volume) of the evidence base for each intervention
- the availability of interventions within the NHS: more commonly used interventions had a priority over less commonly used interventions
- their relative effectiveness: interventions with higher effects within a class were better candidates for selection
- the side-effect profile in the case of pharmacological treatments.

In addition to active interventions, the economic model also considered non-specific GP care as a benchmark treatment option, which, in terms of effectiveness, was reflected in RCT arms informing the reference treatment (TAU arms for less severe depression and placebo arms for more severe depression). GP care was considered as an option for both study populations. Based on the above criteria, the following interventions were included in the economic analysis for each study population [in brackets the classes they belong to]:

<u>Adults with less severe depression</u>

- pharmacological interventions
  - sertraline [selective serotonin reuptake inhibitors (SSRIs)]
  - lofepramine [tricyclic antidepressants (TCAs)]
- psychological interventions
  - computerised cognitive behavioural therapy (cCBT) without or with minimal support [self-help without or with minimal support]
  - cCBT with support [self-help with support]
  - individual behavioural activation (BA) [individual behavioural therapies (BT)]
  - group BA [group BT]
  - individual CBT (under 15 sessions) [individual cognitive therapy (CT)/CBT]
  - group CBT (under 15 sessions) [group CT/CBT]
  - individual problem solving [individual problem solving]
  - non-directive/supportive/person-centred counselling [individual counselling]
  - individual interpersonal psychotherapy (IPT) [individual IPT];
  - individual short-term psychodynamic psychotherapy (PDPT) [individual short-term PDPT]
  - group mindfulness-based cognitive therapy (MBCT) [mindfulness or meditation group]
- physical interventions
  - supervised high intensity individual exercise [individual exercise]
  - supervised high intensity group exercise [group exercise]

- GP care, reflected in the RCT arms of the reference treatment for less severe depression [TAU]

Adults with more severe depression

- pharmacological interventions
  - escitalopram [SSRIs]
  - lofepramine [TCAs]
  - duloxetine [serotonin and norepinephrine reuptake inhibitors (SNRIs)]
  - mirtazapine [own class]
  - trazodone [own class]
- psychological interventions
  - cCBT without or with minimal support [self-help]
  - cCBT with support [self-help with support]
  - individual BA [individual BT]
  - individual CBT (equal to or over 15 sessions) [individual CT/CBT]
  - group CBT (under 15 sessions) [group CT/CBT]
  - individual problem solving [individual problem solving]
  - non-directive/supportive/person-centred counselling [individual counselling]
  - individual IPT [individual IPT];
  - individual short-term PDPT [individual short-term PDPT]
- physical interventions
  - supervised high intensity individual exercise [individual exercise]
  - supervised high intensity group exercise [group exercise]
  - traditional acupuncture [acupuncture]
- combined interventions
  - CBT individual (equal to or over 15 sessions) + escitalopram [combined individual CT/CBT and antidepressant]
  - Traditional acupuncture + escitalopram [combined acupuncture and antidepressant]
- GP care, reflected in the RCT arms of the reference treatment for more severe depression [placebo]

Model structure

A hybrid decision-analytic model consisting of a decision-tree followed by a three-state Markov model was constructed using Microsoft Office Excel 2013. The model estimated the total costs and benefits associated with provision of effective treatment options in two cohorts of adults with a new episode of less severe depression and more severe depression, respectively. The structure of the model, which aimed to simulate the course of depression and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of adults with a new episode of depression were initiated on each of the treatment options assessed, as appropriate, according to their level of symptom severity. People in each cohort either completed treatment or discontinued early due to intolerable side effects or other reasons. The duration of a full course of initial treatment was 12 weeks for drugs and GP care; the duration of psychological and physical interventions varied by intervention (ranging between 6 and 16 weeks). The duration of combined interventions was determined by the component with the longest duration. For practical purposes of estimation of QALYs it was assumed that all interventions lasted 12 weeks, without this assumption affecting resource use associated with each intervention. People who discontinued an active treatment early were assumed to switch to a mixture of available treatments for depression or no treatment; people who

discontinued GP care were assumed to move to no treatment. The mixture of available treatments following discontinuation was assumed to have the effectiveness of the baseline reference treatment (GP care) and the mean management cost of people in a depressive episode. Effects of no treatment were obtained from the guideline NMA; the cost of no treatment was zero. The proportion of people moving to no treatment after active treatment discontinuation equalled the probability of discontinuation of GP care.

Following completion of initial treatment or early discontinuation and switch to a mixture of treatments or no treatment, adults with less severe depression (reflecting subthreshold/mild depression) either responded to treatment or failed to meet criteria for response. Response (defined as 50% improvement in depressive symptom score) in adults with less severe depression was assumed to equal remission (defined as a score below the cut-off point for depression on a scale); this was consistent with available data from RCTs on adults with less severe depression that reported both response and remission. Adults with more severe depression (representing moderate and severe depression) either remitted, or responded to treatment without reaching remission, or failed to meet criteria for response. These states (response equalling remission and no/inadequate response for adults with less severe depression; response reaching remission, response not reaching remission and no/inadequate response for adults with more severe depression) were the endpoints of the decision-tree component of the model. From that point on, all people entered the Markov component of the model, which consisted of 3 states: remission (no depressive episode); depressive episode (either due to persistence of the current episode or due to relapse); and death. People who were in remission at the decision-tree endpoint moved to the remission state; those who did not meet criteria for response at the decision-tree endpoint moved to the depressive episode state; and those with more severe depression who responded but did not meet criteria for remission were assumed to either remit (thus moving to the remission state of the Markov model) or remain in a depressive episode (thus moving to the depressive episode state of the Markov model).

The Markov model was run in yearly cycles with a half-cycle correction being applied. In each model cycle, people entering the Markov component of the model could either remain in the same ‘entrance’ state, move between the remission and the depressive episode states, or move to the death state (absorbing state). Adults with more severe depression, who remitted from their 3rd episode following treatment completion, were assumed to receive optimal relapse prevention treatment, as appropriate, depending on the acute treatment that eventually led to remission, as determined by relevant evidence on relapse prevention treatments in the Evidence review C and the resulting guideline recommendations. Details on the specific maintenance treatment received by each cohort are provided at the end of this section. Maintenance antidepressant treatment lasted 2 years; maintenance psychological treatment lasted 1 year. Benefits of all maintenance treatments were assumed to be enjoyed over 2 years, according to available evidence on pharmacological and psychological interventions aiming at relapse prevention and the committee’s expert opinion. Adults with less severe depression who remitted from their 1st episode following treatment completion were assumed to receive no relapse preventive treatment, apart from 3 extra GP visits in the first year and 1 extra GP visit in the second year they spent in the Markov remission state. Those who remitted following completion of antidepressant treatment were assumed to continue antidepressant treatment for another year, i.e. over the first year of the Markov model.

The duration of the Markov model component was 2 years, to enable the full costs and effects of a course of treatment for depression (including acute and, if appropriate, maintenance treatment) to be modelled. Thus, the total time horizon of the economic analysis was 12 weeks of acute treatment (decision-tree) plus 2 years of follow up which included maintenance treatment, as appropriate, for people who remitted following successful acute treatment (Markov model).

The baseline risk of relapse in the Markov remission state depended on the time (one or two years) people spent in this state (the longer people stayed in remission, the lower their risk of relapse) and their number of previous episodes (the higher the number of their previous episodes, the higher their risk of relapse). Therefore, over the 2 years of the Markov component of the model, the risk of relapse experienced by each cohort was determined by their baseline risk of relapse and the efficacy of the (potential) maintenance treatment option received by each cohort. If people relapsed during this period of 2 years, maintenance treatment was discontinued and the preventative benefit of maintenance treatment ceased at the point of relapse.

The probability of remission for each cohort in the depressive episode state depended on the time (one or two years) people spent in this state (the longer people stayed in the depressive episode, the lower their probability of remission) and the severity of depression (less or more severe depression).

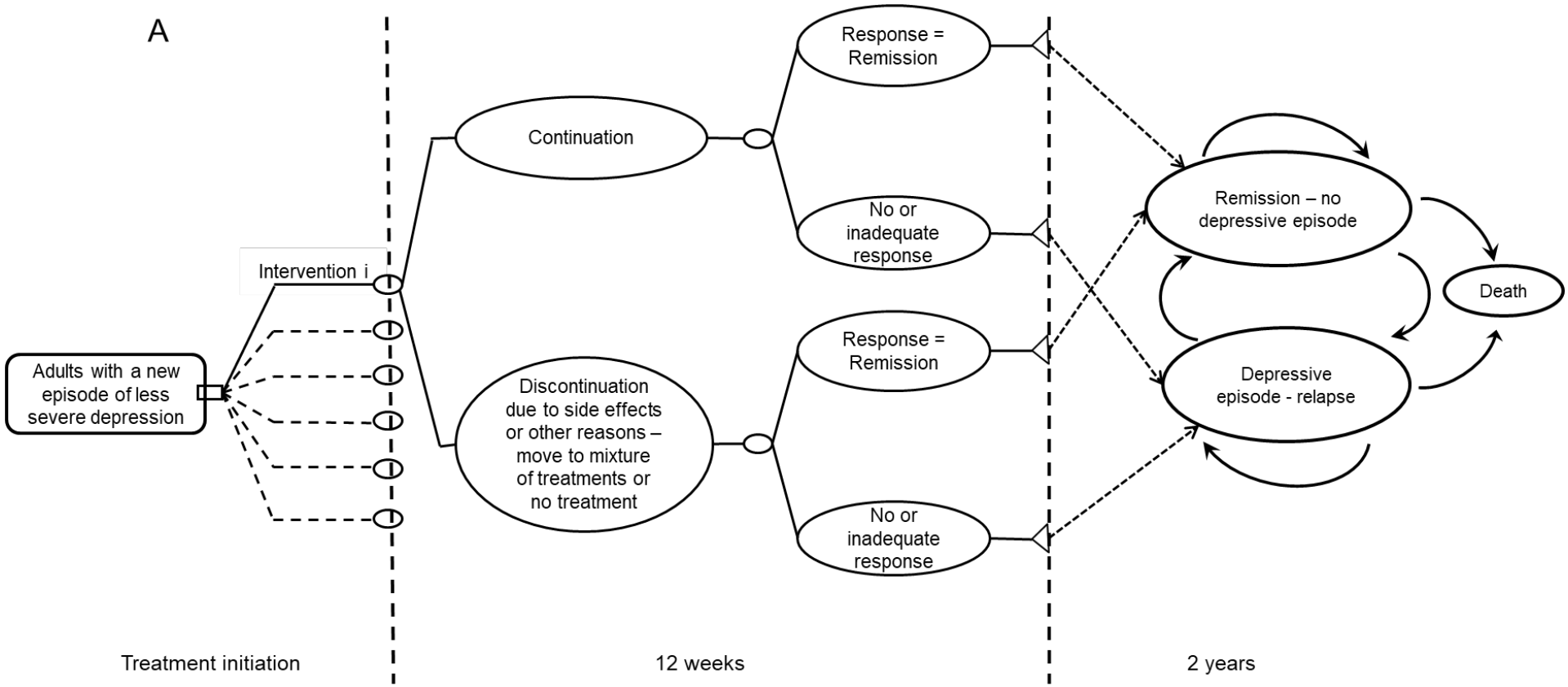
Within the remission and depressive episode states, people entered tunnel states, so that the time they remained in every state (one or two years) could be estimated and a time-dependent probability of relapse or remission, respectively, could be applied.

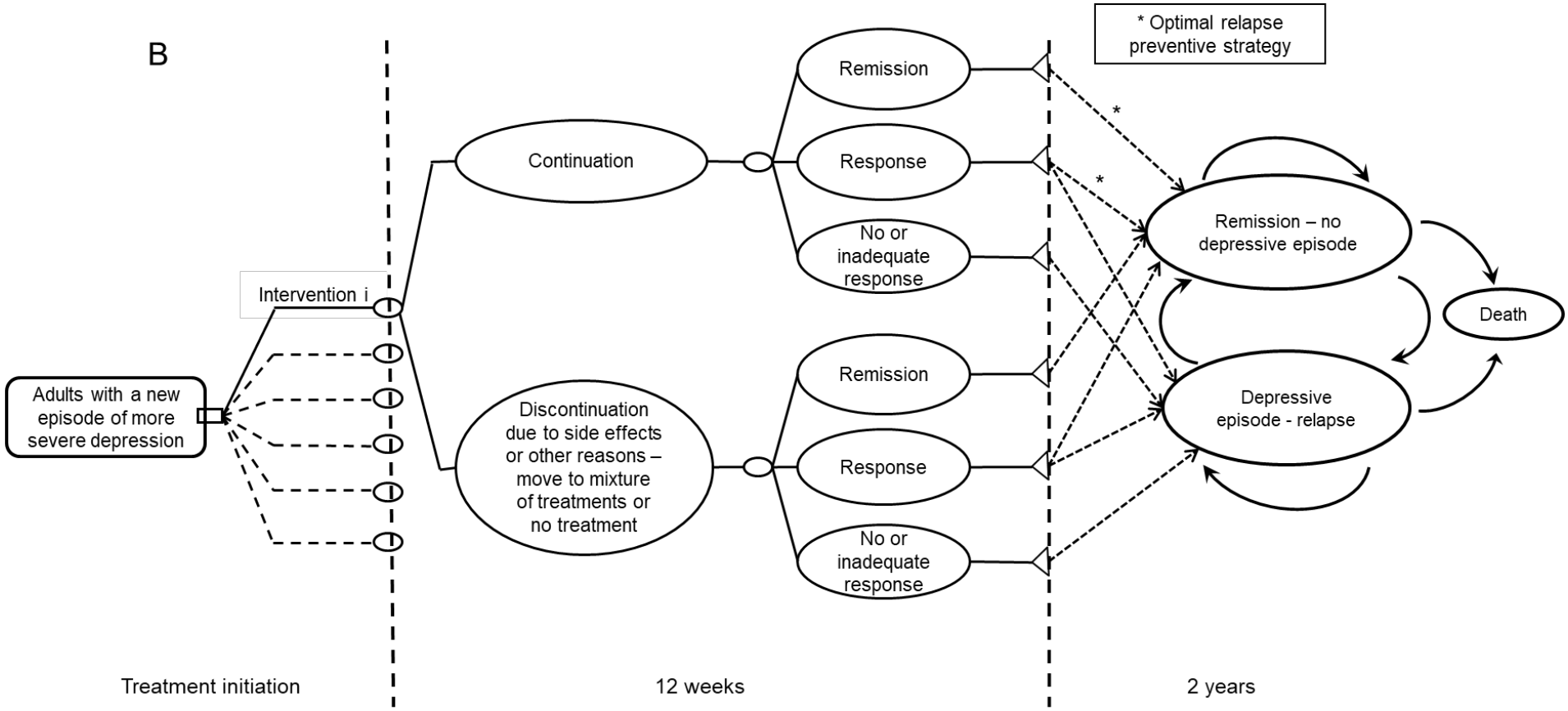
Death was not considered in the acute part of the model. Although the mortality risk in people with depression is higher than that of people in the general population (Cuijpers 2014), suicide (which is the main cause of death in adults with a new episode of depression) is a rare outcome in trials, and there are no substantial differential data on suicide between treatments. The committee expressed the view that consideration of suicide in the acute part of the model would have no significant impact on the relative cost effectiveness between different treatments, and therefore death was considered only in the Markov component of the economic model, for which more relevant, long-term data were available.

Side effects from medication were considered in the model in 2 ways: people who discontinued pharmacological treatment due to side effects were assumed to experience a reduction in their HRQoL over 5 weeks (approximately over the period they were receiving antidepressant treatment) and to incur one extra GP visit. A proportion of people who completed antidepressant treatment was assumed to experience common antidepressant side effects (such as headaches, nausea, agitation, sedation, sexual dysfunction) resulting in a reduction in their HRQoL over the period they experienced side effects, which varied by antidepressant. Moreover, people who experienced side effects from antidepressant treatment were assumed to incur extra costs for the management of their side effects, which comprised GP visits and pharmacological treatment.

The structure of the economic model for interventions for adults with a new episode of depression is shown in Figure 63.

Figure 63. Schematic diagram of the structure of the economic model of treatments for adults with a new episode of (A) less severe depression and (B) more severe depression




B
* Optimal relapse preventive strategy
Adults with a new episode of more severe depression
Intervention i
Continuation
Discontinuation due to side effects or other reasons – move to mixture of treatments or no treatment
Remission
Response
No or inadequate response
Remission
Response
No or inadequate response
*
*
Remission – no depressive episode
Depressive episode - relapse
Death
Treatment initiation
12 weeks
2 years

Relapse-preventive interventions received by adults with more severe depression that responded to (acute) treatment

Adults with more severe depression in their 3rd episode whose depression responded to acute treatment continued treatment aiming at preventing relapses. The choice of continuation treatment was determined by relevant evidence on relapse prevention treatments in the Evidence review C and the resulting guideline recommendations. Table 73 shows the type of continuation treatment people received according to the acute treatment their depression responded to.

Table 73. Continuation treatment aiming at preventing relapses received by people with more severe depression whose depression responded to acute treatment, by type of acute treatment they responded to

Acute treatment	Subsequent maintenance treatment aiming at relapse prevention
More severe depression (remission of 3rd depressive episode)	
Escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: maintenance MBCT + drug tapering
Lofepramine	80%: 2 years of maintenance lofepramine treatment 20%: maintenance MBCT + drug tapering
Duloxetine	80%: 2 years of maintenance duloxetine treatment 20%: maintenance MBCT + drug tapering
Mirtazapine	80%: 2 years of maintenance mirtazapine treatment 20%: maintenance MBCT + drug tapering
Trazodone	80%: 2 years of maintenance trazodone treatment 20%: maintenance MBCT + drug tapering
Individual behavioural activation	80%: 4 sessions of individual behavioural activation 20%: maintenance MBCT
Individual CBT (≥ 15 sessions)	80%: 4 sessions of individual CBT 20%: maintenance MBCT
Individual non-directive counselling	50%: 4 sessions of individual non-directive counselling 50%: maintenance MBCT
Individual IPT	50%: 4 sessions of individual IPT 50%: maintenance MBCT
Individual PDPT	50%: 4 sessions of individual PDPT 50%: maintenance MBCT
Group CBT (under 15 sessions)	80%: maintenance group CBT 20%: maintenance MBCT
cCBT without or with minimal support	50%: maintenance group CBT 50%: maintenance MBCT
cCBT with support	50%: maintenance group CBT 50%: maintenance MBCT
Individual problem solving	50%: maintenance group CBT 50%: maintenance MBCT
Individual exercise	50%: maintenance group CBT 50%: maintenance MBCT
Group exercise	50%: maintenance group CBT 50%: maintenance MBCT
Acupuncture	50%: maintenance group CBT 50%: maintenance MBCT

Acute treatment	Subsequent maintenance treatment aiming at relapse prevention
CBT individual (over 15 sessions) + escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: 4 sessions of individual CBT + drug tapering
Acupuncture + escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: maintenance MBCT + drug tapering
GP care	100%: GP care follow-up

Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE 2014). Costs consisted of intervention costs (drug acquisition, staff time for provision of pharmacological, psychological, physical and combined therapies), including optimal maintenance treatments for relapse prevention in people who remitted, as appropriate, as well as costs associated with the further management of people who discontinued the initiated treatment, those who did not remit or people who relapsed following remission, which included drug acquisition, primary care, hospitalisation, outpatient visits, psychological therapies, and also accident and emergency visits. Costs of management of common side effects from antidepressants in people receiving pharmacological treatment and healthcare costs incurred by people in remission (potentially unrelated to the treatment of depression) were also considered in the analysis. The cost year was 2020.

The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the health states of remission, response without reaching remission, no or inadequate response, as well as utility decrements due to intolerable side effects and common (tolerable) side effects associated with antidepressant and combined treatment (both acute and maintenance).

Relative effects on efficacy, acceptability and tolerability of treatments for a new depressive episode and methods of evidence synthesis

Data on the relative risks of acceptability and efficacy for interventions considered in the economic modelling for a new episode of depression in adults with less severe depression and adults with more severe depression were derived from the NMAs of interventions for adults with a new depressive episode that were undertaken for this guideline. Details on the methods and results of the NMAs, which were conducted in OpenBUGS 3.2.3 (www.openbugs.net) are provided in appendix M. The principles of OpenBUGS are the same as of WinBUGS (Lunn 2000; Spiegelhalter 2003). In summary, binomial likelihood and logit models were used (Dias 2011 [last updated 2016]), to allow estimation of odds ratios of each treatment versus baseline for each outcome of interest, which were then applied onto the respective baseline risk of each outcome. For the economic analysis the first 100,000 iterations undertaken in OpenBUGS were discarded and another 300,000 were run, thinned by 30, so as to obtain 10,000 iterations that populated the economic model.

Although, as discussed in the Evidence review C, appendix J, the probability of recovery in people with depression is reduced over time following a Weibull distribution, the logit model was considered appropriate to use for the estimation of relative effects between acute treatments expressed as odds ratios over a relatively short period of time.

For each population, the following parameters were obtained from the NMAs, expressed as odds ratios versus a selected baseline:

- discontinuation (for any reason)
- discontinuation due to side effects, in those discontinuing pharmacological treatment
- response in those completing treatment
- remission in those completing treatment (only for adults with more severe depression)

These outcomes were a priori selected to inform the economic model as, according to the committee's advice, they reflected main outcomes and events associated with treatment of adults with depression in routine practice.

These data were combined with respective baseline risks for each outcome in adults with less severe depression and in adults with more severe depression, in order to estimate the probabilities of events of each intervention in each endpoint of the decision-tree component of the model, for each population of interest.

For adults with less severe depression, the discontinuation due to side effects outcome was informed by an indirect comparison between SSRIs and TCAs, using placebo as the common comparator.

A NMA of remission in those completing treatment for adults with less severe depression was also conducted; however, available data were very limited and covered only a minority of the treatment classes included in economic modelling. Available data from studies reporting both response and remission data in this population suggested that the probability of response to treatment (defined as at least 50% reduction in baseline depressive symptom score) was approximately equal to the probability of remission (defined as a score below a cut-off point on a scale). This is not unexpected, considering that this population includes adults with mild or subthreshold depression, with a low baseline depressive symptom score, and therefore response to treatment most often meets criteria for remission as well. For this reason, and due to lack of remission data for the majority of the interventions considered for this population, the economic model assumed that adults with less severe depression who respond to treatment are also remitters.

It needs to be noted that, originally, the outcome of interest in order to populate the economic model with numbers of people remitting was remission conditional on response (that is, probability of remission in those responding to treatment). However, the networks constructed for this outcome were sparse and/or disconnected and covered a limited number of interventions, and therefore were not informative for the economic model. For this reason, remission in those completing treatment was selected as an outcome instead, to allow, in combination with data on response in those completing treatment, calculation of numbers of people who responded and remitted. When running the probabilistic analysis, the number of people reaching remission was not allowed to exceed the number of people responding to treatment. In iterations where the probability of remission exceeded the probability of response, the number of people in remission was forced to equal that of people in response (so that all people who responded also remitted in those iterations).

Relative effects were obtained from the NMAs for the individual interventions modelled, with the exception of discontinuation due to side effects in those discontinuing treatment, where drug class effects were used to increase the evidence base. However, when intervention-specific data on an outcome were not available for an intervention included in economic modelling, then either class effects (for single interventions) or effects from another similar intervention within the class (for combined interventions) were used instead.

As described later under 'Baseline probabilities', for two of the outcomes (response in those completing treatment and remission in those completing treatment) the chosen baseline was GP care, reflected in the NMA reference treatment (TAU for less severe depression and placebo for more severe depression). For the other two outcomes (discontinuation and discontinuation due to side effects in those discontinuing treatment) the selected baseline treatment was SSRIs.

For a number of guideline NMA outcomes, bias-adjusted models were run to explore potential bias associated with small study size. These outcomes were the SMD, selected as the primary clinical outcome, and the outcomes of discontinuation and response in completers, selected as the main NMA outcomes that informed the economic analysis with the highest anticipated impact on the economic results (see appendix M). The NMA models

on discontinuation and response in completers for adults with less severe depression did not suggest evidence of small study bias. However, the respective models for adults with more severe depression suggested evidence of bias on both outcomes in the comparisons of active versus inactive treatments or active treatments versus non-directive counselling in studies with larger variance (that is, in smaller studies); hence, a probabilistic bias-adjusted economic analysis was conducted in this population, using bias-adjusted data on these two outcomes.

The results of the base-case NMAs that were used to populate the economic model are provided in Table 74 for adults with less severe depression and Table 75 for adults with more severe depression. The results of the bias-adjusted NMAs of discontinuation and response in completers that informed the bias-adjusted model of treatments for adults with more severe depression are shown in Table 76. Full results for all classes and interventions, including those not considered in the economic analysis, as well as model fit statistics, heterogeneity and results of inconsistency checks for each outcome are provided in appendix M and supplements B5 and B6.

In summary, for less severe depression, and relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for both discontinuation due to any reason, and for response in completers. Some evidence of inconsistency was identified for the response in completers outcome.

For more severe depression, and relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for discontinuation due to any reason, discontinuation due to side effects from medication in those discontinuing treatment, and response in completers, and small for remission in completers. Some evidence of inconsistency was identified for discontinuation, discontinuation due to side effects from medication in those discontinuing treatment, and remission in completers.

It is noted that relative effects and rankings of treatments in the response in completers outcome may differ from those observed for the standardised mean difference (SMD) and response in those randomised outcomes that were considered in the clinical analysis. Possible explanations for this discrepancy include:

- Different studies have been included in different analyses (depending on availability of reported outcome data in each study)
- There was a different way for accounting of drop-outs in each study outcome and each analysis: the response in completers outcome considered improvement after excluding those who have discontinued treatment. On the other hand, the SMD analysis prioritised use of continuous scale data for all trial participants where available, if a study used data imputation methods for trial drop-outs; otherwise completer data were used. Trials that imputed data reported different methods for data imputation, such as last observation carried forward (LOCF), multiple imputation, or baseline observation carried forward (BOCF). The NMA of response in those randomised included a mixture of dichotomous response data (where people who discontinued were considered as non-responders) as a priority, in studies where such dichotomous data were available, and continuous data, where RCTs did not report dichotomous response data. The amount of continuous data and the method of imputation included in the response in those randomised analyses have unavoidably affected the results of these analyses.

The networks of all NMAs that informed the economic analysis are provided in appendix M.

Table 74. Results of the NMAs that informed the economic analysis of interventions for a new depressive episode in adults with less severe depression: log-odds ratios versus baseline for each outcome of interest

Intervention [Class]	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)		
	Discontinuation versus sertraline	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [TAU]
Sertraline [SSRIs]	Baseline	Baseline	2.01 (0.03 to 3.98)
	N=326	Nclass=31	N=50
Loferpamine [TCAs]	0.21 (-1.32 to 1.78)	3.32 (-0.22 to 6.88)	3.15 (0.04 to 6.23)
	N=32	Nclass=40	N=23
Computerised CBT without or with minimal support [Self-help]	-0.64 (-5.55 to 2.92)	Not relevant	0.85 (-0.47 to 2.15)
	N=3,173		N=607
Computerised CBT with support [Self-help with support]	-0.65 (-5.61 to 2.94)	Not relevant	0.95 (-1.03 to 2.86) [class effect]
	N=428		Nclass=327
Individual BA [BT individual]	-1.80 (-7.09 to 2.55)	Not relevant	1.83 (-0.29 to 3.93)
	N=153		N=111
Group BA [BT group]	-0.33 (-5.26 to 3.33)	Not relevant	3.02 (1.05 to 5.02)
	N=107		N=47
Individual CBT (<15 sessions) [individual CT/CBT]	-1.42 (-6.30 to 2.17)	Not relevant	1.79 (0.15 to 3.43)
	N=402		N=233
Group CBT (<15 sessions) [group CT/CBT]	-0.94 (-5.95 to 2.81)	Not relevant	4.63 (2.44 to 6.87)
	N=283		N=59
Individual problem solving [individual problem solving]	-0.50 (-5.41 to 3.15)	Not relevant	0.26 (-1.14 to 1.66)
	N=159		N=98
Non-directive/supportive/person-centred counselling [Counselling]	-1.80 (-6.86 to 2.01)	Not relevant	1.16 (-2.55 to 4.79)
	N=125		N=39

Intervention [Class]	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)		
	Discontinuation versus sertraline	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [TAU]
Individual IPT [individual IPT]	-0.56 (-5.63 to 2.79)	Not relevant	1.04 (-0.28 to 2.36)
	N=108		N=125
Individual short-term PDPT [individual short term PDPT]	-2.12 (-7.17 to 1.75)	Not relevant	1.63 (-1.18 to 4.45)
	N=53		N=43
Group MBCT [mindfulness or meditation group]	-0.83 (-5.76 to 2.82)	Not relevant	1.72 (0.00 to 3.40)
	N=167		N=73
Supervised high intensity individual exercise [individual exercise]	-1.43 (-6.54 to 2.35)	Not relevant	1.16 (-0.47 to 2.79)
	N=39		N=43
Supervised high intensity group exercise [group exercise]	-0.86 (-5.89 to 2.87)	Not relevant	1.43 (-0.12 to 2.95)
	N=121		N=136
GP care [TAU]	-0.81 (-5.77 to 2.70)	Not relevant	Baseline
	N=1,005		N=395
No treatment [No treatment]	Not relevant	Not relevant	-0.16 (-1.43 to 1.10)
			N=1,033

BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Table 75. Results of the base-case NMAs that informed the economic analysis of interventions for a new depressive episode in adults with more severe depression: log-odds ratios versus baseline for each outcome of interest

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
Escitalopram [SSRIs]	Baseline	Baseline	0.81 (0.60 to 1.00)	0.56 (0.44 to 0.71)
	N=5,627	Nclass=661	N=3,396	N=2,457
Lofepramine [TCAs]	0.10 (-0.18 to 0.33)	0.69 (0.18 to 1.21)	1.14 (0.81 to 1.46)	0.70 (-0.12 to 1.24)
	N=296	Nclass=963	N=188	N=55
Duloxetine [SNRIs]	0.14 (-0.02 to 0.33)	0.40 (-0.07 to 0.86)	0.99 (0.75 to 1.23)	0.75 (0.62 to 0.88)
	N=5,226	Nclass=1,272	N=3,700	N=3,674
Mirtazapine	0.06 (-0.14 to 0.26)	0.03 (-0.37 to 0.43)	1.02 (0.70 to 1.33)	0.61 (0.34 to 0.89)
	N=2,637	N=692	N=1,845	N=645
Trazodone	0.35 (0.10 to 0.60)	0.26 (-0.24 to 0.77)	0.68 (0.28 to 1.09)	0.53 (0.26 to 0.81)
	N=1,430	N=365	N=1,003	N=552
cCBT without or with minimal support [Self-help]	-0.22 (-1.08 to 0.67)	Not relevant	0.12 (-1.79 to 1.89)	1.38 (-0.55 to 3.61) [class effect]
	N=115		N=20	Nclass=147
cCBT with support [Self-help with support]	-0.19 (-0.90 to 0.51)	Not relevant	0.82 (-0.36 to 2.02)	0.95 (0.14 to 1.75)
	N=290		N=114	N=165
Individual BA [Individual BT]	-0.65 (-1.33 to 0.03)	Not relevant	1.42 (0.09 to 2.77)	1.08 (0.45 to 1.71)
	N=595		N=310	N=320
Individual CBT (≥15 sessions) [individual CT/CBT]	-0.43 (-0.88 to 0.01)	Not relevant	1.22 (0.55 to 1.89)	1.09 (0.61 to 1.56)
	N=461		N=348	N=391
Group CBT (<15 sessions) [group CT/CBT]	-0.31 (-1.32 to 0.68)	Not relevant	0.99 (-0.27 to 2.21)	0.29 (-0.84 to 1.37)
	N=162		N=64	N=32

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
Individual problem solving [individual problem solving]	-0.64 (-1.47 to 0.16)	Not relevant	2.16 (0.78 to 3.55)	1.15 (0.19 to 2.14)
	N=448		N=123	N=191
Non-directive/supportive/person-centred counselling [Counselling]	-0.35 (-1.15 to 0.45)	Not relevant	1.50 (0.08 to 2.92)	0.30 (-0.85 to 1.47)
	N=332		N=216	N=103
Individual IPT [individual IPT]	-0.68 (-1.51 to 0.15)	Not relevant	0.72 (-0.31 to 1.73)	1.00 (0.34 to 1.67)
	N=63		N=132	N=89
Individual short-term PDPT [individual short term PDPT]	0.04 (-0.85 to 0.95)	Not relevant	1.58 (-0.94 to 4.06)	0.50 (-0.47 to 1.45)
	N=56		N=16	N=42
Supervised high intensity individual exercise [individual exercise]	0.14 (-0.88 to 1.23)	Not relevant	2.40 (-0.31 to 5.05)	0.32 (-0.47 to 1.20)
	N=162		N=47	N=109
Supervised high intensity group exercise [group exercise]	0.26 (-0.42 to 0.93)	Not relevant	2.02 (0.17 to 4.08)	0.63 (0.02 to 1.27)
	N=124		N=18	N=80
Traditional acupuncture [Acupuncture]	-0.25 (-1.28 to 0.64)	Not relevant	-0.17 (-1.38 to 1.01)	0.10 (-1.58 to 1.80)
	N=102		N=130	N=42
Individual CBT (≥15 sessions) + escitalopram [Combined individual CT/CBT individual + AD]	-0.32 (-1.22 to 0.51) [borrowed from individual CBT (≥15 sessions) + imipramine]	1 [risk same as escitalopram]	1.84 (0.61 to 3.00) [borrowed from individual CBT (≥15 sessions) + any SSRI]	1.72 (0.81 to 2.91) [borrowed from individual CBT (≥15 sessions) + imipramine]
	N=25		N=43	N=16
Traditional acupuncture + escitalopram [combined acupuncture + AD]	-0.27 (-1.51 to 0.96) [borrowed from traditional	1	4.07 (2.97 to 5.17) [borrowed from traditional	0.46 (-0.54 to 1.47) [borrowed from traditional

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
	acupuncture + paroxetine]	[risk same as escitalopram]	acupuncture + any SSRI]	acupuncture + paroxetine]
	N=54		N=185	N=51
GP care [placebo]	0.13 (0.02 to 0.24)	Not relevant	Baseline	Baseline
	N=16,577		N=9,333	N=5,850
No treatment	Not relevant	Not relevant	-0.27 (-1.40 to 0.86)	0.17 (-0.52 to 0.87)
			N=266	N=299

AD: antidepressant; BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Table 76. Results of the bias-adjusted NMAs that informed the economic analysis of interventions for a new depressive episode in adults with more severe depression: log-odds ratios versus baseline for each outcome of interest [of those where evidence of bias was tested and identified]

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Escitalopram [SSRIs]	Baseline	0.65 (0.43 to 0.85)
	N=5,627	N=3,396
Lofepramine [TCAs]	0.11 (-0.16 to 0.34)	0.87 (0.53 to 1.20)
	N=296	N=188
Duloxetine [SNRIs]	0.14 (-0.01 to 0.33)	0.84 (0.59 to 1.08)
	N=5,226	N=3,700
Mirtazapine	0.07 (-0.13 to 0.26)	0.77 (0.44 to 1.10)
	N=2,637	N=1,845

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Trazodone	0.34 (0.08 to 0.59)	0.50 (0.10 to 0.91)
	N=1,430	N=1,003
cCBT without or with minimal support [Self-help]	-0.19 (-1.10 to 0.73)	-0.20 (-2.26 to 1.67)
	N=115	N=20
cCBT with support [Self-help with support]	-0.16 (-0.91 to 0.58)	0.39 (-0.87 to 1.68)
	N=290	N=114
Individual BA [Individual BT]	-0.68 (-1.39 to 0.02)	1.18 (-0.19 to 2.49)
	N=595	N=310
Individual CBT (≥15 sessions) [individual CT/CBT]	-0.36 (-0.82 to 0.10)	0.92 (0.21 to 1.62)
	N=461	N=348
Group CBT (<15 sessions) [group CT/CBT]	-0.21 (-1.30 to 0.88)	0.51 (-0.76 to 1.81)
	N=162	N=64
Individual problem solving [individual problem solving]	-0.71 (-1.62 to 0.18)	2.03 (0.61 to 3.46)
	N=448	N=123
Non-directive/supportive/person-centred counselling [Counselling]	-0.33 (-1.15 to 0.51)	1.38 (-0.06 to 2.83)
	N=332	N=216
Individual IPT [individual IPT]	-0.64 (-1.49 to 0.18)	0.43 (-0.65 to 1.50)
	N=63	N=132
Individual short-term PDPT [individual short term PDPT]	0.11 (-0.84 to 1.08)	1.31 (-1.21 to 3.81)
	N=56	N=16
Supervised high intensity individual exercise [individual exercise]	0.21 (-0.82 to 1.30)	1.47 (-1.69 to 4.73)
	N=162	N=47
	0.30 (-0.41 to 1.01)	1.63 (-0.34 to 3.78)

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Supervised high intensity group exercise [group exercise]	N=124	N=18
Traditional acupuncture [Acupuncture]	-0.37 (-1.36 to 0.57)	-0.26 (-1.49 to 0.93)
	N=102	N=130
Individual CBT (≥15 sessions) + escitalopram [Combined individual CT/CBT individual + AD]	-0.28 (-1.19 to 0.59) [borrowed from individual CBT (≥15 sessions) + imipramine]	1.68 (0.43 to 2.82) [borrowed from individual CBT (≥15 sessions) + any SSRI]
	N=25	N=43
Traditional acupuncture + escitalopram [combined acupuncture + AD]	-0.14 (-1.39 to 1.10) [borrowed from traditional acupuncture + paroxetine]	3.85 (2.74 to 4.95) [borrowed from traditional acupuncture + any SSRI]
	N=54	N=185
GP care [placebo]	0.08 (-0.03 to 0.21)	Baseline
	N=16,577	N=9,333
No treatment	Not relevant	-0.24 (-1.40 to 0.94)
		N=266

AD: antidepressant; BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Baseline probabilities

The baseline probabilities of the 4 outcomes of interest were estimated based on published literature and the committee's expert opinion and were applied in the decision-tree component of the economic model. All relative effects of the other interventions versus the intervention serving as baseline were applied onto the baseline probability in order to obtain the absolute probability of every intervention assessed in the economic analysis for each outcome of interest.

The committee expressed the view that absolute probabilities reported in RCTs included in the NMAs did not reflect probabilities seen under non-interventional conditions and routine clinical practice, and therefore these were not utilised in the economic analysis.

Baseline probability of early discontinuation (for any reason)

Burton 2012 analysed prescription data from a Scottish primary care database of adults who commenced treatment with an eligible antidepressant between April 2007 and March 2008 across 237 Scottish practices. Eligible antidepressants comprised SSRIs, SNRIs, lofepramine and trazodone. The authors identified 28,027 people who initiated treatment with an eligible antidepressant over this period, of whom 24.6% did not continue treatment beyond 30 days (they discontinued treatment within the first 30 days) and 44.5% did not continue treatment beyond 90 days (they discontinued treatment within the first 90 days). The authors did not report discontinuation rates by level of severity of depression or by specific drug or drug class.

Hansen 2004 reported rates of discontinuation (defined as people not purchasing antidepressants in the 6 months following first prescription) following analysis of data on 4,860 adult first-time users of antidepressants (regardless of diagnosis) who presented in 174 general practices in Denmark between January 1998 and June 1999. The discontinuation rate was 30.5% for adults prescribed new generation antidepressants, mainly SSRIs (n=4,275) and 56.4% for adults prescribed TCAs (n=585). No information was provided on discontinuation rates in relation to the level of symptom severity.

Bull 2002 assessed the rates of discontinuation at 3 and 6 months in 672 adults that were started on an SSRI (fluoxetine or paroxetine) by a psychiatrist or primary care physician for a new or recurrent case of depression between January and September 1998 in the USA. Participants were conducted via a telephone survey. At 3 months, 34% had discontinued their initiated SSRI.

Goethe 2007 reported discontinuation data on 406 adults with severe depression who were treated with SSRIs in a secondary care setting (208 as outpatients and 198 as inpatients) in the USA between July 2001 and January 2003. The reported discontinuation rate at 3 months was 24.6%.

Lewis 2004 reported rates of early discontinuation among 26,888 adults who filled an SSRI prescription, by analysing data from a large database in the USA. Of these, 61.3% were seen in primary care, 14.9% were treated by psychiatrists and another 23.8% were treated by another medical specialist. Early discontinuation was defined as failure to refill a prescription for any antidepressant medication within 30 days of the end of the first SSRI prescription. The authors reported early discontinuation of 37.1% for adults prescribed an SSRI by primary care providers, 31.8% for those treated by psychiatrists and 41.4% for those treated by other medical specialists. No information was provided on discontinuation rates in relation to level of severity of symptoms.

Olfson 2006 analysed data on 829 adults with depression who were initiated on antidepressant treatment, derived from the household component of the Medical Expenditure Panel Survey conducted in the USA for the years 1996 to 2001. The authors reported rates

of discontinuation during the first 30 days of treatment and between 31-90 days of treatment by mental status. In the first 30 days of treatment, discontinuation reached 42.7% in adults with “excellent to good” mental status and 42.0% in adults with “fair or poor” mental status. Between 31-90 days of treatment, discontinuation reached 57.3% in adults with “excellent to good” mental status and 41.1% in adults with “fair or poor” mental status. In total, discontinuation over 90 days reached 75% and 65% in adults with “excellent to good” and those with “fair or poor” mental status, respectively. Discontinuation was lower in people taking SSRIs or SNRIs (40.9% in first 30 days, 48.0% in 31-90 days) compared with other new medications (49.9% in first 30 days, 63.0% in 31-90 days) and TCAs and other old antidepressants (45.2% in first 30 days, 68.2% in 31-90 days). Discontinuation in the first 30 days was lower in adults who had private health insurance (39.9%) compared with those who had public (48.6%) or no (50.6%) insurance. No other information was provided on discontinuation rates in relation to severity of depressive symptoms or type of provider (primary or specialist care).

The committee reviewed the data reported in the studies. The figures of 24.6% and 44.5% for continuation up to 30 and 90 days, respectively, that were reported by Burton 2012 are directly relevant to primary care practice in the UK; the figure of 44.5% is likely to include people who took a full first course of treatment but did not continue because of treatment failure (lack of efficacy); therefore the risk of discontinuation of initiated treatment prior to completion of a full course lies between the two figures of 24.6% and 44.5%. It is likely that the figure is relevant to SSRIs, since these are among the most commonly used antidepressants. Hansen 2004 reported a discontinuation risk of 30.5% over a period of 6 months for SSRIs prescribed in primary care in Denmark. The USA figures are higher, as Lewis 2004 reported a 37.1% discontinuation within 30 days for SSRIs prescribed in primary care, while Olfson 2006 reported the highest rates, 75% and 65% over 90 days, in adults with ‘excellent to good’ and those with ‘fair or poor’ mental status, respectively. Discontinuation rates were reported to be higher in people treated in primary compared with specialist care.

Following consideration of the data and the committee’s expert opinion, estimated figures of 37% for early discontinuation of SSRIs in adults with less severe depression, and 34% for early discontinuation of SSRIs in adults with more severe depression were used. These figures are within the range of percentages reported by Burton 2012 for 30 and 90 days, but lower than the figures reported by Olfson 2006 over 90 days. Discontinuation was assumed to be higher in adults with less severe depression, based on data reported in Olfson 2006 and the committee’s expert opinion.

Using the guideline NMA relative SSRI class and individual drug effects versus placebo, the figure of 0.38 was estimated and used as the baseline probability of discontinuation for sertraline, in the economic analysis for adults with less severe depression. The figure of 0.34 was estimated and used as the baseline probability of discontinuation for escitalopram in the economic analysis for adults with more severe depression.

Baseline probability of discontinuation due to side effects in those discontinuing treatment early

Discontinuation due to side effects was relevant to cohorts treated with pharmacological treatments or combined treatments with a pharmacological intervention component.

Bull 2002 reported reasons for drug discontinuation at 3 and 6 months in 672 adults that were started on an SSRI (fluoxetine or paroxetine) by a psychiatrist or primary care physician for a new or recurrent case of depression between January and September 1998 in the USA. Participants were conducted via a telephone survey. Overall, 15% of people who were initiated on a SSRI discontinued due to intolerable side effects over the first 3 months of the study.

Goethe 2007 reported discontinuation data on 406 adults with severe depression who were treated with SSRIs in a secondary care setting (208 as outpatients and 198 as inpatients) in the USA between July 2001 and January 2003. Overall, 13% of people who were initiated on an SSRI discontinued due to intolerable side effects over the first 3 months of the study.

The risk of discontinuation due to side effects was considered to be independent of the depressive symptom severity. A risk of 0.15 was therefore applied to people initiated on SSRIs with both less severe and more severe depression. Since the risk of discontinuation with SSRI treatment was estimated to be 0.38 (sertraline) in adults with less severe depression and 0.34 (escitalopram) in adults with more severe depression, the estimated risk of discontinuation due to side effects in those discontinuing these specific SSRI treatments was estimated to be 0.15/0.38 = 0.39 (sertraline) and 0.15/0.34 = 0.44 (escitalopram) in adults with less severe depression and more severe depression, respectively.

The figure of 0.39 was used as the baseline probability of discontinuation due to side effects in those discontinuing sertraline in the economic analysis for adults with less severe depression. The figure of 0.44 was used as the baseline probability of discontinuation due to side effects in those discontinuing escitalopram in the economic analysis for adults with more severe depression.

Baseline probability of response and remission in treatment completers

The only study identified in the literature reporting relevant data by level of depressive symptom severity was conducted by Simon 1999, who reported 12-month outcomes of 948 people with major depression attending primary care services who participated in a multinational, longitudinal study conducted at 15 sites in 14 countries including the UK. All study participants had been assessed at baseline by study researchers using the Composite International Diagnostic Interview (CIDI), the 28-item General Health Questionnaire (GHQ), and the Brief Disability Questionnaire (BDQ) and were classified as having mild, moderate or severe major depression. Participants also underwent assessment by their primary care physicians at baseline; depression or a psychological disorder and a comorbid condition was correctly recognised by physicians in 42% of them. However, no information on follow-up care or treatment received was available for any of the participants. At 12 month follow-up the diagnostic status (ICD-10 depressive disorder) of participants was reported by their baseline symptom severity, stratified according to whether they had been recognised by their physicians at baseline. Recognised and unrecognised groups did not differ significantly in change in diagnostic status from baseline. Results were consistent across study sites.

Table 77 shows the 12-month diagnostic status of people who had been diagnosed with mild, moderate and severe depression at baseline, and who had been recognised by their physician to have a depression or another psychological disorder.

Table 77. Diagnostic status at 12 months of people with major depression that were diagnosed by their physicians at baseline, by baseline severity status, as reported in Simon 1999

12-month status	Baseline mild depression	Baseline moderate depression	Baseline severe depression
Recovery	79.3%	64.5%	54.9%
Mild depression	6.9%	3.2%	7.8%
Moderate depression	6.9%	19.4%	9.8%
Severe depression	6.9%	12.9%	27.5%
TOTAL	100.0%	100.0%	100.0%

It can be seen that at 12-months the probability of recovery is highest for people with mild depression (0.79), lower for people with moderate depression (0.65) and lowest for people

with severe depression at baseline (0.55). Based on the data above, it is possible to estimate the probability of improvement from baseline to 12 months for each category of symptom severity, considering improvement as movement to a lower level of severity or recovery. For mild depression the probability of improvement equals that of recovery (0.79); for moderate depression improvement of status is reflected by recovery or a move to mild depression (0.68 in total); and for severe, the probability of improvement is reflected in recovery or reduction of symptoms from severe to mild or moderate (0.73).

These data formed the basis for estimating the 3-month probability of response (as expressed by improvement) and remission at baseline in the economic model for adults with less severe depression and those with more severe depression. Although the study reported data on both people recognised by their physicians as having a psychological disorder and those that were not recognised, the economic analysis utilised data on people whose disorder was recognised by their physicians, as the study population of the economic analysis comprises adults with recognised depression initiating treatment. The committee advised that reported data be used to represent the baseline probability of response and remission in those completing GP care. This was decided as there was no information in the study on the specific treatment received by study participants; the committee considered that a mixture of treatments would have been received, with some people having received more intensive treatment and some others less intensive or no treatment. The committee inspected the available 12-month recovery and improvement data reported for each level of symptom severity and expressed the view that, on balance, they reflect baseline changes in status that are observed under GP care.

As reported in Evidence review C, appendix J, synthesis of remission data from cohort studies following people with depression showed that the probability of remission in people with depression follows a Weibull distribution in which the remission rate is proportional to a power of time. People have a higher probability of remission soon after initiation of the depressive episode, and this probability is reduced over time, as they remain in that episode; the cumulative hazard rate for the Weibull distribution is given by the following mathematical formula:

$$H(t) = \lambda t^{\gamma}$$

where lambda (λ) and gamma (γ) are the scale and shape parameters of the distribution, respectively.

A literature review and synthesis of relevant cohort data determined the parameters of the Weibull distribution characterising the probability of remission over time. These parameters, shown in Table 78, were estimated using data from studies on cohorts with depression followed over long periods of time, irrespective of their level of symptom severity (Gonzales 1985, Holma 2008, Keller 1981, 1984, 1992; Mueller 1996; Skodol 2011). Details of the literature review and data synthesis are provided in Evidence review C, appendix J.

Table 78. Parameters of the Weibull distribution of the probability of remission over time, in people experiencing a depressive episode

Parameter	Mean	SD	Median	95% Credible intervals
Lambda	1.16	0.04	1.16	1.08 to 1.24
Gamma	0.42	0.03	0.42	0.37 to 0.47

In order to estimate the 3-month probabilities of remission and response in people completing GP care it was assumed that both followed a Weibull distribution with the same shape parameter gamma across all symptom severity levels that was equal to that estimated from synthesis of cohort studies (Table 78). The lambda parameter for response and remission at each level of severity was estimated from the available 12-month data (Simon 1999). The estimated 3-month probabilities of response and remission at each symptom

severity level as well as the estimated hazard ratios of response and remission at each level of severity versus the 'baseline' remission, estimated from data synthesis, are shown in Table 79.

Table 79. Parameters of the Weibull distribution and 3-month probabilities of response and remission, in people experiencing a depressive episode according to their level of symptom severity

Mean values	Baseline remission – based on synthesis of studies	Data based on Simon 1999 for people with major depression recognised by their physician					
Parameter		Mild depression		Moderate depression		Severe depression	
		Resp	Remis	Resp	Remis	Resp	Remis
12-month probability	0.69	0.79	0.79	0.68	0.65	0.73	0.55
Hazard (lambda)	1.16	1.58	1.58	1.13	1.04	1.29	0.80
Hazard ratio vs baseline (lambda)	1 (reference)	1.36	1.36	0.97	0.89	1.11	0.69
Gamma	0.42						
3-month probability	0.46	0.57	0.57	0.45	0.43	0.50	0.35
Notes: Resp: response; Remis: remission							

The 3-month probability of response (and remission) for adults with less severe depression was equal to that for people with mild depression (0.57). The 3-month probabilities of response and remission for adults with more severe depression were estimated as an average of respective probabilities estimated for people with moderate and severe depression (0.48 and 0.39, respectively).

When running the probabilistic analysis, the number of people reaching remission were not allowed to exceed the number of people responding to treatment in the population with more severe depression. In iterations where the probability of remission exceeded the probability of response, the number of people in remission was forced to equal that of people in response (so that all people who responded also remitted in those iterations).

Other clinical input parameters

Progression of depression in adults with more severe depression who responded to acute treatment without reaching remission

Adults with more severe depression who responded to initial treatment but did not meet criteria for remission at the end of the 12 weeks of treatment were assumed to receive a course of further treatment and either remit or remain in a depressive episode. For the purposes of simplicity, people in this branch of the model were assumed to move to one of the two respective states of the Markov model (remission or depressive episode) at the end of 12 weeks, although in reality this transition would not occur immediately. The probability of moving to the Markov remission state was based on the committee's expert opinion, due to lack of relevant data. According to this, the probability of adults with more severe depression moving to remission following response to treatment (but without remission) at 12 weeks was 0.30.

Risk of relapse in the Markov component of the economic model

The risk of relapse in people who were in the remission state in the Markov component of the economic model was determined by the time spent in the remission state (one or two years), the number of previous episodes experienced by each cohort assessed in the analysis, and,

in people with more severe depression who received maintenance treatment, by the efficacy of relapse preventive treatment.

- Baseline risk of relapse

As reported in the Evidence review C, appendix J, the risk of relapse in people with depression that is in remission is dependent on time, following a Weibull distribution in which the relapse rate is proportional to a power of time. People have a higher risk of relapse in the early years following remission, and this risk is reduced with every year they remain in remission; the cumulative hazard rate for the Weibull distribution is given by the following mathematical formula:

$$H(t) = \lambda t^{\gamma}$$

where lambda (λ) and gamma (γ) are the scale and shape parameters of the distribution, respectively.

Moreover, there is evidence that the risk of relapse increases with the number of previous episodes.

A literature review and synthesis of data from cohort studies following people who remitted from a single (first) episode of depression (Eaton 2008; Mattisson 2007) determined the parameters of the Weibull distribution characterising the baseline risk of relapse after remission of a single episode over time. These parameters are shown in Table 80. Details of the literature review and data synethis are provided in Evidence review C, appendix J. Their use in the model allowed estimation of the baseline risk of relapse in people in the remission state according to the time they remained in the state (one or two years).

Table 80. Parameters of the Weibull distribution of risk of relapse over time, in people who are in remission following a single (first) episode

Parameter	Mean	SD	Median	95% Credible intervals
Lambda	0.09	0.01	0.09	0.07 to 0.12
Gamma	0.63	0.06	0.63	0.52 to 0.75

The increase in the risk of relapse for every additional depressive episode was considered by applying the hazard ratio of relapse with every additional episode as estimated by Kessing 1999, who reported the results of a case register study that included all hospital admissions with primary affective disorder in Denmark during 1971-1993. A total of 7,925 people with unipolar depression were included in the study. The authors reported that the risk of relapse increased with every new episode by a mean hazard ratio of 1.15 (95% CI 1.11-1.18). Use of this ratio allowed estimation of the baseline relapse risk for people with more severe depression who, following successful treatment, recovered from their third episode.

- Risk of relapse associated with interventions aiming at relapse prevention

The effect of relapse preventive treatments in people who completed acute treatment and moved to the remission state in the Markov component of the model was expressed as a hazard ratio versus baseline, and was applied onto the baseline risk of relapse over the first 2 years of the Markov model. The hazard ratios of maintenance treatments versus baseline (GP care, expressed by placebo trial arms) were derived from the NMAs conducted for this guideline to inform the relapse prevention guideline economic models (see details on Evidence review C, appendix J), as described below.

The hazard ratios versus GP care that were utilised in the Markov component of this economic analysis for cost-effective maintenance treatments were obtained from the relapse

prevention model conducted for this guideline and are presented in Table 81. Hazard ratios of relapse preventive interventions were determined by the type of acute treatment (pharmacological, psychological, physical or combined) people received, that led to response of their depressive episode, as estimated in the Evidence review C, appendix J. For people who received acute combined treatment in the economic analysis, efficacy data on relapse prevention treatment were received from the NMA of treatments for people who responded to acute pharmacological treatment, due to lack of relevant data on people who responded to acute combined treatment. For people who received acute physical treatment in the economic analysis, efficacy data on relapse prevention treatment were received from the NMA of treatments for people who responded to acute psychological treatment, due to lack of relevant data on people who responded to acute physical treatment. The hazard ratios of 4 sessions of psychological interventions received as maintenance treatment were assumed to equal the hazard ratios of maintenance individual CT/CBT, in the guideline relapse prevention NMAs.

Table 81. Hazard ratios of cost-effective maintenance treatments received by people with more severe depression who responded to treatment - Results of the NMAs conducted to inform the guideline economic analyses of interventions aiming at relapse prevention in people whose depression has responded to treatment (Evidence review C, appendix J)

Intervention	Mean hazard ratio versus placebo (95% credible intervals)
Adults whose (more severe) depression responded to acute pharmacological treatment [data also applied to adults whose depression responded to acute combined treatment]	
Maintenance AD treatment	0.49 (0.44 to 0.55)
MBCT + GP care (AD drug tapering)	0.46 (0.31 to 0.65)
Individual CT/CBT + GP care (AD drug tapering)	0.50 (0.30 to 0.79)
Adults whose (more severe) depression responded to acute psychological treatment [data also applied to adults whose depression responded to phsycial treatment]	
4 sessions of intervention received as acute treatment (assumed to equal effect of maintenance individual CT/CBT)	0.67 (0.31 to 1.26)
MBCT	0.90 (0.30 to 2.11)
Group CT/CBT	1.03 (0.30 to 2.59)

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness based cognitive therapy

Probability of remission in the Markov component of the economic model

The probability of remission in people who are in the depressive episode state in the Markov component of the economic model was determined by the time spent in the depressive episode state. As discussed earlier, the probability of remission in people with depression follows a Weibull distribution in which the remission rate is proportional to a power of time. People have a higher annual probability of remission in the early years following initiation of the depressive episode, and this probability is reduced with every year they remain in the episode.

A literature review and synthesis of data from cohort studies following people with depression determined the parameters of the Weibull distribution characterising the probability of remission over time, as it has been shown in Table 78. Their use in the model allowed estimation of the risk of remission in people in the depressive episode state according to the time they remained in the state (one or two years).

These parameters were estimated using data from studies on cohorts with depression followed over long periods of time, irrespective of their level of symptom severity.

In order to estimate the Weibull parameters of remission for adults with less severe depression and adults with more severe depression, data were taken from Simon 1999, as discussed earlier. The probability of remission at 12 months by baseline symptom severity reported in this study was used to estimate lambda parameters for the underlying distribution at each level of symptom severity. The shape parameter gamma that was estimated for recovery from synthesis of cohort studies was assumed to apply across all symptom severity levels. This way a Weibull distribution for recovery was determined for each level of symptom severity; details of the distribution for each level of recovery have been shown in Table 79.

The probability of remission for adults with less severe depression in their first and second year in the depressive episode state of the Markov model was estimated using the Weibull parameters for people with mild depression shown in Table 79. The probability of remission for adults with more severe depression in their first and second year in the depressive episode state of the Markov model was estimated as an average of respective probabilities estimated for people with moderate and severe depression using the Weibull parameters relevant to each population shown in the same table.

People who entered the Markov component via the depressive state were already in non-remission for 12 weeks and therefore their probability of remission in the first and second year following entrance to the Markov depressive state corresponded to model time points between 12-64 weeks and 64-116 weeks, respectively. This was accounted for in the estimation of probability of remission for this sub-group in the economic analysis.

Probability of development of side effects from antidepressant treatment

Treatment with antidepressants is associated with the development of various side effects. These can be serious, including death, attempted suicide or self-harm, falls, fractures, stroke or transient ischaemic attack, epilepsy/seizures, myocardial infarction, hyponatraemia and upper gastrointestinal bleeding (Coupland 2011; Coupland 2018; Jakobsen 2017) or less serious but more common, such as headaches, nausea and other gastrointestinal symptoms, dizziness, agitation, sedation, sexual dysfunction, tremor, sweating, fatigue, dry mouth, sleepiness during the day or sleeplessness, weight gain and arrhythmia (Anderson 2012, Bet 2013; Jakobseon 2017; Uher 2009).

Serious side effects from antidepressants are costly to treat and are likely to reduce the HRQoL of people who experience them more significantly compared with less serious side effects. However, they do not occur frequently. Coupland 2011 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in older people with depression, in a retrospective cohort study that utilised data from 60,746 people aged 65 and over diagnosed as having a new episode of depression, obtained across 570 general practices in the UK between 1996 and 2008. The authors reported that SSRIs were associated with the highest adjusted hazard ratios for falls (1.66, 95%; CIs 1.58 to 1.73) and hyponatraemia (1.52; 95% CIs 1.33 to 1.75) compared with when antidepressants were not being used, while a group of ‘other antidepressants’ defined according to the British National Formulary, which included mirtazapine and venlafaxine, among others, was associated with the highest adjusted hazard ratios for all-cause mortality (1.66; 95% CIs 1.56 to 1.77), attempted suicide or self-harm (5.16; 95% CIs 3.90 to 6.83), stroke/transient ischaemic attack (1.37; 95% CIs 1.22 to 1.55), fracture (1.64; 95% CIs 1.46 to 1.84), and epilepsy/seizures (2.24; 95% CIs 1.60 to 3.15), compared with when antidepressants were not being used. However, for most of these side effects, with the exception of all-cause mortality, the difference in absolute risks between people who received antidepressants and those who were not taking antidepressants during the assessment period was small (lower than 1%) with few exceptions: considering the drugs and classes that were included in the guideline economic analysis, for SSRIs, the absolute increase in risk of falls compared with people who were not taking antidepressants was 2.21%; for mirtazapine, the absolute increase in risk of attempted suicide or self-harm compared with people who did not take

antidepressants was 1.31%. It is noted that these data were derived from older adults with depression, who are likely to have a higher baseline risk for these events compared with younger populations. Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants, is expected to be lower than that observed between respective groups in older populations.

Similarly, Coupland 2018 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in 238,963 adults aged 20-64 years registered with general practices across the UK, who had a first diagnosis of depression between 2000 and 2011. Relative to other antidepressant treatment classes, SSRIs were associated with the highest adjusted hazard ratios for falls (1.48, 95%; CIs 1.39 to 1.59), and fracture (1.30; 95% CIs 1.21 to 1.39), compared with when antidepressants were not being used, while TCAs were associated with the highest adjusted hazard ratios for upper gastrointestinal bleeding (1.43; 95% CIs 1.13 to 1.81) and all cause mortality (1.92; 95% CIs 1.68 to 2.19). Other antidepressants were associated with the highest adjusted hazard ratio for adverse drug reaction (2.81; 95% CIs 2.11 to 3.75). Again, the difference in absolute risks between people who received antidepressants and those who were not receiving antidepressants during the assessment period was very small (e.g. difference 0.001% in falls between people under SSRIs and those under no antidepressant treatment; 0.002% in fractures between people under other antidepressants and those under no antidepressant treatment). Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants is very small and expected to have a negligible impact on costs and HRQoL.

Jakobsen 2017 conducted a systematic review and meta-analysis to assess the effects (including adverse events) of SSRIs versus placebo, 'active' placebo, or no intervention in adult participants with major depressive disorder. The authors reported that SSRIs significantly increased the risks of serious adverse events (odds ratio 1.37; 95% CI 1.08 to 1.75) corresponding to 31/1000 SSRI participants experiencing a serious adverse event compared with 22/1000 control participants (that is a 0.9% difference).

Bet 2013 assessed the risk of common side effects in 846 adults with depression and/or anxiety who received antidepressant monotherapy on 927 occassions, recruited from primary care and specialist mental health settings in the Netherlands. Participants were asked to fill in a short 12-question antidepressant side effect checklist, to self-report patient-perceived common side effects related to their antidepressant therapy. Common side effects included sleeplessness, sleepiness during the day, restlessness, muscle spasms and twitching, dry mouth, profuse sweating, sexual dysfunction, nausea, constipation, diarrhea, weight gain and dizziness. Large percentages of participants in the study reported at least 1 side effect as shown in Table 82.

Table 82. Percentages of people under antidepressant medication reporting zero, 1-2 or 3 side effects and above (from Bet 2013)

Antidepressant	N	% reporting zero side effects	% reporting 1-2 side effects	% reporting ≥ 3 side effects
SSRI	584	36%	33%	31%
TCA	97	28%	33%	39%
Venlafaxine	145	27%	37%	36%
Mirtazapine	58	36%	40%	24%
Other	19	47%	26%	26%

However, it is not known whether these common side effects have a significant impact on HRQoL or lead to the use of additional healthcare resources, e.g. trigger extra GP visits.

Moreover, as this was an uncontrolled study, it cannot be determined whether the side effects reported were indeed a result of antidepressant use.

Cascade 2009 conducted a cross-sectional study on approximately 700 patients receiving SSRI medication, to explore the prevalence of side effects and their impact on HRQoL and healthcare service contacts. The study reported that 38% of study participants experienced a side effect. However, only 25% of the side effects were considered “very bothersome” or “extremely bothersome” by the respondents. Moreover, regardless of how bothersome the side effects were, only 40% of SSRI users mentioned the side effects to their prescribing physicians.

Anderson 2012 estimated the prevalence of 5 common side effects that included headaches, nausea or vomiting, agitation, sedation and sexual dysfunction associated with treatment with antidepressants, by undertaking a retrospective analysis of data derived from a large USA managed care claims form on 40,017 people aged 13 years and above, of whom 36,400 were adults aged 19 years and above, who were newly diagnosed with depression and were initiated on antidepressant monotherapy between 1998 and 2008. Antidepressant groups included, among others, SSRIs, SNRIs, TCAs, phenylpiperazines (which, in 84% of cases were represented by trazodone) and tetracyclic antidepressants (which, in 99% of cases, were represented by mirtazapine). The authors reported that the most common side effect of those assessed was headaches, followed by nausea. The prevalence, rates of experiencing at least one of the 5 common side effects considered in the study, and the estimated length of time of people experiending at least one common side effect for the antidepressants of interest in the economic analysis are shown in Table 83.

Table 83. Prevalence, rates and length of time experiencing at least one common side effect of antidepressants in adults with depression (from Anderson 2012)

Antidepressant	N	% developing ≥ 1 side effect	Rate[1] experiencing ≥ 1 side effect	Length of time with ≥ 1 side effect (years)
SSRI	23,620	7.0%	0.117	1.68
SNRI	4,762	9.2%	0.150	1.63
TCA	776	6.7%	0.152	2.26
Trazodone	1,200	4.7%	0.182	3.84
Mirtazapine	901	6.0%	0.163	2.72

1 per person-years

The committee considered the available evidence and agreed that, although side effects are common, only a proportion of them have a measurable impact on HRQoL and result in an increase in healthcare resource use, and have thus an impact on the cost effectiveness of antidepressant treatments. This is supported by data reported in Cascade 2009. They also expressed the view that studies asking specifically participants to self-report the presence of side effects choosing from a side-effect checklist (such as the Bet 2013 study) tend to overestimate the prevalence of side effects in the study population, in particular as these use uncontrolled study designs and the causality between the antidepressant use and the reported side effects is not established. Using data from Bet 2013 (or other similar study designs) to inform the risk of side effects for pharmacological treatment options in the economic model would likely overestimate the impact of side effects on the relative cost-effectiveness between pharmacological and non-pharmacological treatments, especially as psychological treatments were assumed to have a zero risk of side effects.

On the other hand, the committee expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, such as those reported in Anderson 2012, are more representative of the risk of side effects that have an impact on HRQoL and healthcare costs. Therefore, the committee agreed to use the data reported in Anderson 2012 in order to inform the base-case economic analysis on the risk of side effects from

antidepressant medication use. The economic model took into account the percentage of people experiencing at least 1 side effect for each antidepressant of interest (and their combinations with psychological or physical treatment), and the length of time those people spent experiencing at least 1 side effect. This equalled the duration of the model (2.25 years) for people receiving TCAs, trazodone and mirtazapine. People receiving SSRIs or SNRIs who experienced at least 1 common side effect did so for the first 12 weeks and the 1st year of maintenance treatment [where relevant], and for 0.43 and 0.38, respectively, of their time in 2nd year of maintenance treatment. The model considered the impact of common side effects on treatment costs and people's HRQoL.

After consideration of all available data on the risk of side effects from antidepressant medication use, in a sensitivity analysis, the committee advised that a risk of side effects of 40% be explored, as the higher end of the risk that might have an impact on HRQoL and management costs.

No side effects were considered for people receiving non-pharmacological interventions; however, people receiving non-pharmacological interventions are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Anderson 2012 was an uncontrolled study and did not examine the rate of side effects that were attributable to drugs. Therefore, in this aspect, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness.

The economic model did not incorporate the impact of less common but more severe side effects on costs and people's HRQoL, as this would require most complex modelling and detailed data on the course and management of these side effects. However, omission of these severe side effects is not expected to have considerably affected the results of the economic analysis, due to their low incidence in the study population. Nevertheless, omission of less common but severe side effects from the economic analysis may have potentially somewhat overestimated the cost effectiveness of pharmacological and combined treatments regarding the risk of severe side effects associated with drugs.

Mortality

Depression is associated with an increased risk of mortality relative to the general population. A comprehensive systematic review of 293 studies that assessed the increased risk of people with depression relative to non-depressed individuals, which included 1,813,733 participants (135,007 depressed and 1,678,726 non-depressed) reported a risk ratio of mortality in depressed relative to non-depressed participants of 1.64 (95% CI 1.56 to 1.76). After adjustment for publication bias, the overall risk ratio was reduced to 1.52 (95% CI 1.45 to 1.59) (Cuijpers 2014).

The risk of mortality for people with a new episode of depression was not considered in the decision-tree part of the model (12 weeks), because death (mainly due to suicide) is a rare outcome in RCTs of acute treatments for depression, and no substantial differential data on mortality or, specifically, on the risk of suicide between treatments assessed in the economic analysis are available.

In the Markov component of the model, the adjusted risk ratio of mortality in depressed relative to non-depressed participants (Cuijpers 2014) was applied onto general mortality statistics for the UK population (Office for National Statistics 2020), to estimate the absolute annual mortality risk in people experiencing a depressive episode relative to people not experiencing a depressive episode within each cycle of the model. People with a depressive episode were assumed to be at increased mortality risk due to depression only in the years they experienced a depressive episode. The same mortality risk was assumed for both men and women experiencing a relapse, as no gender-specific data were reported in the study.

People not experiencing a depressive episode in each model cycle were assumed to be subject to the mortality risk of the general UK population.

Utility data and estimation of quality adjusted life years (QALYs)

In order to express outcomes in the form of QALYs, the health states of the economic model (remission, response not reaching remission, no response or relapse) need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic review of utility data on depression-related heath states identified 7 studies that reported utility data corresponding to depression-related health states, which were derived from EQ-5D measurements on adults with depression valued by the general UK population (Kaltenthaler 2006; Koeser 2015; Kolovos 2017; Mann 2009; Sapin 2004; Sobocki 2006 & 2007; Soini 2017). Four of the studies analysed EQ-5D data obtained from adults with depression or common mental health problems participating in RCTs, 3 of which were conducted in the UK (Kaltenthaler 2006, Mann 2009, Koeser 2015) and one in various European countries, including the UK (Soini 2017). One study reported findings from an individual patient-level meta-analysis of EQ-5D data from 1629 adults mainly with depression (although a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands (Kolovos 2017). The other two studies analysed naturalistic primary care EQ-5D data from adults with depression in France (Sapin 2004) and in Sweden (Sobocki 2006 & 2007). All studies reported utility values associated with severity of depression (mild, moderate or severe) and/or states of depression relating to treatment response (response, remission, no response) and were thus relevant to the health states considered in economic modelling conducted for this guideline. All studies defined health states using validated measures of depressive symptoms, such as the BDI, the HAMD-17, the PHQ-9, the MADRS, the CGI, the CES-D, the HADS-D or the IDS-SR (inventory of depressive symptomatology self-report).

An overview of the study characteristics, the methods used to define health states, and the health-state utility values reported by each of the studies is provided in Table 84.

Table 84. Summary of available EQ-5D derived health-state utility data for depression (UK tariff)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
Kaltenthaler 2006	Analysis of EQ-5D and CORE-OM data obtained from 62 people with common mental health problems participating in a multi-centre RCT of supervised self-help CBT in the UK (Richards 2003). CORE-OM data were first mapped onto the BDI, which was used to categorise people into 3 groups of mild to moderate, moderate to severe and severe depression. BDI cut-off scores used for categorisation were not reported. EQ-5D utility value for no depression obtained from age- and gender-matched normal population in the UK (Kind 1999).	No depression Mild to moderate Moderate to severe Severe	NA NR NR NR	0.88 (0.22) 0.78 (0.20) 0.58 (0.31) 0.38 (0.32)
Koeser 2015	Analysis of EQ-5D and HAMD17 data obtained from people with recurrent depression in full or partial remission participating in a RCT of MBCT in the UK (N=123) (Kuyken 2008). Definition of health states by HAMD scores: remission ≤ 7; response 8-14; no response ≥ 15	Remission Response No response	NR NR NR	0.80 (0.02) 0.62 (0.04) 0.48 (0.05)
Kolovos 2017	Analysis of EQ-5D and symptom scale score data (CES-D or MADRS or PHQ-9 or IDS-SR or HADS-D) from 1629 adults mainly with depression (although a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands; 4979 observations considered. Definition of health states by CES-D score: remission 0-15; minor 16-19; mild 20-25; moderate 26-30; severe 31-60; definition of health states by MADRS score: remission 0-8; minor 9-18; mild 19-26; moderate 27-34; severe 35-60; definition of health states by PHQ-9 score: remission 0-4; minor 5-9; mild 10-14; moderate 15-19; severe 20-27; definition of health states by IDS-SR score: remission 0-13; minor 14-25; mild 26-38; moderate 39-48; severe 49-84; definition of health states by HADS-D score: remission 0-7; minor 8-13; mild 14-19; moderate 20-25; severe 26-52.	Minor Mild Moderate Severe Remission	NR NR NR NR NR	0.62 (0.58-0.65) 0.57 (0.54-0.61) 0.52 (0.49-0.56) 0.39 (0.35-0.43) 0.70 (0.67-0.73)
Mann 2009	Analysis of EQ-5D and PHQ-9 data collected from 114 people with depression participating in a cluster RCT of collaborative care across 19 UK primary care practices based in urban and rural communities (Richards 2008). Definition of health states by PHQ-9 score: mild 5-9; moderate 10-14; moderately severe 15-19; severe 20-27	Mild Moderate Moderate to severe Severe	10 24 39 35	0.65 (0.23) 0.66 (0.21) 0.56 (0.27) 0.34 (0.29)
Sapin 2004	Analysis of EQ-5D and MADRS data collected from 250 people with major depression recruited from 95 French primary care practices for inclusion in an 8-week follow-up cohort. Definition of health states by MADRS score: remission MADRS ≤ 12; response at least 50% reduction in the	Response – remission Response – no remission No response	144 34 46	0.85 (0.13) 0.72 (0.20) 0.58 (0.28)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
	MADRS baseline score over 8 weeks. Baseline mean MADRS score 32.7 (SD 7.7)	Baseline	250	0.33 (0.25)
Sobocki 2006 & 2007	Analysis of EQ-5D and CGI-S and CGI-I data collected from 447 adults with depression enrolled in a naturalistic longitudinal observational 6-month study conducted in 56 primary care practices in 5 regions of Sweden. People who started a new or changed antidepressant treatment were eligible for inclusion. Definition of health states by CGI-S score: mild 2-3; moderate 4; severe 5-7; remission 'much or very much improved' score (1-2) combined with clinical judgement	Mild Moderate Severe Remission No remission	110 268 69 207 191	0.60 (0.54 to 0.65) 0.46 (0.30 to 0.48) 0.27 (0.21 to 0.34) 0.81 (0.77 to 0.83) 0.57 (0.52 to 0.60)
Soini 2017	Analysis of EQ-5D, MADRS and HAMD data obtained from people with depression and an inadequate response to a SSRI/SNRI participating in a RCT of vortioxetine versus agomelative in a multi-national RCT conducted in inpatient and outpatient settings in 14 European countries, including the UK (N=501) (Montgomery 2014). Mean MADRS score at baseline: 28.9; remission defined as MADRS score ≤10 or HAMD score ≤7	Baseline Remission No remission	NR NR NR	0.54 0.85 0.62

N: number of participants who provided ratings on each state
BDI: Beck Depression Inventory; CBT: cognitive behavioural therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CGI-I: Clinical Global Impression – Improvement scale; CGI-S: Clinical Global Impression – Severity scale; CI: confidence intervals; CORE-OM: Clinical Outcomes in Routine Evaluation – Outcome Measure); HADS-D: Hospital Anxiety and Depression Scale Depression subscale; HAMD: Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Ssymptomatology Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfullness Based Cognitive Therapy; NR: not reported; PHQ: Patient Health Questionnaire; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; RCT: randomised controlled trial; SD: standard deviation

All reported utility data comply with the NICE criteria on selection of utility data for use in NICE economic evaluations (NICE 2013). The data from Kaltenthaler 2006 were derived following mapping of CORE-OM data onto BDI data; however, the BDI cut-off scores used to determine the health states by depressive symptom severity were not reported, and therefore it is not clear the exact level of symptom severity the resulting utility scores correspond to. All other studies provided details on the scale cut-off scores used to determine the depression-related health states by severity or by response to treatment. Mann 2009 used the original PHQ-9 cut-off scores to determine severity levels of depression. However, it is noted that a PHQ-9 score of 5-9, which corresponded to the state of mild depression according to the PHQ-9 manual, is also below the cut-off point for clinically detected depression (Gilbody 2007a & 2007b). Kolovos 2017 used a number of different scales to determine severity levels of depression in their study sample, with cut-off scores being determined based on the literature and not necessarily to scale manuals.

The economic analysis utilised a combination of data from Sapin 2004 and Sobocki 2006 & 2007 for the states of acute treatment, corresponding to the decision-tree component of the model. This was decided because these two studies provided data for all states included in the model, i.e. less and more severe depression at initiation of treatment or following a relapse, remission, response not reaching remission, and no or inadequate response, and were based on larger study samples compared with other studies providing utility data for similar health states, together with Kolovos 2017 and Soini 2017. It is noted though, that remission in Sobocki 2006 & 2007 was defined as an improved or very much improved score on the CGI-Improvement scale, combined with a clinical judgement by the treating doctor of being in full remission. It is acknowledged that this definition of remission may actually include response to treatment not reaching full remission.

For less severe depression the utility value corresponding to mild depression (0.60) was used, because the study population with less severe depression includes populations with sub-threshold and mild depression. This value for less severe depression (0.60) is consistent with the average of the utility values for minor (0.62) and mild (0.57) depression reported by Kolovos 2017.

For more severe depression, a weighted average of the utility of moderate and severe depression of 0.42 (obtained from Sobocki 2006 & 2007) was used. This estimated value for more severe depression (0.42) is somewhat lower but broadly consistent with the average of the utility values for moderate (0.52) and severe (0.39) depression reported by Kolovos 2017.

For people reaching remission and those with more severe depression responding to acute treatment without reaching remission (i.e. at the end of the decision-tree component of the model) the reported values of 0.85 and 0.72 from Sapin 2004 were used, respectively. It is noted that the value of 0.85 for remission is supported by Soini 2017. On the other hand, both values of remission and response without remission reported in Sapin 2004 are higher than the utility value of remission of 0.70 reported by Kolovos 2017. People with no or inadequate response to treatment were assumed to remain in the same state of less severe (0.60) or more severe (0.42) depression.

For the Markov component of the model, the slightly more conservative value of 0.81, reported by Sobocki 2006 & 2007, rather than the value of 0.85, reported by Sapin 2004 was used for people in remission, to reflect the fact that some people may not be in full remission for the whole model cycle, but may experience some symptoms which, nevertheless, are not adequate to indicate relapse. The values of 0.60 and 0.42 were used for people in the depressive less severe and more severe states, respectively, of the Markov component of the model.

In sensitivity analysis, the values of 0.80 (Koeser 2015) and 0.70 (Kolovos 2017) for remission and 0.62 for response not reaching remission (Koeser 2015) were tested as a

more conservative scenario. It is noted that Soini 2017 also reported a value of 0.62 for people not reaching remission. Moreover, in another scenario, the values of 0.65 and 0.56, reported by Mann 2009 for mild and moderate-to-severe depression were attached to the states of less severe and more severe depression, respectively.

Changes in utility between baseline and endpoint of the decision-tree part of the model were assumed to occur linearly over time.

According to the committee's expert opinion, an average depressive episode lasts 6 months. This estimate is supported by data from a prospective study on 250 adults with a newly originated (first or recurrent) major depressive episode, drawn from a prospective epidemiological Dutch survey on 7,046 people in the general population (Spijker 2002). According to this study, the mean duration of a recurrent episode was 6.1 months (95% CI 4.7-7.5). The economic model assumed that people in the Markov component of the model experiencing a depressive episode that resolved in the next year (i.e. people who spent only a year in the depressive episode and then moved to the remission state in the next cycle), experienced a reduction in their HRQoL for 6 months out of the 12 months of the cycle they remained in the 'depressive' state. Thus, people relapsing to depressive episodes that lasted only for one year were assumed to have the utility of remission for 6 months and the utility of depression (less or more severe) for another 6 months. However, people whose depressive episode was expected to last for 2 cycles (years) or more, were attached the utility of depression over the number of years (1 or 2) they remained in the depressive episode except their final year in the episode, in which they were assumed to have the utility of depression for 6 months and the utility of remission for another 6 months.

Side effects from medication are expected to result in a reduction in utility scores of adults with depression. Sullivan 2004 applied regression analysis on EQ-5D data (UK tariffs) obtained from participants in the 2000 national USA Medical Expenditure Panel Survey to derive age-adjusted utility values for health states associated with depression and with side effects of antidepressants. Health states were defined based on descriptions in the International Classification of Diseases (9th Edition) (ICD-9) and the Clinical Classification Categories (CCC) (clinically homogenous groupings of ICD-9 codes derived by the Agency for Healthcare Research and Quality). Table 85 shows the health states determined by Sullivan 2004 and the corresponding utility values obtained from regression analysis of EQ-5D data. The mean utility decrements due to side effects from antidepressants ranged from -0.044 (diarrhoea) to -0.129 (excitation, insomnia and anxiety), with a mean decrement of -0.087. This mean utility decrement was used in the economic model for people who discontinued treatment due to intolerable side effects, as no specific information on the type and frequency of side effects that led to discontinuation was available across RCTs; it was applied over 5 weeks, based on the committee's advice on the duration of reduction in HRQoL due to intolerable side effects. This utility decrement was also applied to the proportion of people who completed antidepressant treatment and experienced tolerable side effects, over the whole period of antidepressant treatment, i.e. over 12 weeks (acute antidepressant treatment) and the following 2 years (only in those receiving maintenance antidepressant treatment).

Table 85. Summary of EQ-5D derived health-state utility data for side effects from antidepressants (UK tariff)

Study	Definition of health states	Health state	Mean (95% CI)
Sullivan 2004	Censored least absolute deviations (CLAD) regression analysis of EQ-5D data from the 2000 national US Medical Expenditure Panel Survey (MEPS) [http://meps.ahrq.gov/mepsweb/] Definitions of health states Gastrointestinal symptoms (GI): average Diarrhoea: clinical classification categories (CCC) - Agency for Healthcare Research and Quality): 144 regional enteritis Dyspepsia: CCC 138 oesophageal disorders Nausea & constipation: assumed average of GI Sexual: ICD-9 302 sexual disorders Excitation: average Insomnia: assumed equal to anxiety Anxiety: CCC 072 anxiety, somatoform, dissociative disorders Headache: CCC 084 headache Drowsiness & other: assumed average of all side effects Untreated depression ICD-9 311 depressive disorder; CLAD 25% Treated depression: ICD-9 311 depressive disorder; CLAD 75%; baseline utility estimate (not a decrement)	GI symptoms Diarrhoea Dyspepsia Nausea Constipation Sexual Excitation Insomnia Anxiety Headache Drowsiness Other Untreated depression Treated depression	-0.065 (-0.082 to -0.049) -0.044 (-0.056 to -0.034) -0.086 (-0.109 to -0.065) -0.065 (-0.082 to -0.049) -0.065 (-0.082 to -0.049) -0.049 (-0.062 to -0.037) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.115 (-0.144 to -0.087) -0.085 (-0.107 to -0.065) -0.085 (-0.107 to -0.065) -0.268 (-0.341 to -0.205) 0.848 (0.514 to 0.971)

Intervention resource use and costs

Intervention costs were estimated by combining resource use associated with each intervention with appropriate unit costs (drug acquisition costs, healthcare professional unit costs, and costs of equipment and infrastructure, as relevant).

Pharmacological interventions

Pharmacological intervention costs consisted of drug acquisition and GP visit costs. In addition to pharmacological treatment, the model also considered GP care (reflected in RCT arms of the reference treatment, which was TAU for less severe depression and placebo for more severe depression), which comprised GP visits only.

The average daily dosage for each drug was determined according to optimal clinical practice (British National Formulary 2021), following confirmation by the committee's expert opinion to reflect routine clinical practice in the NHS, and was consistent with dosages reported in the RCTs that were included in the RCTs of pharmacological interventions included in the NMA.

Titration was not explicitly considered in the model; however, in each cohort different percentages of people were allowed to receive different drug daily doses to reflect that some people require titration to a higher dose to achieve optimal intervention effects.

Acute pharmacological treatment was administered over 12 weeks. After this period, adults with less severe depression who achieved remission received their drug for another year and had it gradually discontinued (tapered) towards the end of this year; this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over a period of three months (according to routine clinical practice, as advised by the committee) towards the end of year 1 into the remission state of the Markov model. Adults with more severe depression who responded to pharmacological or combined treatment either received maintenance pharmacological treatment with the same drug over 2 years (with gradual discontinuation (tapering) of the drug at the end of year 2 into the Markov model, or received psychological treatment combined with 1 year continuation of the pharmacological treatment and gradual discontinuation (tapering) of the drug at the end of year 1 into the Markov model. Tapering was modelled as a linear reduction in the drug acquisition cost at the end of year 1 or 2 into the remission state of the Markov model, as relevant, and over a period of three months, according to routine clinical practice, as advised by the committee.

Provision of acute pharmacological treatment involved 4 GP visits. Four GP visits were also assumed for people under GP care. These resource use estimates were based on the committee's expert advice; they represent UK optimal routine clinical practice but may be lower than some of the descriptions of medical resource use in pharmacological trial protocols, where resource use is more intensive than clinical practice.

People who received TCAs were assumed to receive a liver function test (LFT) at treatment initiation, and an electrocardiogram (ECG) at treatment initiation and at 6 weeks, according to optimal clinical practice, as advised by the committee.

The drug acquisition costs and the GP unit cost were taken from national sources (Curtis 2020, NHS Business Services Authority 2021). The reported GP unit cost included remuneration, direct care staff costs and other practice expenses, practice capital costs and qualification costs. The latter represented the investment costs of pre-registration and postgraduate medical education, annuitised over the expected working life of a GP; ongoing training costs were not considered due to lack of available information. The unit cost per patient contact was estimated taking into account the GPs' working time as well as the ratio of direct (surgeries, clinics, telephone consultations & home visits) to indirect (referral letters, arranging admissions) patient care, and time spent on general administration. The LFT unit

cost was taken from Akhtar 2014. The ECG cost comprised the cost of the machine and disposables, obtained from National Clinical Guidelines Centre 2016, and 20 minutes of a practice nurse's (Band 5) time. The unit cost for a practice nurse was obtained from Curtis 2020; the cost included wages/salary, salary oncosts, capital and other overheads, In estimating the unit cost per hour of client contact, the ratio of direct (face-to-face) to indirect time (reflecting time for preparation of therapeutic sessions and other administrative tasks) of the practice nurse was also taken into account.

Intervention costs of acute pharmacological treatment and GP care are shown in Table 86.

Table 86. Intervention costs of pharmacological interventions for the acute treatment of adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Drug	Mean daily dosage	Drug acquisition cost[1]	12-week drug cost	Total intervention cost (drug, GP[2], testing[3]) – acute treatment
Sertraline	50% 50mg; 25% 100mg; 15% 150mg; 10% 200mg	50mg, 28 tab, £2.30 100mg, 28 tab, £3.23	£10.30	£166.30
Escitalopram	80% 10mg; 20% 20mg	10mg, 28 tab, £1.40 20mg, 28 tab, £1.55	£4.29	£160.29
Lofepramine	80% 140mg; 20% 210mg	70mg, 56 tab, £16.95	£55.94	£255.83
Duloxetine	80% 60mg; 20% 120mg	60mg, 28 caps, £3.38	£12.17	£168.17
Mirtazapine	30% 15mg; 50% 30mg; 20% 45mg	15mg, 28 tab, £1.73 30mg, 28 tab, £1.74 45mg, 28 tab, £2.11	£5.43	£161.43
Trazodone	80% 150mg; 20% 300mg	150mg, 28 tabs, £2.40	£8.64	£164.64
GP care	Non-applicable	Non-applicable	Non-applicable	£156.00

1 NHS Business and Services Authority 2021
2 GP cost includes 4 visits for active acute pharmacological treatment and 4 visits for GP care; GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020)
3 The cost of lofepramine includes the additional costs of liver function test (LFT) at treatment initiation and electrocardiogram (ECG) at treatment initiation and at 6 weeks. LFT unit cost £3.07 (Akhtar 2014). ECG unit cost £20.41, comprising £3.28 for machine and disposables (National Clinical Guidelines Centre 2016) and £17.13 for 20 minutes of a practice nurse's (Band 5) time (Curtis 2020).

Psychological interventions

Resource use estimates of each psychological therapy in terms of number and duration of sessions and also number of therapists and participants in the case of group interventions were determined by resource use data described in respective RCTs that were included in the NMAs that informed the economic analysis, modified by the committee to represent routine clinical practice in the UK. For most psychological interventions, resource use differed between less severe and more severe depression, according to reported data in the RCTs (see Appendix N) and the committee's expert opinion.

High intensity individual psychological interventions were assumed to be delivered by agenda for change (AfC) band 7 high intensity therapists with a range of background qualifications, including clinical psychologists, counsellors, therapists that started their career as psychological well-being practitioners (PWPs), nurses (the latter is more often seen in secondary care), etc. (NHS England and Health Education England 2016a). High-intensity

interventions delivered in groups, such as group CBT, group BA and group MBCT were assumed to be delivered by one AfC band 7 high intensity therapist, who led and actively facilitated the delivery of the therapy, supported by one AfC band 6 therapist, who observed the delivery of the intervention according to optimal practice, who might be, for example, a PWP who had received additional Improving Access to Psychological Therapies (IAPT) training or a trainee clinical psychologist. Low intensity psychological interventions (self-help with support and individual problem solving) were assumed to be delivered by an AfC band 5 low intensity therapist, who in IAPT services is usually a PWP. These assumptions were based on the committee's expert advice regarding the optimal delivery of psychological interventions in routine clinical practice (predominantly IAPT services), although it was acknowledged that there may be some further variation in the types of therapists delivering psychological interventions across different settings in the UK.

Therapist unit costs were estimated using a combination of data derived from national sources and included wages/salary, salary on-costs, capital and other overheads, qualification costs, and the cost of monthly supervision where relevant. In estimating the unit cost of each type of therapist per hour of client contact, the ratio of direct (face-to-face) to indirect time (reflecting time for preparation of therapeutic sessions and other administrative tasks) of the therapist was also taken into account. This ratio of direct to indirect time was either directly obtained, where available, from national sources (Curtis 2020) or estimated by the committee, using their expertise and after taking into account relevant information in the same document.

Unit cost elements associated with wages/salary, salary on-costs, capital and other overheads were obtained, for each salary band level, from national data for community-based health care scientific and professional staff (Curtis 2020).

Qualification costs were estimated from a variety of sources. The qualification cost of a PWP was assumed to equal a 1-year cost of a AfC Band 4 health professional, which is the salary of PWP trainees (https://www.healthcareers.nhs.uk/explore-roles/psychological-therapies/roles/psychological-wellbeing-practitioner). The qualification cost of a band 7 high intensity therapist is variant, ranging from the qualification cost of a therapist originally trained as PWP to the qualification cost of a clinical psychologist (NHS England and Health Education England 2016b). Other high intensity therapists (counsellors, nurses) have qualification costs that lie between the PWP and the clinical psychologist qualification cost. For simplicity, the mean qualification cost of a band 7 high intensity therapist was calculated as the average between the PWP and the clinical psychologist qualification cost. In addition, for all band 7 high intensity therapists, regardless of their background qualifications, an additional IAPT high intensity therapist training cost of £10,000 (committee's expert advice) was estimated. The qualification cost of a band 6 therapist was estimated as the average between the PWP qualification cost (plus the £10,000 IAPT training cost) and a clinical psychology year 2 trainee cost (NHS England and Health Education England 2016b). Delivery of MBCT by high intensity therapists requires extra training that is not included in qualification costs. This training cost was estimated to approximate on average £18,000 per trainee, based on published fees for MBCT training courses offered by the Universities of Oxford and Bangor. All qualification costs were uplifted, where needed, to 2020 prices using the NHS cost inflation index (Curtis 2020) and annuitised using the formula reported in Netten 1998, assuming a useful working life ranging between 23-25 years, a time from obtaining the qualification until retirement ranging between 41-44 years, and an equal distribution of the useful working life over the period until retirement, due to lack of specific information on this distribution.

Other ongoing training costs of healthcare professionals delivering psychological interventions were not considered, because no relevant data are available. It is noted that this approach is consistent with the lack of consideration of ongoing training costs in the estimation of the reported GP unit cost, also due to lack of relevant data.

The committee also advised that supervision costs be considered in the estimation of the therapist unit costs, as supervision is essential for the delivery of psychological therapies and may incur considerable costs. According to the British Association for Behavioural and Cognitive Therapies (2016), high intensity therapists should receive regular supervision in groups of no more than 6 participants, with a mean duration of 1.5 hour per month for a full time practitioner. Based on this information, supplemented with the committee's expert advice, the supervision cost estimated for high intensity therapists comprised 1.5 hour of individual supervision per month, delivered by a Band 7 (50%) or Band 8a (50%) therapist. Low intensity therapists were assumed to receive 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4 by a band 6 PWP. The supervision cost included the cost of the supervisor's time, but not the cost of the supervised therapist's time, as this is indirectly included in the unit cost of each therapist.

Using the above information and assumptions, the unit costs of each therapist providing psychological interventions considered in the model are summarised in Table 87. Details on the methods of estimation of each unit cost are provided in Table 88, Table 89, and Table 90.

Table 87. Unit costs of therapists delivering psychological interventions used in the guideline economic analysis (2020 prices)

Type of therapist	Unit cost[1]	Details
PWP (Band 5)	£50	See Table 88
High intensity therapist Band 7	£110	See Table 89
High intensity MBCT therapist Band 7	£112	See Table 89
Therapist Band 6	£89	See Table 90
Therapist Band 6 with training in MBCT	£91	See Table 90

1 per hour of client contact
MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 88. Unit cost of psychological well-being practitioner band 5 (2020 prices)

Cost element	Cost	Source
Wages – salary – annual	£25,023	Curtis 2020; costs for community-based scientific and professional staff AfC band 5
Salary on-costs – annual	£7,437	
Overheads, staff – annual	£7,953	
Overheads, non-staff – annual	£12,400	
Capital overheads – annual	£5,237	
Qualifications – annuitised	£4,141	Based on a 1-year cost of £50,659 for community-based scientific and professional staff AfC band 4 (salary level of PWP trainee) (Curtis 2020), annuitised using the formula by Netten 1998, assuming a useful working life of 25 years, a period life up to retirement of 44 years, and an equal distribution of the useful working life over the period until retirement.
Supervision – annual	£1,249	Assuming 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4, for a period of 42.6 weeks per year (working time per year), by a band 6 PWP (with unit cost per hour estimated using salary cost elements from Curtis 2020 plus annuitised qualification cost of £4,141).
SUM of unit costs	**£63,440**	
Working time (hours/year)	1,599	Curtis 2020
Total cost per hour	**£40**	

Cost element	Cost	Source
Ratio of direct to indirect time*	1-to-0.25	assumption - committee's expert opinion
Cost/hour of direct contact	**£50**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change

Table 89. Unit cost of high intensity therapist band 7 (with and without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£41,226		Curtis 2020; costs for community-based scientific and professional staff AfC band 7
Salary on-costs – annual	£13,024		
Overheads, staff – annual	£13,291		
Overheads, non-staff – annual	£20,723		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£10,821	£12,485	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from 3-year training cost of clinical psychologist (NHS England and Health Education England 2016b) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 23 years, a time up to retirement of 42 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from Curtis 2020 and qualification costs for therapists with/without MBCT training).
SUM of unit costs	**£105,359**	**£107,038**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£66**	**£67**	

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£110**	**£112**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 90. Unit cost of therapist band 6 (with/without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£33,734		Curtis 2020; costs for community-based scientific and professional staff AfC band 6
Salary on-costs – annual	£10,440		
Overheads, staff – annual	£10,823		
Overheads, non-staff – annual	£16,875		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£7,527	£9,190	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist trainee in year 2. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from training cost of clinical psychologist up to 2 years of training (NHS England and Health Education England 2016b), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from

Cost element	Cost		Source
	without MBCT training	with MBCT training	
			Curtis 2020 and qualification costs for band 7 and 8 therapists with/without MBCT training).
SUM of unit costs	**£85,673**	**£87,352**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£54**	**£55**	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£89**	**£91**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

In addition to therapists' time, the intervention costs of all psychological therapies included an initial GP visit for referral to psychological services. It is acknowledged that this assumption (100% GP referral to psychological services) is a conservative estimate, as a proportion of people with a new episode of depression may self-refer to psychological services. On the other hand, it is possible that some of the people self-referring may have consulted their GP prior to self-referral. The impact of this assumption was tested in a sensitivity analysis, under a scenario that assumed 100% self-referral to psychological services.

Moreover, the intervention costs of computerised self-help therapies included the cost of the provider of digital mental health programmes and related equipment required for their delivery (personal computers [PCs] and capital overheads). The cost of provision of a computerised CBT programme per client by the main provider of digital mental health programmes comprised a fixed fee of £39, which is independent of the number of sessions attended (committee's expert advice). The annual costs of hardware and capital overheads (space around the PC) were based on reported estimates made for the economic analysis undertaken to inform the NICE Technology Appraisal on computerised CBT for depression and anxiety (Kaltenthaler 2006). Kaltenthaler 2006 estimated that one PC can serve around 100 people with mental disorders treated with computerised programmes per year. Assuming that a PC is used under full capacity (that is, it serves no less than 100 people annually, considering that it is available for use not only by people with depression, but also by people with other mental health conditions), the annual cost of hardware and capital overheads was divided by 100 users, leading to a hardware and capital overheads cost per user of £14 (2020 price). It must be noted that if users of such programmes can access them from home or a public library, then the cost of hardware and capital overheads to the NHS is zero.

Details on the resource use and total costs of psychological interventions for less and more severe depression are provided in Table 91.

Table 91. Intervention costs of psychological therapies for adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Intervention	Resource use details	Total intervention cost per person[1]
Computerised CBT without support – LS and MS depression	Fixed cost of provider of digital mental health programmes is £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006). Cost includes 30 minutes of setup time by a band 5 PWP.	£78 + £39
Computerised CBT with support – LS and MS depression	1 session of 30 minutes and 7 sessions of 15 minutes each = 2.25 therapist hours per service user (band 5 PWP); fixed cost of provider of digital mental health programmes £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006)	£165 + £39
BA individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
BA group – LS depression	8 sessions x 90 minutes each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 24 therapist hours per group and 3 therapist hours per service user	£297 + £39
CBT individual < 15 sessions – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
CBT group < 15 sessions – LS depression	8 sessions x 90 minutes each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 24 therapist hours per group and 3 therapist hours per service user	£297 + £39
Problem solving individual – LS depression	1 session of 60 minutes and 5 sessions of 30 minutes = 3.5 therapist hours per service user (band 5 PWP)	£174 + £39
Non-directive counselling individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
IPT individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
Short term PDPT individual – LS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
MBCT group – LS depression	8 sessions x 2 hours each; 2 MBCT therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 32 therapist hours per group and 4 therapist hours per service user	£405 + £39
BA individual – MS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
CBT individual ≥ 15 sessions – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39
CBT group < 15 sessions – MS depression	10 sessions x 1.5 hours each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 30 therapist hours per group and 3.75 therapist hours per service user	£372 + £39
Problem solving individual – MS depression	1 session of 60 minutes and 8 sessions of 30 minutes = 5 therapist hours per service user (band 5 PWP)	£248 + £39

Intervention	Resource use details	Total intervention cost per person[1]
Non-directive counselling individual – MS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
IPT individual – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39
Short term PDPT individual – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39

[1] Cost of psychological intervention plus 1 GP referral visit, at a GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020); cost of psychological intervention based on resource use combined with unit cost of the appropriate level of therapist, estimated as described in Table 88, Table 89 and Table 90.
BA: behavioural activation; CBT: cognitive behavioural therapy; HI: high intensity; IPT: interpersonal psychotherapy; LS: less severe; MS: more severe; PDPT: psychodynamic psychotherapy; PWP: psychological well-being practitioner

Physical interventions

Resource use estimates for supervised high intensity exercise (individual and group) and for acupuncture were estimated based on resource use data described in respective RCTs that were included in the guideline NMA that informed the economic analysis (see Appendix N), modified by the committee to represent routinely offered exercise programmes in the UK. It is acknowledged that exercise programmes are not routinely offered within the NHS context, although people with depression may be advised to attend exercise programmes at their own expense. Nevertheless, in order to consider the potential cost of such interventions to the NHS, exercise programmes were assumed to be delivered by an AfC band 5 practitioner, with a unit cost equivalent to that of PWP (although it is acknowledged that a different professional group, and not a PWP, may deliver this intervention within the NHS). Acupuncture is also not routinely offered for the management of depression within the NHS setting. In order to consider the potential cost of acupuncture to the NHS, it was assumed that this is delivered by AfC band 6 physiotherapists, which is the salary band level at which a practitioner can carry out invasive interventions. For acupuncture, an additional £1 cost per session was included for consumables (disposable needles).

The PWP unit cost was estimated at £50 per hour of client contact as shown in Table 88. The cost of band 6 physiotherapist was estimated at £71 per hour of client contact as shown in Table 92.

Table 92. Unit cost of physiotherapist band 6 (2020 prices)

Cost element	Cost	Source
Wages – salary – annual	£33,734	Curtis 2020; costs for community-based scientific and professional staff AfC band 6
Salary on-costs – annual	£10,440	
Overheads, staff – annual	£10,823	
Overheads, non-staff – annual	£16,875	
Capital overheads – annual	£5,237	
Qualifications – annuitised	£5,446	
SUM of unit costs	**£82,555**	
Working time (hours/year)	£1,599	
Total cost per hour	**£52**	
Ratio of direct to indirect time*	1-to-0.37	
Cost/hour of direct contact	**£71**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change

In addition, the intervention costs of all physical treatments included an initial GP visit for referral to each service.

Details on the resource use and total costs of physical interventions for less and more severe depression are provided in Table 93.

Table 93. Intervention cost of physical interventions for adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Intervention	Resource use details	Total intervention cost per person[1]
Exercise individual – LS depression	25 sessions x 1 hour each = 25 therapist hours per service user (unit cost equivalent to band 5 PWP)	£1,240 + £39
Exercise group – LS depression	30 sessions x 1 hour each; 1 therapist (unit cost equivalent to band 5 PWP) and 8 participants per	£186 + £39

Intervention	Resource use details	Total intervention cost per person[1]
	group = 30 therapist hours per group and 3.75 therapist hours per service user	
Exercise individual – MS depression	30 sessions x 1 hour each = 30 therapist hours per service user (unit cost equivalent to band 5 PWP)	£1,488 + £39
Exercise group – MS depression	40 sessions x 1 hour each; 1 therapist (unit cost equivalent to band 5 PWP) and 8 participants per group = 40 therapist hours per group and 5 therapist hours per service user	£248 + £39
Acupuncture – MS depression	25 sessions x 30 minutes each = 12.5 acupuncturist hours per service user (band 6 physiotherapist) plus cost of needles of £1 per session (assumption)	£909 + £39

[1] Cost of physical interventions plus 1 GP visit, at a GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020); cost of physical interventions based on resource use combined, as relevant, with the unit cost of a band 5 PWP, estimated at £42 per hour of direct client contact as described in Table 88, or the unit cost of a band 6 physiotherapist, as described in Table 92.
LS: less severe; MS: more severe; PWP: psychological well-being practitioner

Combined pharmacological and psychological interventions

The intervention cost of combined interventions was estimated as the sum of the intervention costs of the individual treatment components.

In cohorts receiving a pharmacological intervention combined with a psychological or physical intervention, no extra GP visits were added in the psychological or physical intervention, since people were already receiving GP care as part of their antidepressant treatment.

Intervention costs in people who discontinued treatment early

People who discontinued treatment early consumed part of the acute intervention resources: people who discontinued pharmacological treatment incurred the cost of 1 GP visit and 1 pack of drugs (and lab testing at initiation of treatment, where relevant); people who discontinued a high intensity individual psychological therapy incurred the cost of 25% of the intended number of visits plus the initial GP visit; people who discontinued computerised CBT incurred the cost of the initial GP visit, the full fixed cost of the provider of the programme plus the cost of 2 of the therapist contacts if they attended a therapist supported programme. People under GP care who discontinued treatment incurred the cost of 1 GP visit. People who discontinued a group psychological therapy or group exercise were assumed to incur the full cost of therapy, since participants in a group intervention are not replaced in the group if they discontinue and therefore the full cost of therapy per participant is incurred, whether the participant attends the full course or not.

Interventions received as continuation treatments aiming at preventing relapses

People with more severe depression that responded to treatment moved on to an appropriate relapse preventive intervention, the cost of which was based on the resource use estimates made to inform the guideline economic modelling of interventions for relapse prevention that is described in Evidence review C, appendix J.

An overview of the resource use and cost estimates of relapse preventive interventions received by the cohorts who responded to treatment of a new depressive episode is shown in Table 94.

Table 94. Intervention costs of continuation treatments considered in the guideline economic analysis on relapse prevention (2020 prices)

Maintenance treatment	Resource use	Total cost
Sertraline **Escitalopram** **Lofepramine** **Duloxetine** **Mirtazapine** **Trazodone**	Same dosage as in acute treatment with drug tapering represented as a linear reduction in dosage over the 3 last months of maintenance treatment (which lasted 2 years in total) plus 6 GP visits in the 1st year and 3 GP visits in the 2nd year, plus 3 GP visits during tapering	£552 £503 £924 £567 £512 £538
GP care & AD drug tapering	3 GP visits in the first year plus 1 extra GP visit for drug tapering plus linear reduction of the drug dosage over a month; 1 GP visit in the second year	£196-£205 depending on drug
4 sessions of individual psychological therapy	4 individual sessions lasting 1 hour each = 4 therapist hours per service user (HI therapist Band 7), plus 2 GP visits	£517 + £78
MBCT	8 group sessions + 4 group booster sessions lasting 2 hours each; 2 MBCT therapists (1 HI Band 7 and 1 Band 6) and 8 participants per group, plus 2 GP visits	£608 + £78
Group CBT	8 group sessions lasting 2 hours each; 2 therapists (1 HI Band 7 and 1 Band 6) and 8 participants per group, plus 2 GP visits	£398 + £78
GP care	3 GP visits in the first year and 1 GP visit in the second year	£156

Unit costs of drugs and health professionals shown in Table 86 and Table 87, respectively.
AD: antidepressant; CBT: cognitive behavioural therapy; HI: high intensity; MBCT: mindfulness-based cognitive therapy

Other healthcare costs considered in the economic analysis

Healthcare costs associated with the Markov states of remission and depressive episode

The costs of the states of remission and depressive episode in the Markov component of the economic model were estimated using primarily data from Byford 2011. This was a naturalistic, longitudinal study that aimed to estimate the health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database between 2001 and 2006. The study analysed 12-month healthcare resource use data on 88,935 adults with depression and in receipt of at least two antidepressant prescriptions (for amitriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) in the first 3 months after the index prescription. The study provided data on resource relating to medication (antidepressant use and concomitant medication such as anxiolytics, hypnotics, mood stabilizers and neuroleptics), GP contacts, psychological therapy, psychiatrist and other specialist contacts, inpatient stays and accident and emergency attendances. Data were reported separately for people who remitted within 12 months, and those who did not remit.

The study provided cost data for the subgroup of study participants with severe depression. Using the cost figures reported in the paper and the numbers of people in each remission status and symptom severity level it was possible to estimate costs for adults with non-severe (mild or moderate) depression. The cost figures corresponding to each remission status and level of symptom severity are shown in Table 95.

Table 95. Healthcare costs of adults with depression who remitted within 12 months and people who did not remit within 12 months from index prescription, by symptom severity status, as reported in Byford 2011

Remission status	Cost and N in each category		
	All levels of symptom severity N = 88,935 (reported costs)	Severe depression N = 8,106 (reported costs)	Mild or moderate depression N = 80,829 (estimated costs)
People who remitted within 12 months	£656 (N=53,654)	£749 (N=4,423)	£648 (N= 49,231)
People who did not remit within 12 months	£973 (N=35,281)	£1,037 (N=3,683)	£966 (N=31,598)

Costs for severe depression could be potentially attached to states experienced by adults with more severe depression in the economic model, while costs for mild or moderate depression could be potentially attached to states experienced by adults with less severe depression. However, it can be seen that the mean healthcare costs of people with mild or moderate depression were very similar (only 1% lower) to the respective mean healthcare costs of all participants in the study. Mean costs of people with severe depression were somewhat higher than the mean respective costs of the total study sample (7% higher for people who did not remit and 14% higher for people who remitted). These differences in costs according to symptom severity were not considered to have a substantial impact on the model results. Moreover, adults with severe depression in the study are likely to have more severe symptoms than adults with more severe depression in the economic analysis (which includes people with moderate and severe depression). Therefore, it was decided to use the mean total costs reported in the study for the whole study sample (regardless of symptom severity) as the basis for estimation of healthcare costs for people with both less severe and more severe depression. These costs were tested in sensitivity analysis.

Healthcare resource use and cost data reported for the whole study sample in Byford 2011 were modified following the committee's advice and attached to the health states of the Markov component of the economic model: data on people in a depressive episode who remitted within 12 months in the study were attached onto people in the depressive state of the model if they were expected to move to the remission state in the following year. Resource use and cost data on people who did not remit within 12 months in the naturalistic study were used as the basis for estimating healthcare costs incurred by people who were expected to remain in the depressive episode state in the next cycle of the model. Costs incurred after remission was achieved in the naturalistic study were used to estimate annual healthcare costs associated with the remission state of the model. In people that experienced remission whilst being in the Markov component of the model (i.e. not those entering the Markov component in the remission state), an annual cost of maintenance drug treatment plus the cost of 3 GP visits was added to this figure for the first year of remission only, to reflect optimal maintenance antidepressant therapy after remission was achieved, as discussed in Evidence review C, appendix J.

Following the committee's advice, some of the resource use and drug acquisition cost data reported in the paper were modified, to reflect current clinical practice and the fact that some drugs are now available off-patent. Where detailed resource use data were provided, these were combined with appropriate 2020 unit costs; where only cost figures were available, these have been uplifted to 2020 prices using the hospital & community health services (HCHS) index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020), so that all costs in the guideline economic analysis reflect 2020 prices.

Details on the methods used to modify and update the resource use and unit costs reported in Byford 2011 in order to estimate costs associated with the 2 states of the Markov model

component are provided in Evidence review C, appendix J. The healthcare costs associated with each health state in the Markov component of the guideline economic model of treatments for new episodes of depression are presented in Table 96.

Table 96. Annual healthcare costs associated with the states of remission and depressive episode in the guideline economic analysis (2020 prices)

Health state	Cost	Comments
Depressive episode – people expected to remain in this state in the next model cycle	£1,449	Includes costs of antidepressants, concomitant medication, GP visits or phone calls, psychological therapy contacts, psychiatrist or other specialist contacts, hospitalisations, and accident and emergency attendances. Costs estimated by multiplying relevant resource use for non-remitters and remitters reported in Byford 2011 with appropriate national unit costs for 2020 (Curtis 2020). Treatment costs estimated by published sources of relevant resource use and costs Radhakrishnan 2013; NHS England 2016. All costs expressed in 2020 prices using the hospital & community health services inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020) and the estimated net ingredient cost per antidepressant or concomitant medication prescription item ratio for 2015:2006, estimated using national data (NHS The Information Centre 2007; NHS Business Services Authority 2020 (Details provided in Evidence review C, table 110)
Depressive episode – people expected to move to the remission state in the next model cycle	£1,102	
Remission	£528	3-month healthcare cost of people having achieved remission obtained from graphs published by Byford 2011, read using digital software (http://www.digitizeit.de), extrapolated to 12 months and uplifted to 2020 prices using the HCHS inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020).
Maintenance antidepressant therapy – 1st year extra cost	£136	Additional cost reflecting optimal duration of maintenance antidepressant therapy following remission, comprising an annual antidepressant drug cost equal to that estimated for remitters and 3 GP contacts at the GP unit cost of £39 per patient contact lasting 9.22 minutes for 2020 (Curtis 2020). This was considered only in people experiencing a remission while being in the Markov model, not in those entering the Markov model in the remission state; the latter received an active relapse preventive intervention or no relapse preventive intervention.

Treatment costs in people who discontinued initiated treatment early in the decision-tree component of the model

People who switched to a mixture of available treatments following early treatment discontinuation were assumed to incur a 'mixed treatment' cost over 8 out of the 12 weeks of the decision-tree. This cost was estimated as a proportion (8/52) of the annual cost of a depressive episode (for people remaining in depression for longer than one model cycle) that was estimated for the Markov component of the model, which equalled £223.

The cost of no treatment over 8 weeks was assumed to be zero; over this period people receiving no treatment were assumed to incur no depression-specific costs. However, those who entered the depressive state of the Markov model were assumed to re-start receiving depression-related care and incur the cost associated with the depressive Markov state.

Cost of management of intolerable and tolerable common side effects from antidepressant treatment

People who discontinued antidepressant or combined treatment due to intolerable side effects were assumed to have one extra GP contact costing £39 (Curtis 2020).

People who experienced common side effects were assumed to have one extra GP contact every 3 months costing £39 (Curtis 2020) and to consume a cost of £10 per year for medication relating to the management of common side effects (for example, paracetamol or anti-inflammatory drugs for headaches).

Discounting

Costs and benefits were discounted at an annual rate of 3.5% in the second year of the Markov component of the model as recommended by NICE 2014.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates); this approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each intervention) were calculated by averaging across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The distributions of the odds ratios of relative effects of all treatments versus the reference treatment were obtained from the respective NMAs, defined directly from values recorded in each of the 10,000 iterations performed in OpenBUGS.

Beta distribution was assigned to the following parameters: proportion of women in the study sample; the baseline risks of discontinuation and discontinuation due to side effects in those discontinuing; the proportion of people experiencing side effects; the probability of responders with more severe depression who moved to the remission state of the Markov model; and the probability of moving to specific relapse preventive treatments following successful completion of acute treatment (in adults with more severe depression). Utility values were also assigned a beta distribution after applying the method of moments on data reported in the relevant literature.

The 12-month probabilities of response and remission at various levels of symptom severity were given a beta distribution. The probabilities of response and remission following acute treatment, as well as the probability of remission and the baseline risk of relapse after a single (first) episode that were utilised in the Markov component of the model were determined by a Weibull distribution, as described earlier. The probability distributions of the Weibull parameters (gamma and lambda) of recovery (‘baseline recovery’) that came from evidence synthesis in OpenBUGS were defined directly from values recorded in each of 10,000 iterations performed in OpenBUGS. This allowed the correlation between the Weibull parameters to be taken into account. The 12-month probabilities of response and remission at various levels of symptom severity and the 12-month probability of ‘baseline recovery’ estimated from data synthesis were used to estimate hazard ratios of each parameter versus baseline recovery (see Table 79). These hazard ratios were then applied onto the ‘baseline’ lambda value obtained from data synthesis, in order to maintain the correlation between the lambda parameters for response and remission at each severity level and the gamma parameter that was estimated from data synthesis.

The hazard ratio of the risk of relapse for every additional depressive episode that was utilised in the Markov element of the model was given a log-normal distribution. The risk ratio of mortality was also assigned a log-normal distribution.

Uncertainty in intervention costs was taken into account by assigning probability distributions to the number of GP contacts and the number of individually delivered psychological therapy sessions. Different distributions around the number of GP contacts were used for people receiving active pharmacological interventions and for those receiving only GP care (reference treatment). The number of therapist sessions per person attending group psychological interventions was not assigned a probability distribution because the number of group sessions remains the same, whether a participant attends the full course of treatment or a lower number of sessions. Drug acquisition costs were not given a probability distribution as these costs are set and characterised by minimal uncertainty. However, if people receiving maintenance pharmacological therapy attended fewer GP visits than the mode in the second year of maintenance treatment, then they were assumed to be prescribed smaller amounts of medication than optimal, and to subsequently incur lower drug acquisition costs. Unit costs of healthcare staff (GPs and therapists delivering psychological and physical interventions) were assigned a normal distribution.

Healthcare costs associated with discontinuation of acute treatment and the states of relapse and remission in the Markov element of the model were assigned a gamma distribution.

Table 97 reports the mean values of all input parameters utilised in the economic model and provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

A number of deterministic one-way sensitivity analyses were undertaken to explore the impact of alternative hypotheses on the results. The following scenarios were explored:

- Change in the number of previous episodes, resulting in a change in the risk of relapse in the Markov component of the model; the number of previous episodes was increased from 0 to 2 in adults with less severe depression and was varied between 0 and 5 in adults with more severe depression
- Use of higher utility values of 0.65 and 0.56 for less severe and more severe depression, respectively, reported in Mann 2009
- Use of the value of 0.70 for remission reported in Kolovos 2017; and 0.62 for response not reaching remission reported in Koeser 2015.
- Changing the cost of a depressive episode (relapse) by ±50%
- Change in the baseline discontinuation of SSRIs by ± 20%.
- Use of a probability of developing side effects of 0.40 throughout the period people under pharmacological antidepressant treatment received antidepressants.
- Assuming that 100% of people attending psychological services have self-referred (instead of being referred to services by their GP)
- Assuming the same number of sessions across all individual high intensity psychological interventions, either a lower number of sessions (8 sessions for less severe depression and 12 sessions for more severe depression) or a higher number of sessions (12 sessions for less severe depression and 16 sessions for more severe depression). At the same time, the number of group psychological interventions was doubled, to explore the impact of change in resource use intensity on the relative cost effectiveness between group and individual psychological interventions.

In addition, a probabilistic bias-adjusted economic analysis was conducted for adults with more severe depression, using bias-adjusted data on discontinuation for any reason and response in completers, derived from the bias-adjusted NMA models, as described earlier.

The bias-adjusted data for adults with more severe depression that were used in the probabilistic sensitivity analysis are also shown in Table 97.

Table 97. Input parameters (deterministic values and probability distributions) that informed the economic models of interventions for the treatment of a new depressive episode in adults with less severe depression and adults with more severe depression

Input parameter	Deterministic value	Probability distribution	Source of data - comments
General characteristics of population			
Age of onset (years)	32	No distribution	Kessler 2005; Fernandez 2015; committee's advice
Mean interval between episodes (years)	2	No distribution	Committee's expert opinion
Number of previous episodes			
- less severe depression	0	No distribution	Committee's expert advice
- more severe depression	2	No distribution	
Proportion of women	0.56	Beta: α=279; β=219	McManus 2016; weighted prevalence of depression 2.9% in men, 3.7% in women, survey sample N=7,546
Adults with less severe depression: discontinuation – log-odds ratios vs sertraline			
Loferpamine	0.21	-1.32 to 1.78	Guideline NMA; distribution based on 10,000 iterations
cCBT without or with minimal support	-0.64	-5.55 to 2.92	
cCBT with support	-0.65	-5.61 to 2.94	
Individual BA	-1.80	-7.09 to 2.55	
Group BA	-0.33	-5.26 to 3.33	
Individual CBT (<15 sessions)	-1.42	-6.30 to 2.17	
Group CBT (<15 sessions)	-0.94	-5.95 to 2.81	
Individual problem solving	-0.50	-5.41 to 3.15	
Non-directive counselling	-1.80	-6.86 to 2.01	
Individual IPT	-0.56	-5.63 to 2.79	
Individual short-term PDPT	-2.12	-7.17 to 1.75	
Group MBCT	-0.83	-5.76 to 2.82	
Supervised HI individual exercise	-1.43	-6.54 to 2.35	
Supervised HI group exercise	-0.86	-5.89 to 2.87	
GP care [TAU]	-0.81	-5.77 to 2.70	
Adults with less severe depression: discontinuation due to side effects in those discontinuing treatment – log-odds ratios vs SSRIs			
TCAs (lofepramine)	3.32	-0.22 to 6.88	Guideline NMA; distribution based on 10,000 iterations

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Adults with less severe depression: response in completers – log-odds ratios vs GP care (TAU)			
Sertraline	2.01	0.03 to 3.98	Guideline NMA; distribution based on 10,000 iterations
Loferpamine	3.15	0.04 to 6.23	
cCBT without or with minimal support	0.85	-0.47 to 2.15	
cCBT with support (class effect)	0.95	-1.03 to 2.86	
Individual BA	1.83	-0.29 to 3.93	
Group BA	3.02	1.05 to 5.02	
Individual CBT (<15 sessions)	1.79	0.15 to 3.43	
Group CBT (<15 sessions)	4.63	2.44 to 6.87	
Individual problem solving	0.26	-1.14 to 1.66	
Non-directive counselling	1.16	-2.55 to 4.79	
Individual IPT	1.04	-0.28 to 2.36	
Individual short-term PDPT	1.63	-1.18 to 4.45	
Group MBCT	1.72	0.00 to 3.40	
Supervised HI individual exercise	1.16	-0.47 to 2.79	
Supervised HI group exercise	1.43	-0.12 to 2.95	
No treatment	-0.16	-1.43 to 1.10	
Adults with more severe depression: discontinuation, base-case analysis – log-odds ratios vs escitalopram			
Lofepramine	0.10	-0.18 to 0.33	Guideline NMA; distribution based on 10,000 iterations; data for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥ 15sessions) + imipramine; data for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Duloxetine	0.14	-0.02 to 0.33	
Mirtazapine	0.06	-0.14 to 0.26	
Trazodone	0.35	0.10 to 0.60	
cCBT without or with minimal support	-0.22	-1.08 to 0.67	
cCBT with support	-0.19	-0.90 to 0.51	
Individual BA	-0.65	-1.33 to 0.03	
Individual CBT (≥15 sessions)	-0.43	-0.88 to 0.01	
Group CBT (<15 sessions)	-0.31	-1.32 to 0.68	
Individual problem solving	-0.64	-1.47 to 0.16	
Non-directive counselling	-0.35	-1.15 to 0.45	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Individual IPT	-0.68	-1.51 to 0.15	
Individual short-term PDPT	0.04	-0.85 to 0.95	
Supervised HI individual exercise	0.14	-0.88 to 1.23	
Supervised HI group exercise	0.26	-0.42 to 0.93	
Traditional acupuncture	-0.25	-1.28 to 0.64	
Individual CBT (≥ 15sessions) + escitalopram	-0.32	-1.22 to 0.51	
Traditional acupuncture + escitalopram	-0.27	-1.51 to 0.96	
GP care [placebo]	0.13	0.02 to 0.24	
Adults with more severe depression: discontinuation, bias-adjusted analysis – log-odds ratios vs escitalopram			
Lofepramine	0.11	-0.16 to 0.34	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥ 15sessions) + imipramine; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Duloxetine	0.14	-0.01 to 0.33	
Mirtazapine	0.07	-0.13 to 0.26	
Trazodone	0.34	0.08 to 0.59	
cCBT without or with minimal support	-0.19	-1.10 to 0.73	
cCBT with support	-0.16	-0.91 to 0.58	
Individual BA	-0.68	-1.39 to 0.02	
Individual CBT (≥15 sessions)	-0.36	-0.82 to 0.10	
Group CBT (<15 sessions)	-0.21	-1.30 to 0.88	
Individual problem solving	-0.71	-1.62 to 0.18	
Non-directive counselling	-0.33	-1.15 to 0.51	
Individual IPT	-0.64	-1.49 to 0.18	
Individual short-term PDPT	0.11	-0.84 to 1.08	
Supervised HI individual exercise	0.21	-0.82 to 1.30	
Supervised HI group exercise	0.30	-0.41 to 1.01	
Traditional acupuncture	-0.37	-1.36 to 0.57	
Individual CBT (≥ 15sessions) + escitalopram	-0.28	-1.19 to 0.59	
Traditional acupuncture + escitalopram	-0.14	-1.39 to 1.10	
GP care [placebo]	0.08	-0.03 to 0.21	
Adults with more severe depression: discontinuation due to side effects in those discontinuing treatment – log-odds ratios vs SSRIs			

Input parameter	Deterministic value	Probability distribution	Source of data - comments
TCAs (lofepramine)	0.69	0.18 to 1.21	Guideline NMA; distribution based on 10,000 iterations; risk for individual CBT (≥ 15sessions) + escitalopram and for traditional acupuncture + escitalopram assumed to equal that for escitalopram alone
SNRIs (duloxetine)	0.40	-0.07 to 0.86	
Mirtazapine	0.03	-0.37 to 0.43	
Trazodone	0.26	-0.24 to 0.77	
Adults with more severe depression: response in completers, base-case analysis – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.81	0.60 to 1.00	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + any SSRI; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + any SSRI
Lofepramine	1.14	0.81 to 1.46	
Duloxetine	0.99	0.75 to 1.23	
Mirtazapine	1.02	0.70 to 1.33	
Trazodone	0.68	0.28 to 1.09	
cCBT without or with minimal support	0.12	-1.79 to 1.89	
cCBT with support	0.82	-0.36 to 2.02	
Individual BA	1.42	0.09 to 2.77	
Individual CBT (≥15 sessions)	1.22	0.55 to 1.89	
Group CBT (<15 sessions)	0.99	-0.27 to 2.21	
Individual problem solving	2.16	0.78 to 3.55	
Non-directive counselling	1.50	0.08 to 2.92	
Individual IPT	0.72	-0.31 to 1.73	
Individual short-term PDPT	1.58	-0.94 to 4.06	
Supervised HI individual exercise	2.40	-0.31 to 5.05	
Supervised HI group exercise	2.02	0.17 to 4.08	
Traditional acupuncture	-0.17	-1.38 to 1.01	
Individual CBT (≥ 15sessions) + escitalopram	1.84	0.61 to 3.00	
Traditional acupuncture + escitalopram	4.07	2.97 to 5.17	
No treatment	-0.27	-1.40 to 0.86	
Adults with more severe depression: response in completers, bias-adjusted analysis – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.65	0.43 to 0.85	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + any SSRI; effect for
Lofepramine	0.87	0.53 to 1.20	
Duloxetine	0.84	0.59 to 1.08	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Mirtazapine	0.77	0.44 to 1.10	traditional acupuncture + escitalopram borrowed from traditional acupuncture + any SSRI
Trazodone	0.50	0.10 to 0.91	
cCBT without or with minimal support	-0.20	-2.26 to 1.67	
cCBT with support	0.39	-0.87 to 1.68	
Individual BA	1.18	-0.19 to 2.49	
Individual CBT (≥15 sessions)	0.92	0.21 to 1.62	
Group CBT (<15 sessions)	0.51	-0.76 to 1.81	
Individual problem solving	2.03	0.61 to 3.46	
Non-directive counselling	1.38	-0.06 to 2.83	
Individual IPT	0.43	-0.65 to 1.50	
Individual short-term PDPT	1.31	-1.21 to 3.81	
Supervised HI individual exercise	1.47	-1.69 to 4.73	
Supervised HI group exercise	1.63	-0.34 to 3.78	
Traditional acupuncture	-0.26	-1.49 to 0.93	
Individual CBT (≥ 15sessions) + escitalopram	1.68	0.43 to 2.82	
Traditional acupuncture + escitalopram	3.85	2.74 to 4.95	
No treatment	-0.24	-1.40 to 0.94	
Adults with more severe depression: remission in completers – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.56	0.44 to 0.71	Guideline NMA; distribution based on 10,000 iterations; effect for cCBT without or with minimal support borrowed from class effect; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + imipramine; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Lofepramine	0.70	-0.12 to 1.24	
Duloxetine	0.75	0.62 to 0.88	
Mirtazapine	0.61	0.34 to 0.89	
Trazodone	0.53	0.26 to 0.81	
cCBT without or with minimal support	1.38	-0.55 to 3.61	
cCBT with support	0.95	0.14 to 1.75	
Individual BA	1.08	0.45 to 1.71	
Individual CBT (≥15 sessions)	1.09	0.61 to 1.56	
Group CBT (<15 sessions)	0.29	-0.84 to 1.37	
Individual problem solving	1.15	0.19 to 2.14	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Non-directive counselling Individual IPT Individual short-term PDPT Supervised HI individual exercise Supervised HI group exercise Traditional acupuncture Individual CBT (≥ 15sessions) + escitalopram Traditional acupuncture + escitalopram No treatment	0.30 1.00 0.50 0.32 0.63 0.10 1.72 0.46 0.17	-0.85 to 1.47 0.34 to 1.67 -0.47 to 1.45 -0.47 to 1.20 0.02 to 1.27 -1.58 to 1.80 0.81 to 2.91 -0.54 to 1.47 -0.52 to 0.87	
Baseline risk of discontinuation			
Less severe depression - sertraline More severe depression - escitalopram	0.38 0.34	Beta: α=191; β=309 Beta: α=169; β=331	Risk of discontinuation for SSRIs based on a review of studies (Bull 2002, Hansen 2004, Lewis 2004, Olfson 2006, Goethe 2007, Burton 2012) and further expert opinion. Risk of individual SSRI drugs estimated using the guideline NMA SSRI class and individual drug effects versus placebo. Distribution based on assumption.
Baseline risk of discontinuation due to side effects in those discontinuing			
Less severe depression - sertraline More severe depression - escitalopram	0.39 0.44	Beta: α=196; β=304 Beta: α=222; β=278	Based on discontinuation due to side effects data reported in Goethe 2007 and Bull 2002 for SSRIs, using the estimated baseline risk of discontinuation of sertraline and escitalopram for less and more severe depression, respectively, and assuming that discontinuation due to side effects is independent of depressive symptom severity. Probability distribution based on assumption.
Response and remission in completers – GP care			
Less severe depression – response More severe depression – response More severe depression – remission Hazards ratios of the above states versus 12-month baseline probability of recovery were estimated using the probabilities	0.57 0.48 0.39	Based on Weibull parameters (lambda and gamma) for baseline probability of recovery [shown below]	Synthesis of data from Gonzales 1985; Holma 2008; Keller 1981, 1984 & 1992; Mueller 1996; and Skodol 2011, using a Bayesian approach – fixed effects model (see Evidence review C, appendix J)

Input parameter	Deterministic value	Probability distribution	Source of data - comments
below: 12-month response – mild depression – moderate depression – severe depression 12-month remission – mild depression – moderate depression – severe depression	 0.79 0.68 0.73 0.79 0.65 0.55	 Beta: α=235; β=61 Beta: α=265; β=126 Beta: α=233; β=88 Beta: α=235; β=61 Beta: α=252; β=139 Beta: α=176; β=145	Simon 1999. For more severe depression, the mean value of moderate and severe depression was used.
Probability of responders (without remission) moving to remission Markov state			
– more severe depression	0.30	Beta: α=30; β=70	Based on the committee's expert opinion
Proportion of people developing common side effects – SSRIs alone or in combination – SNRIs – TCAs – trazodone – mirtazapine	 0.07 0.09 0.07 0.05 0.06	 Beta: α=1,643; β=21,977 Beta: α=437; β=4,325 Beta: α=52; β=724 Beta: α=57; β=1,143 Beta: α=54; β=847	Anderson 2012
Duration of experiencing common side effects over the model time horizon – SSRIs alone or in combination – SNRIs – TCAs – trazodone – mirtazapine	 1.68 years 1.63 years 2.25 years 2.25 years 2.25 years	 No distribution assumed	Anderson 2012
Probability of moving to specific relapse preventive treatment according to acute treatment received – more severe depression			
Acute AD or combined treatment -> maintenance AD Acute individual CBT, BA ->	0.80	Beta: α=80; β=20	Based on the committee's expert opinion

Input parameter	Deterministic value	Probability distribution	Source of data - comments
maintenance 4 sessions	0.80	Beta: α=80; β=20	
Acute individual non-directive counselling, IPT, PDPT -> Maintenance 4 sessions	0.50	Beta: α=50; β=50	
Acute group CBT -> Maintenance group CBT	0.80	Beta: α=80; β=20	
Acute other psychological or physical treatment -> maintenance group CBT	0.50	Beta: α=50; β=50	
Baseline risk of relapse after a single (first) episode			
Weibull distribution – lambda	0.09	95% CI 0.07 to 0.12	Synthesis of data from Eaton 2008 and Mattison 2007, using a Bayesian approach – fixed effects model
Weibull distribution – gamma	0.63	95% CI 0.52 to 0.75	
Hazard ratio – new vs previous episode	1.15	Log-normal: 95% CI 1.11 to 1.18	Kessing 1999
Baseline probability of recovery			Synthesis of data from Gonzales 1985; Holma 2008; Keller 1981, 1984 & 1992; Mueller 1996; Skodol 2011; Stegenga 2012, using a Bayesian approach – fixed effect model
Weibull distribution – lambda	1.16	95% CI 1.08 to 1.24	
Weibull distribution – gamma	0.42	95% CI 0.38 to 0.47	
Mortality			
Risk ratio – depressed vs non-depressed	1.52	Log-normal: 95% CI 1.45 to 1.59	Cuijpers 2014
Baseline mortality – non-depressed	Age/sex specific	No distribution	General mortality statistics for the UK population (Office for National Statistics 2020)
Utility values			
Less severe depression	0.60	Beta: α=182; β=122	Distributions determined using method of moments, based on data reported in Sapin 2004, Sullivan 2004, Sobocki 2006 & 2007, and further assumptions
More severe depression	0.42	Beta: α=54; β=75	
Remission	0.85	Beta: α=923; β=163	
Response not reaching remission	0.72	Beta: α=123; β=48	
Decrement in utility due to side effects	0.09	Beta: α=6; β=59	
Remission state in Markov component	0.81	Beta: α=531; β=125	
Intervention costs – resource use			Probabilities assigned to numbers of sessions

Input parameter	Deterministic value	Probability distribution	Source of data - comments
COMPLETERS			
Number of GP contacts – drug treatment			
- Acute treatment	4	0.70: 4, 0.30: 2-3	Number of visits based on the committee's expert opinion; probabilities based on assumption. If number of GP visits in 2nd year of maintenance pharmacological treatment was lower than 3, only 50% of the drug acquisition cost was incurred and 50% of annual GP contacts due to side effects were made
- 1st year continuation / maintenance	6	0.70: 6, 0.20: 4-5, 0.10: 2-3	
- 2nd year maintenance	3	0.70: 3, 0.30: 1-2	
- Tapering	3	0.70: 3, 0.30: 1-2	
- Discontinuation due to side effects	1	0.80: 1, 0.20: 0	
- Side effects – every 3 months	1	No distribution assigned	
Number of GP contacts – GP care			
- Acute treatment	4	0.50: 4, 0.50: 2-3	
- 1st year maintenance	3	0.70: 3, 0.20: 1-2, 0.10: 0	
- 2nd year maintenance	1	0.70: 1, 0.30: 0	
Number of GP contacts – psych therapy			
- Acute treatment	1	No distribution	
- Maintenance treatment	2	0.60: 2, 0.40: 1	
Psychological interventions - number of sessions			Details on costs of psychological interventions (duration of sessions, type of therapists delivering interventions, and number of participants per group in group therapies) are provided in Table 91. For cCBT without support and cCBT with support one extra initial set-up contact added. For individual problem solving 1 extra initial longer visit added. Participants missing one or more group sessions assumed not to be replaced by others; therefore there was no impact on number of sessions and the total intervention cost.
- cCBT without support	0	No distribution	
- cCBT with support	7	0.70: 7, 0.20: 5-6, 0.10: 4	
- BA individual – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- BA group – less severe depression	8	No distribution	
- CBT individual – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- CBT group – less severe depression	8	No distribution	
- Problem solving – less severe depression	5	0.70: 5, 0.20: 4, 0.10: 3	
- Counselling – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- IPT – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- Short-term PDPT – less severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	
- MBCT (group) – less severe depression	8	No distribution	
- BA individual – more severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
- CBT individual – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	Number of visits based on RCTs included in the NMAs that informed the economic analysis modified by the committee's expert opinion; probabilities based on assumption.
- CBT group – more severe depression	10	No distribution	
- Problem solving – more severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- Counselling – more severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	
- IPT – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	
- Short-term PDPT – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	
Physical interventions - number of sessions			Details on costs of physical interventions (duration of sessions, type of therapists delivering interventions, and number of participants per group in group therapies are provided in Table 93. Participants missing one or more group sessions assumed not to be replaced by others; therefore there was no impact on number of sessions and the total intervention cost. Number of visits based on RCTs included in the NMAs that informed the economic analysis modified by the committee's expert opinion; probabilities based on assumption.
- Exercise individ – less severe depression	25	0.70: 25, 0.20: 20-24, 0.10: 15-19	
- Exercise group – less severe depression	30	No distribution	
- Exercise individ – more severe depression	30	0.70: 30, 0.20: 23-29, 0.10: 16-22	
- Exercise group – more severe depression	40	No distribution	
- Acupuncture – more severe depression	25	0.70: 25, 0.20: 20-24, 0.10: 15-19	
Maintenance psychological therapies – number of sessions			Details on costs of maintenance psychological therapies are provided in Table 94.
MBCT (group)	12	No distribution	
CBT group	8	No distribution	
4 individual sessions	4	0.60: 4, 0.40: 2-3	
DISCONTINUERS (acute treatment)			
Number of GP contacts – drug treatment or GP care	1	No distribution	One pack of drugs assumed to be consumed by those discontinuing acute drug treatment
Number of GP contacts – psych therapy	1	No distribution	
Number of psychological intervention sessions			For psychological and physical interventions: initial GP visit added
- cCBT without support	0	No distribution	For cCBT without support and cCBT with support: 1 extra initial set-up contact assumed.

Input parameter	Deterministic value	Probability distribution	Source of data - comments
- cCBT with support	1	No distribution	For individual problem solving: 1 extra initial longer visit assumed. People discontinuing group psychological therapies or exercise were assumed to incur the full cost of therapy
- BA individual – less severe depression	2	No distribution	
- BA group – less severe depression	8	No distribution	
- CBT individual – less severe depression	2	No distribution	
- CBT group – less severe depression	8	No distribution	
- Problem solving – less severe depression	1	No distribution	
- Counselling – less severe depression	2	No distribution	
- IPT – less severe depression	2	No distribution	
- Short-term PDPT – less severe depression	3	No distribution	
- MBCT (group) – less severe depression	8	No distribution	
- BA individual – more severe depression	3	No distribution	
- CBT individual – more severe depression	4	No distribution	
- CBT group – more severe depression	10	No distribution	
- Problem solving – more severe depression	2	No distribution	
- Counselling – more severe depression	3	No distribution	
- IPT – more severe depression	4	No distribution	
- Short-term PDPT – more severe depression	4	No distribution	
Number of physical intervention sessions			
- Exercise individ – less severe depression	7	No distribution	
- Exercise group – less severe depression	30	No distribution	
- Exercise individ – more severe depression	8	No distribution	
- Exercise group – more severe depression	40	No distribution	
- Acupuncture – more severe depression	7	No distribution	
Intervention costs - unit costs (2020 price)			
Drug acquisition costs	Table 86	No distribution	NHS Business Services Authority 2021
Medication for management of side effects	£2.50	No distribution	Assumption – 3-month cost
LFT	£3.07	No distribution	Akhtar 2014
ECG machine and disposables	£3.28	No distribution	National Clinical Guidelines Centre 2016
cCBT provider, hardware & capital overheads	£53	No distribution	Committee's expert advice and Kaltenthaler 2006
Disposable needles per acupuncture session	£1	No distribution	Assumption

Input parameter	Deterministic value	Probability distribution	Source of data - comments
GP	£39	Normal, SE=0.05*mean	Curtis 2020; distribution based on assumption
HI therapist Band 7	£110	Normal, SE=0.05*mean	See Table 89; distribution based on assumption
Therapist Band 6	£89	Normal, SE=0.05*mean	See Table 90; distribution based on assumption
HI MBCT therapist Band 7	£112	Normal, SE=0.05*mean	See Table 89; distribution based on assumption
MBCT therapist Band 6	£91	Normal, SE=0.05*mean	See Table 90; distribution based on assumption
PWP (Band 5)	£50	Normal, SE=0.05*mean	See Table 88; distribution based on assumption
Physiotherapist band 6	£71	Normal, SE=0.05*mean	Curtis 2020, see Table 92; distribution based on assumption
Practice nurse band 5 [delivering ECG]	£51	Normal, SE=0.05*mean	Curtis 2020, taking into account ratio of direct to indirect time
Annual NHS health state cost (2020 price)		Gamma	
Relapse - remaining in state	£1,601	SE=0.20*mean	Based primarily on cost data reported in Byford 2011 supplemented with data from Radhakrishnan 2013, Curtis 2020, NHS England 2016, expressed in 2020 prices using the HCHS inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020). Distribution based on assumption
Relapse - final year before remission	£1,165	SE=0.20*mean	
Remission	£533	SE=0.20*mean	
Remission – 1st year extra cost	£206	SE=0.20*mean	
Cost of treatment after discontinuation	£246	SE=0.20*mean	
Annual discount rate	0.035	No distribution	Applied to both costs and outcomes (NICE 2014)

AD: antidepressant; BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; ECG: electrocardiogram; HI: ihigh ntensity; IPT: interpersonal psychotherapy; LFT: liver function test; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Presentation of the results

Results are reported separately for each population examined in the economic model. In each analysis, mean intervention costs, total costs and QALYs are presented for each intervention, averaged across 10,000 iterations of the model. For each treatment option, the Net Monetary Benefit (NMB) has been estimated for each iteration and averaged across the 10,000 iterations, determined by the formula

$$NMB = E \bullet \lambda - C$$

where E and C are the effects (QALYs) and total costs, respectively, of each treatment option, and λ represents the moneterised value of each QALY, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE, 2014). The treatment with the highest NMB is the most cost-effective option (Fenwick 2001).

Incremental mean costs and effects (QALYs) of each treatment option versus GP care are also presented in the form of cost effectiveness planes.

The mean (95%CI) ranking by cost-effectiveness is reported for each treatment (out of 10,000 iterations), where a rank of 1 suggests that a treatment is the most cost-effective amongst all evaluated treatment options. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds (λ), and the probability that this treatment is the most cost-effective among those assessed (Fenwick 2001).

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a health economics sub-group formed by members of the committee. The validity of the model structure, assumptions and input parameters were confirmed by the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The base-case results and results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Economic modelling results

Adults with less severe depression

The results of the economic analysis are provided in Table 98. This table shows interventions ordered from the most to the least cost-effective and provides mean QALYs and mean intervention and total costs for each intervention, mean NMBs and rankings by cost effectiveness (with higher NMBs and lower rankings indicating higher cost-effectiveness). Intervention costs include costs for treatment completers and costs for those who discontinued treatment. According to the results, CBT group appeared to be the most cost-effective intervention, followed by BA group, exercise group, sertraline, MBCT group, cCBT without or with minimal support, lofepramine, cCBT with support, CBT individual, BA individual, problem solving individual, IPT, GP care, non-directive counselling, short-term PDPT, and exercise individual. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Table 98. Results of economic analysis: interventions for adults with a new episode of less severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
CBT group	£32,900	1,731	£337,653	£1,711,356	2.61 (1 to 12)
BA group	£32,622	1,719	£337,653	£1,764,595	5.06 (1 to 14)
Exercise group	£32,501	1,709	£225,146	£1,679,809	5.48 (1 to 13)
Sertraline	£32,420	1,707	£108,286	£1,719,661	6.17 (1 to 14)
MBCT group	£32,370	1,713	£444,276	£1,885,364	7.35 (2 to 15)
cCBT	£32,328	1,697	£117,009	£1,618,769	6.96 (2 to 13)
Lofepramine	£32,272	1,707	£177,443	£1,876,104	7.86 (1 to 15)
cCBT with support	£32,271	1,697	£173,726	£1,675,563	7.47 (1 to 16)
CBT individual	£32,255	1,719	£710,808	£2,119,240	8.08 (3 to 15)
BA individual	£32,233	1,718	£724,433	£2,133,287	8.10 (1 to 16)
Problem solving individual	£31,928	1,683	£170,092	£1,728,566	11.04 (3 to 16)
IPT	£31,883	1,701	£636,945	£2,129,449	12.01 (5 to 16)
GP care	£31,871	1,676	£94,525	£1,651,096	11.96 (4 to 16)
Non-directive counselling	£31,770	1,699	£733,336	£2,210,591	10.27 (2 to 16)
Short-term PDPT	£31,731	1,713	£1,113,482	£2,534,599	11.94 (3 to 16)
Exercise individual	£31,668	1,707	£1,013,382	£2,467,523	13.63 (8 to 16)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Figure 64 provides the cost effectiveness plane of the analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care (TAU), which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that non-directive counselling, short-term PDPT, and individual exercise may be less cost-effective than with GP care at this threshold (since they all lie on the left side of the dotted line).

The CEAF of the analysis is shown in Figure 65. It can be seen that cCBT is the most cost-effective option at a cost-effectiveness threshold between zero and £2,500/QALY, with a rather low probability that reaches 0.37 at zero cost effectiveness threshold and then drops down to 0.23. For higher cost-effectiveness thresholds, CBT group is the most cost-effective option, with a probability of cost effectiveness that starts at 0.30 and reaches 0.58 at a cost effectiveness threshold of £40,000/QALY.

Figure 64. Cost effectiveness plane of interventions for the treatment of a new episode of less severe depression in adults plotted against GP care (reference treatment reflected in TAU) – incremental costs and QALYs versus GP care per 1,000 adults with less severe depression

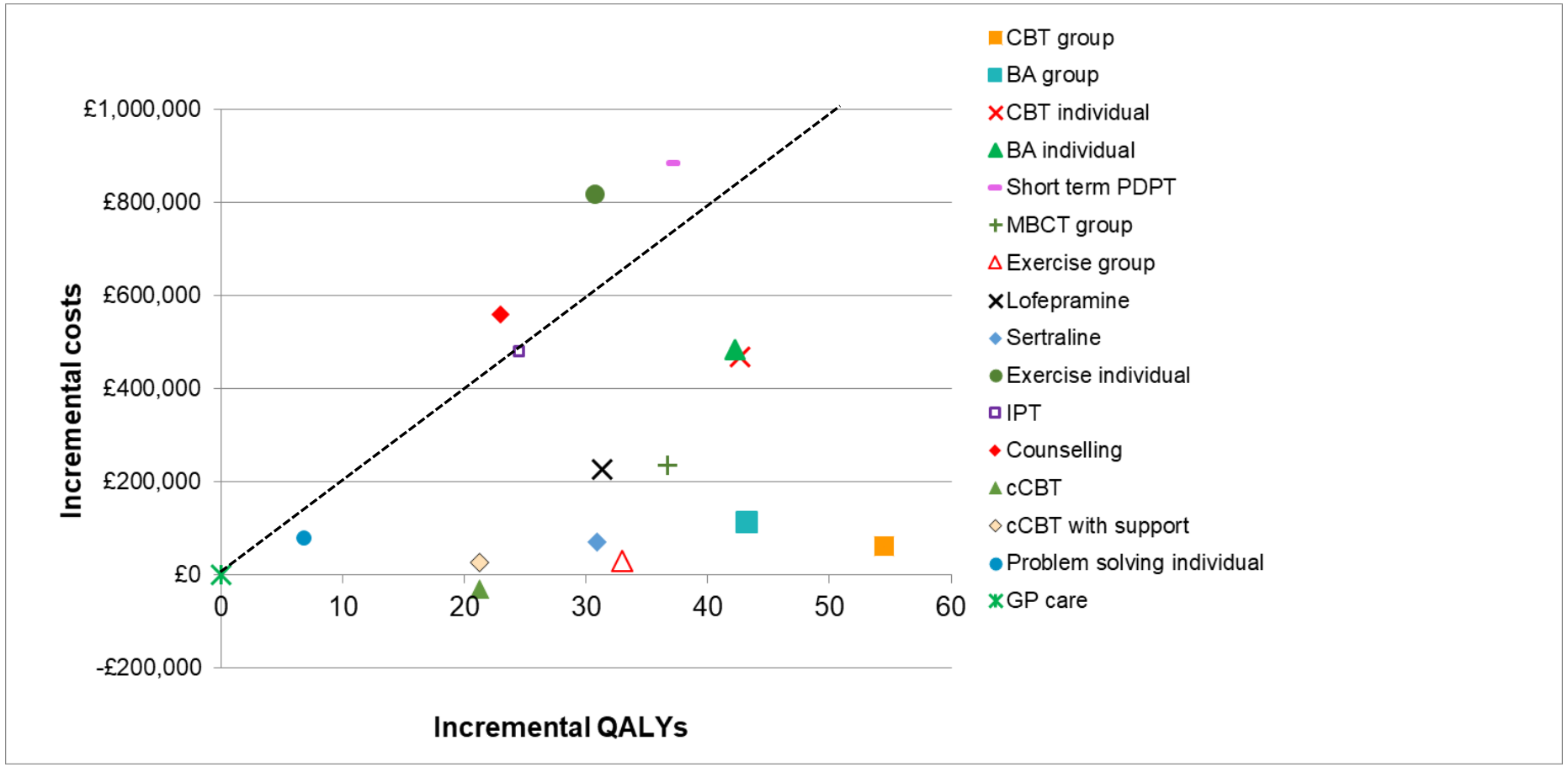
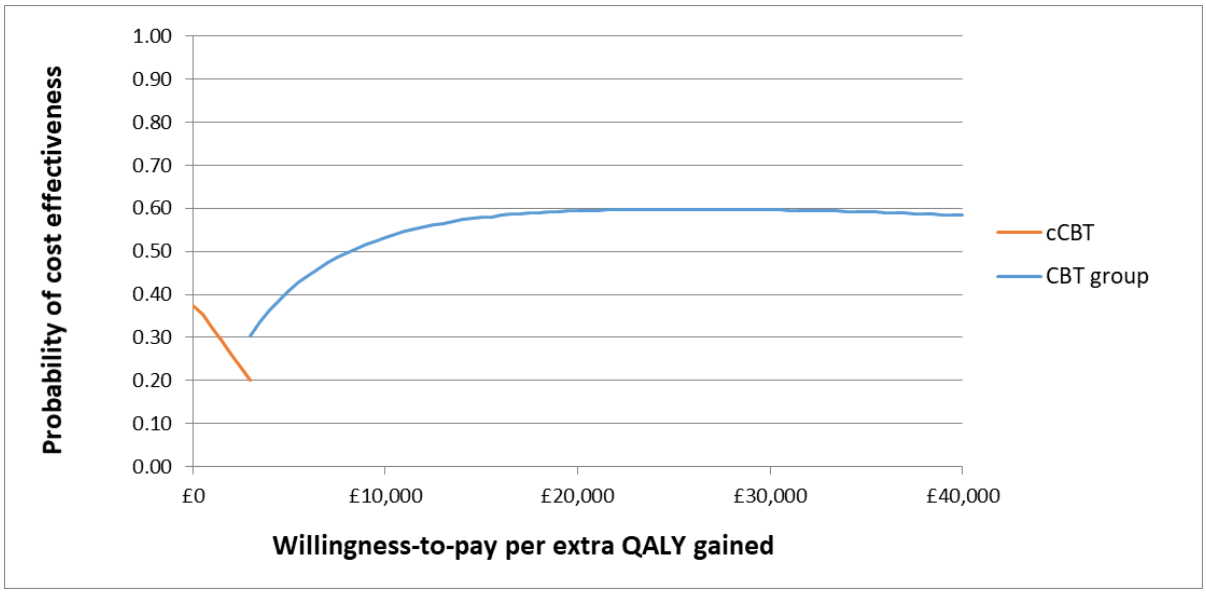


Figure 65 Cost-effectiveness acceptability frontier of interventions for the treatment of a new episode of less severe depression in adults



Results were overall robust to the scenarios explored through deterministic sensitivity analysis (Table 99) with small changes in the ranking of interventions. When the number of sessions of group psychological interventions was doubled, the relative cost-effectiveness of MBCT and, to a lesser degree, group BA, was reduced; however, group CBT remained the most cost-effective intervention. The impact of changes in the number of sessions of individual high-intensity psychological interventions was less profound. The cost-effectiveness of pharmacological interventions was reduced when the risk of developing side effects was increased.

Table 99. Results of deterministic sensitivity analysis – adults with less severe depression

Base-case deterministic analysis		Increase in the number of previous episodes (2 from 0)		Utility values from Mann 2009		Utility values from Koeser 2015 / Kolovos 2017		50% reduction in the cost of a depressive episode		50% increase in cost of depressive episode	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
CBT group	£33,114	CBT group	£33,003	CBT group	£32,841	CBT group	£32,773	CBT group	£33,238	CBT group	£32,989
BA group	£32,801	BA group	£32,696	BA group	£32,841	BA group	£32,485	BA group	£32,966	BA group	£32,635
Exercise group	£32,701	Exercise group	£32,600	Exercise group	£32,841	Exercise group	£32,405	Exercise group	£32,899	Exercise group	£32,503
MBCT group	£32,592	MBCT group	£32,489	MBCT group	£32,841	MBCT group	£32,287	MBCT group	£32,774	MBCT group	£32,410
cCBT	£32,456	cCBT	£32,362	cCBT	£32,841	cCBT	£32,190	cCBT	£32,702	BA individual	£32,253
Sertraline	£32,453	Sertraline	£32,357	cCBT with support	£32,841	cCBT with support	£32,175	cCBT with support	£32,684	Sertraline	£32,248
cCBT with support	£32,445	cCBT with support	£32,351	Sertraline	£32,841	Sertraline	£32,162	Sertraline	£32,658	cCBT	£32,209
BA individual	£32,407	BA individual	£32,300	BA individual	£32,841	BA individual	£32,084	BA individual	£32,560	cCBT with support	£32,207
CBT individual	£32,359	CBT individual	£32,254	CBT individual	£32,841	CBT individual	£32,042	CBT individual	£32,522	CBT individual	£32,196
Lofepramine	£32,313	Lofepramine	£32,216	Lofepramine	£32,841	Lofepramine	£32,015	Lofepramine	£32,508	Lofepramine	£32,118
Counselling	£32,080	Counselling	£31,980	Problem solving	£32,841	Counselling	£31,785	Counselling	£32,279	Counselling	£31,881
Problem solving	£31,964	Problem solving	£31,878	Counselling	£32,841	Problem solving	£31,734	Problem solving	£32,268	Short-term PDPT	£31,769
Short-term PDPT	£31,930	Short-term PDPT	£31,824	GP care	£32,841	IPT	£31,643	GP care	£32,181	IPT	£31,683
IPT	£31,917	IPT	£31,821	IPT	£32,841	GP care	£31,634	IPT	£32,150	Problem solving	£31,659
GP care	£31,845	GP care	£31,764	Short-term PDPT	£32,841	Short-term PDPT	£31,611	Short-term PDPT	£32,090	Exercise individual	£31,521
Exercise individual	£31,726	Exercise individual	£31,627	Exercise individual	£32,841	Exercise individual	£31,435	Exercise individual	£31,931	GP care	£31,509
20% reduction in baseline discontinuation		**20% increase in baseline discontinuation**		**100% self-referral to psychological therapies**		**All HI individual psych interventions delivered in 8 sessions; group psych intervention sessions doubled**		**HI individual psych interventions delivered in 12 sessions; group psych intervention sessions doubled**		**40% risk of developing side effects from antidepressants**	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
CBT group	£33,212	CBT group	£33,004	CBT group	£33,153	CBT group	£32,815	CBT group	£32,815	CBT group	£33,114
BA group	£32,930	BA group	£32,666	BA group	£32,840	Exercise group	£32,701	Exercise group	£32,701	BA group	£32,801
Exercise group	£32,772	Exercise group	£32,622	Exercise group	£32,701	BA group	£32,502	BA group	£32,502	Exercise group	£32,701
MBCT group	£32,671	MBCT group	£32,503	MBCT group	£32,631	cCBT	£32,456	cCBT	£32,456	MBCT group	£32,592
Sertraline	£32,548	cCBT	£32,392	cCBT	£32,495	Sertraline	£32,453	Sertraline	£32,453	cCBT	£32,456
cCBT	£32,514	cCBT with support	£32,383	cCBT with support	£32,475	cCBT with support	£32,445	cCBT with support	£32,445	cCBT with support	£32,445
cCBT with support	£32,503	BA individual	£32,378	Sertraline	£32,453	BA individual	£32,407	Lofepramine	£32,313	BA individual	£32,407
BA individual	£32,430	Sertraline	£32,359	BA individual	£32,442	CBT individual	£32,359	MBCT group	£32,187	CBT individual	£32,359

Lofepramine	£32,427	CBT individual	£32,322	CBT individual	£32,393	Short-term PDPT	£32,339	BA individual	£32,008	Counselling	£32,080
CBT individual	£32,391	Lofepramine	£32,203	Lofepramine	£32,313	Lofepramine	£32,313	CBT individual	£31,977	Sertraline	£32,018
Counselling	£32,095	Counselling	£32,063	Counselling	£32,116	MBCT group	£32,187	Problem solving	£31,964	Problem solving	£31,964
Problem solving	£31,987	Problem solving	£31,939	Problem solving	£31,992	Counselling	£32,080	Short-term PDPT	£31,930	Short-term PDPT	£31,930
IPT	£31,947	Short-term PDPT	£31,918	Short-term PDPT	£31,966	Problem solving	£31,964	GP care	£31,845	IPT	£31,917
Short-term PDPT	£31,940	IPT	£31,885	IPT	£31,946	IPT	£31,917	Exercise individual	£31,726	Lofepramine	£31,889
GP care	£31,848	GP care	£31,842	GP care	£31,845	GP care	£31,845	Counselling	£31,682	GP care	£31,845
Exercise individual	£31,738	Exercise individual	£31,712	Exercise individual	£31,726	Exercise individual	£31,726	IPT	£31,592	Exercise individual	£31,726

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; HI: high intensity; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; psych: psychological; PWP: psychological well-being practitioner

Adults with more severe depression

The unadjusted results of the economic analysis are provided in Table 100. The results of the probabilistic bias-adjusted analysis that utilised data on discontinuation and response in completers from the respective bias NMA models are shown in Table 101. Interventions have been ordered from the most to the last cost-effective. The tables provide the mean QALYs and mean intervention and total costs for each intervention, mean NMBs and rankings by cost effectiveness (with higher NMBs and lower rankings indicating higher cost-effectiveness). Intervention costs include costs for treatment completers and costs for those who discontinued treatment.

According to the bias-adjusted results, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Table 100. Results of unadjusted economic analysis: interventions for adults with a new episode of more severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
Individual problem solving	£28,967	1,554	£242,818	£2,104,317	2.05 (1 to 10)
CBT individual + escitalopram	£28,073	1,565	£1,418,661	£3,224,319	6.39 (1 to 17)
Duloxetine	£27,989	1,501	£110,823	£2,038,483	5.97 (2 to 10)
cCBT with support	£27,952	1,502	£176,303	£2,090,004	7.15 (1 to 17)
Mirtazapine	£27,950	1,498	£107,574	£2,019,872	6.62 (2 to 12)
BA individual	£27,944	1,542	£1,070,325	£2,896,732	7.14 (1 to 17)
Exercise group	£27,868	1,503	£287,131	£2,199,976	7.77 (2 to 16)
Escitalopram	£27,833	1,493	£108,101	£2,023,604	8.24 (4 to 13)
Lofepramine	£27,823	1,503	£188,176	£2,232,436	8.06 (2 to 16)
Acupuncture + escitalopram	£27,804	1,524	£796,277	£2,681,709	8.77 (1 to 18)
Trazodone	£27,598	1,482	£102,704	£2,040,012	10.89 (6 to 15)
CBT individual	£27,556	1,538	£1,375,691	£3,206,707	10.96 (4 to 17)
CBT group	£27,302	1,482	£412,549	£2,329,921	12.39 (2 to 19)
cCBT	£27,194	1,463	£116,960	£2,072,382	12.07 (1 to 20)
Non-directive counselling	£26,998	1,497	£1,022,816	£2,939,938	14.42 (3 to 20)
IPT	£26,951	1,513	£1,419,832	£3,314,372	14.83 (4 to 20)
Exercise individual	£26,887	1,493	£1,054,538	£2,980,498	15.47 (6 to 20)
GP care	£26,865	1,439	£87,557	£1,910,907	16.15 (12 to 19)
Short-term PDPT	£26,703	1,494	£1,254,238	£3,171,873	15.92 (5 to 20)
Acupuncture	£25,873	1,430	£724,128	£2,718,558	18.77 (12 to 20)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Table 101. Results of bias-adjusted economic analysis: interventions for people with a new episode of more severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
Individual problem solving	£28,929	1,552	£243,567	£2,108,870	1.85 (1 to 9)
CBT individual + escitalopram	£27,947	1,558	£1,402,841	£3,219,785	6.18 (1 to 16)
Duloxetine	£27,911	1,498	£110,867	£2,043,891	5.24 (2 to 9)
Mirtazapine	£27,824	1,493	£107,606	£2,027,931	6.48 (2 to 12)
BA individual	£27,768	1,534	£1,072,316	£2,910,213	7.28 (1 to 18)
Escitalopram	£27,746	1,489	£108,290	£2,029,963	7.52 (4 to 12)
Acupuncture + escitalopram	£27,735	1,520	£780,179	£2,672,040	8.08 (1 to 17)
Exercise group	£27,702	1,496	£287,188	£2,209,098	7.81 (2 to 17)
Lofepramine	£27,689	1,496	£187,942	£2,236,393	7.91 (2 to 15)
Trazodone	£27,507	1,478	£103,309	£2,046,731	10.17 (5 to 15)
cCBT with support	£27,488	1,480	£176,015	£2,114,443	9.39 (1 to 19)
CBT individual	£27,309	1,526	£1,353,628	£3,201,785	11.50 (4 to 17)
CBT group	£26,952	1,465	£412,310	£2,349,604	13.51 (2 to 20)
Non-directive counselling	£26,934	1,493	£1,012,410	£2,934,391	13.63 (3 to 20)
GP care	£26,868	1,439	£89,097	£1,911,976	14.94 (11 to 18)
cCBT	£26,797	1,445	£117,009	£2,094,139	13.17 (1 to 20)
IPT	£26,575	1,495	£1,410,358	£3,326,426	15.52 (5 to 20)
Short-term PDPT	£26,554	1,486	£1,231,776	£3,159,256	15.56 (5 to 20)
Exercise individual	£26,504	1,475	£1,044,561	£2,990,588	15.84 (7 to 20)
Acupuncture	£25,758	1,425	£738,364	£2,738,737	18.43 (11 to 20)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Figure 66 provides the cost-effectiveness plane of the bias-adjusted analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care (placebo), which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture may be less cost-effective than GP care at this threshold.

The CEAF of the analysis is shown in Figure 67. It can be seen that GP care is the most cost-effective option at cost effectiveness thresholds up to £2,500/QALY, with a probability that reaches 0.94 at a zero cost effectiveness threshold, which then drops down to 0.27. For higher cost-effectiveness thresholds, individual problem solving is the most cost-effective option for the treatment of more severe depressive episodes, with a probability of cost effectiveness that starts at 0.43, reaches its highest probability of 0.78 at a cost-effectiveness threshold of £10,000/QALY, and then falls at 0.56 at a cost effectiveness threshold of £40,000/QALY.

Figure 66. Cost-effectiveness plane of interventions for the treatment of a new episode of more severe depression in adults plotted against GP care (placebo) – incremental costs and QALYs versus GP care per 1,000 adults with more severe depression, bias-adjusted analysis

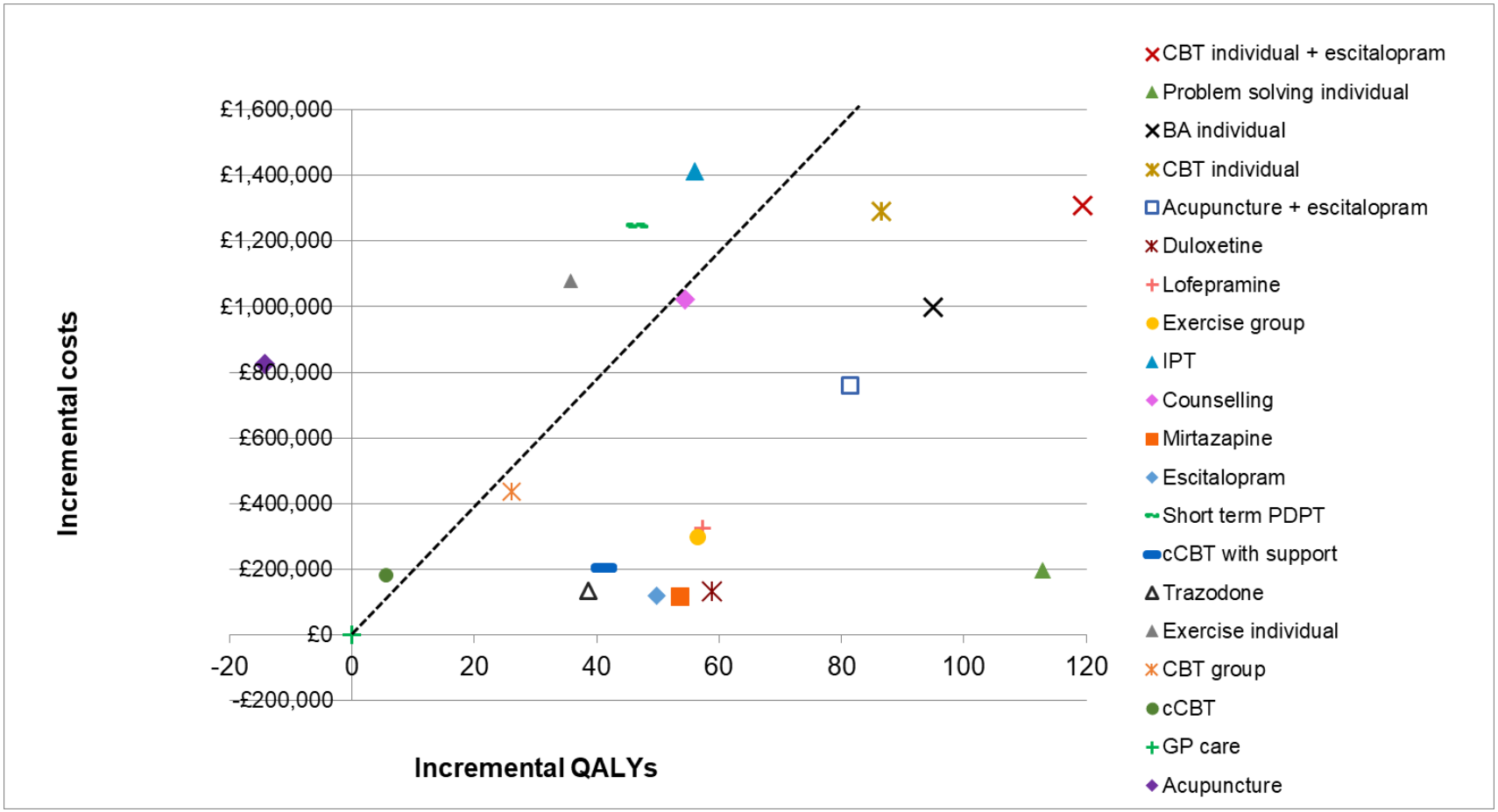
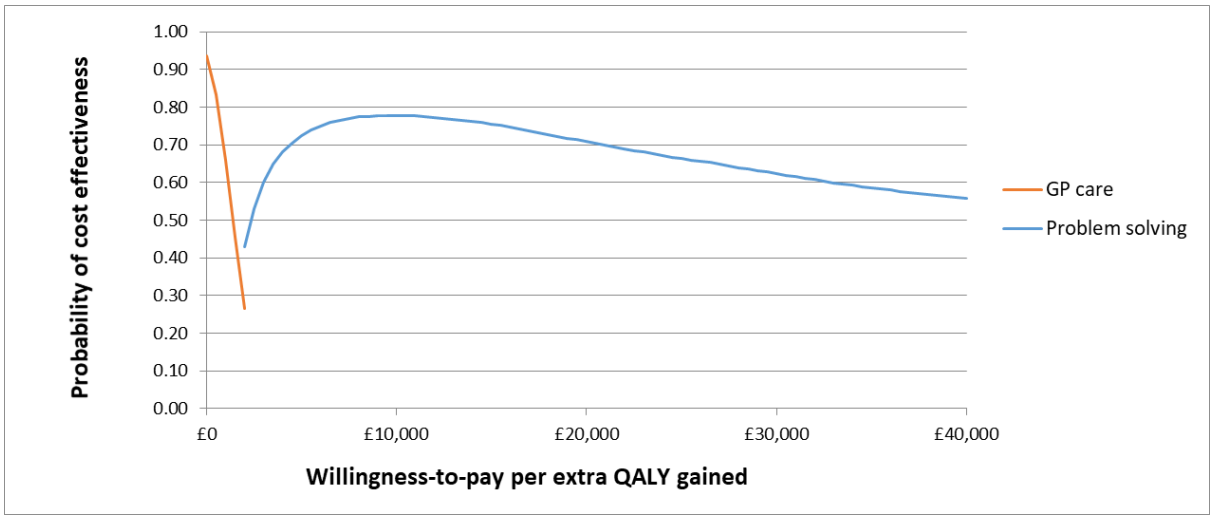


Figure 67. Cost-effectiveness acceptability frontier of interventions for the treatment of a new episode of more severe depression in adults – bias-adjusted analysis



Results were overall robust to alternative scenarios tested in one-way deterministic sensitivity analysis (Table 102), with the following exceptions: when the higher utility value from Mann 2009 was attached to more severe depression (translating into a more limited scope for HRQoL improvement following successful treatment), the relative cost-effectiveness of combined and high intensity psychological interventions was greatly reduced; all high intensity psychological interventions became less cost-effective than GP care and the rankings of pharmacological interventions and cCBT with support were substantially improved. Also, when the risk of developing side effects from antidepressants was increased (40%), the cost-effectiveness of pharmacological and combined interventions was reduced.

Table 102. Results of deterministic sensitivity analysis – adults with more severe depression, bias-adjusted analysis

Bias-adjusted, base-case deterministic analysis		Increase in the number of previous episodes (5 from 2)		Utility values from Mann 2009		Utility values from Koeser 2015 / Kolovos 2017		50% reduction in the cost of a depressive episode		50% increase in cost of depressive episode	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
Problem solving	£29,066	Problem solving	£28,728	Problem solving	£30,745	Problem solving	£28,792	Problem solving	£29,431	Problem solving	£28,701
CBT indiv + escit	£28,084	CBT indiv + escit	£27,853	Duloxetine	£29,972	CBT indiv + escit	£27,818	CBT indiv + escit	£28,405	CBT indiv + escit	£27,764
Duloxetine	£27,908	Duloxetine	£27,699	Exercise group	£29,932	Duloxetine	£27,696	Duloxetine	£28,361	Duloxetine	£27,456
Exercise group	£27,857	Mirtazapine	£27,616	Mirtazapine	£29,930	Exercise group	£27,628	Exercise group	£28,322	Exercise group	£27,392
Mirtazapine	£27,822	Exercise group	£27,565	cCBT with support	£29,909	Mirtazapine	£27,613	Mirtazapine	£28,286	Mirtazapine	£27,357
cCBT with support	£27,745	Escitalopram	£27,535	Escitalopram	£29,878	cCBT with support	£27,545	cCBT with support	£28,222	Acupunct + escit	£27,301
Escitalopram	£27,738	Acupunct + escit	£27,510	Lofepramine	£29,768	Escitalopram	£27,534	Escitalopram	£28,210	cCBT with support	£27,268
Acupunct + escit	£27,719	Lofepramine	£27,492	Trazodone	£29,741	Lofepramine	£27,484	Lofepramine	£28,152	Escitalopram	£27,266
Lofepramine	£27,697	cCBT with support	£27,460	CBT indiv + escit	£29,637	Acupunct + escit	£27,456	Acupunct + escit	£28,137	Lofepramine	£27,242
Trazodone	£27,524	Trazodone	£27,317	Acupunct + escit	£29,586	Trazodone	£27,330	Trazodone	£28,014	Trazodone	£27,033
CBT individual	£27,322	CBT individual	£27,057	GP care	£29,457	CBT individual	£27,091	CBT individual	£27,728	CBT individual	£26,916
BA individual	£27,249	BA individual	£26,997	CBT group	£29,399	BA individual	£27,036	BA individual	£27,685	BA individual	£26,814
CBT group	£27,100	CBT group	£26,828	cCBT	£29,333	CBT group	£26,905	CBT group	£27,618	CBT group	£26,583
GP care	£26,950	GP care	£26,700	BA individual	£29,259	GP care	£26,786	GP care	£27,516	Counselling	£26,457
Counselling	£26,932	Counselling	£26,679	CBT individual	£29,206	Counselling	£26,703	Counselling	£27,407	GP care	£26,384
cCBT	£26,846	cCBT	£26,600	Counselling	£29,038	cCBT	£26,684	cCBT	£27,404	cCBT	£26,288
Exercise individual	£26,740	Short-term PDPT	£26,475	Exercise individual	£28,911	Exercise individual	£26,519	Exercise individual	£27,232	Short-term PDPT	£26,263
Short-term PDPT	£26,734	Exercise individual	£26,461	Short-term PDPT	£28,838	Short-term PDPT	£26,511	Short-term PDPT	£27,205	Exercise individual	£26,249
IPT	£26,692	IPT	£26,432	IPT	£28,759	IPT	£26,485	IPT	£27,143	IPT	£26,241
Acupuncture	£26,074	Acupuncture	£25,832	Acupuncture	£28,596	Acupuncture	£25,916	Acupuncture	£26,640	Acupuncture	£25,507
20% reduction in baseline discontinuation		**20% increase in baseline discontinuation**		**100% self-referral to psychological therapies**		**All HI individual psych interventions delivered in 12 sessions; group psych intervention sessions doubled**		**All HI individual psych interventions delivered in 16 sessions; group psych intervention sessions doubled**		**40% risk of developing side effects from antidepressants**	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
Problem solving	£29,197	Problem solving	£28,924	Problem solving	£29,097	Problem solving	£29,066	Problem solving	£29,066	Problem solving	£29,066
CBT indiv + escit	£28,227	CBT indiv + escit	£27,938	CBT indiv + escit	£28,112	CBT indiv + escit	£28,401	CBT indiv + escit	£28,084	Exercise group	£27,857
Duloxetine	£28,034	Duloxetine	£27,787	Duloxetine	£27,908	Duloxetine	£27,908	Duloxetine	£27,908	cCBT with support	£27,745
Exercise group	£28,007	Mirtazapine	£27,717	Exercise group	£27,857	Exercise group	£27,857	Exercise group	£27,857	Duloxetine	£27,410

Mirtazapine	£27,929	Exercise group	£27,715	Mirtazapine	£27,822	Mirtazapine	£27,822	Mirtazapine	£27,822	CBT indiv + esci	£27,330
Escitalopram	£27,832	cCBT with support	£27,661	cCBT with support	£27,772	cCBT with support	£27,745	cCBT with support	£27,745	CBT individua	£27,322
cCBT with support	£27,829	Escitalopram	£27,646	Escitalopram	£27,738	Escitalopram	£27,738	Escitalopram	£27,738	Mirtazapin	£27,309
Acupunct + escit	£27,828	Acupunct + escit	£27,610	Acupunct + escit	£27,719	Acupunct + escit	£27,719	Acupunct + escit	£27,719	BA individual	£27,249
Lofepramine	£27,805	Lofepramine	£27,593	Lofepramine	£27,697	Lofepramine	£27,697	Lofepramine	£27,697	Escitalopram	£27,221
Trazodone	£27,617	Trazodone	£27,437	Trazodone	£27,524	CBT individual	£27,646	Trazodone	£27,524	Lofepramine	£27,190
CBT individual	£27,388	CBT individual	£27,255	CBT individual	£27,351	Trazodone	£27,524	CBT individual	£27,322	Acupunct + escit	£27,135
BA individual	£27,289	BA individual	£27,207	BA individual	£27,280	BA individual	£27,249	GP care	£26,950	CBT group	£27,100
CBT group	£27,149	CBT group	£27,052	CBT group	£27,139	IPT	£27,039	BA individual	£26,900	Trazodone	£27,066
Counselling	£26,960	GP care	£26,961	Counselling	£26,961	Short-term PDPT	£27,014	cCBT	£26,846	GP care	£26,950
GP care	£26,939	Counselling	£26,905	GP care	£26,950	GP care	£26,950	Exercise individual	£26,740	Counselling	£26,932
cCBT	£26,847	cCBT	£26,846	cCBT	£26,885	Counselling	£26,932	Short-term PDPT	£26,734	cCBT	£26,846
Exercise individual	£26,767	Exercise individual	£26,717	Short-term PDPT	£26,759	cCBT	£26,846	CBT group	£26,727	Exercise individual	£26,740
Short-term PDPT	£26,763	Short-term PDPT	£26,708	Exercise individual	£26,740	Exercise individual	£26,740	IPT	£26,692	Short-term PDPT	£26,734
IPT	£26,706	IPT	£26,679	IPT	£26,723	CBT group	£26,727	Counselling	£26,611	IPT	£26,692
Acupuncture	£26,030	Acupuncture	£26,121	Acupuncture	£26,074	Acupuncture	£26,074	Acupuncture	£26,074	Acupuncture	£26,074

Acupunct: acupuncture; BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; escit: escitalopram; HI: high intensity; indiv: individual; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; psych: psychological; PWP: psychological well-being practitioner

Discussion – conclusions, strengths and limitations of economic analysis

The guideline economic analysis assessed the cost effectiveness of a range of pharmacological, psychological, physical and combined interventions for the treatment of new depressive episodes in adults with less severe depression and adults with more severe depression treated in primary care. The interventions assessed were determined by the availability of efficacy and acceptability data obtained from the NMAs that were conducted to inform this guideline. Specific interventions were used as exemplars within each class, so that results of interventions can be extrapolated to other interventions of similar effectiveness and resource intensity within their class.

In adults with less severe depression, group CBT appeared to be the most cost-effective intervention, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

In adults with more severe depression, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Results for both populations were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals around their mean rankings. On the other hand, results of the economic analysis were overall robust to different scenarios explored through deterministic sensitivity analysis, especially in the analysis of interventions for the management of a new episode of less severe depression. Attaching higher utility values to the states of less and more severe depression, which reduced the scope for HRQoL improvement following successful treatment had a strong impact on the results for people with more severe depression: under this scenario, the relative cost-effectiveness of combined and high intensity psychological interventions was greatly reduced, all high intensity psychological interventions became less cost-effective than GP care and the rankings of pharmacological interventions and cCBT with support were substantially improved. Increasing the risk of developing side effects from antidepressant medication resulted in a reduction of the relative cost-effectiveness of antidepressants and combined interventions.

The analysis utilised clinical effectiveness parameters derived from NMAs conducted specifically to inform economic modelling. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Lu 2004, Caldwell 2005). The quality and limitations of RCTs considered in the NMAs have unavoidably impacted on the quality of the economic model clinical input parameters. For example, economic results may be have been affected by reporting and publication bias, although bias-adjusted models and respective sensitivity analyses tested the impact of bias relating to small study size on the results of the economic analyses. Some evidence of inconsistency between the direct and indirect evidence was identified for the response in completers outcome in the analyses of less severe depression and for discontinuation, discontinuation due to side effects from medication in those discontinuing treatment, and remission in completers in the analyses for more severe depression. The limitations characterising the data included in the NMAs and the NMA outputs informing the economic analyses should be considered when interpreting the cost effectiveness results.

Each NMA informing the economic analysis assessed a range of psychological, pharmacological, physical or combined interventions. A key assumption when conducting NMA is that the populations included in all RCTs considered in the NMA are similar. However, participants in pharmacological and non-pharmacological (psychological or physical intervention) trials may differ to the extent that some participants find different interventions more or less acceptable in light of their personal circumstances and preferences (so that they might be willing to participate in a pharmacological trial but not a psychological one and vice versa). Similarly, self-help trials may recruit participants who would not seek or accept face-to-face interventions. However, a number of trials included in the NMAs that informed the economic analysis have successfully recruited participants who are willing to be randomised to either pharmacological or psychological intervention and to either self-help or face-to-face treatment. The NMAs have assumed that service users are willing to accept any of the interventions included in the analyses; in practice, treatment decisions may be influenced by individual values and goals, and people's preferences for different types of interventions. These factors were taken into account when interpreting the results of the economic analysis and when formulating recommendations.

Baseline risks (discontinuation, discontinuation due to intolerable side effects, response and remission) were estimated based on a review of naturalistic studies. Available data suggested that recovery over time is characterised by a Weibull distribution, in which the events rates are proportional to a power of time. Estimation of the distribution parameters determined the probability of response and remission at 12 weeks for less and more severe depression, as relevant, based on a study that provided relevant data specific to different levels of depressive symptom severity.

The time horizon of the analysis was 12 weeks of acute treatment plus 2 years of follow up, which included maintenance treatment, as appropriate, for people with more severe depression following response to treatment. This time horizon was considered adequate to capture the full costs and effects of a course of treatment for depression (including acute and, if appropriate, maintenance treatment).

Utility data used in the economic model were derived from a systematic review of studies reporting utility data for depression-related health states that were generated using the EQ-5D and the UK population tariff, as recommended by NICE.

Intervention costs were estimated based on relevant information provided in the studies included in the NMA supplemented by the committee's expert opinion, in order to reflect routine NHS practice. NHS and PSS costs incurred by adults with depression following remission, treatment discontinuation, lack of adequate response or relapse were derived from a large (N=88,935) naturalistic study that aimed to estimate health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database (Byford 2011). Resource estimates and unit costs were updated with 2020 cost data and supplemented with further evidence according to the committee's expert advice, where appropriate, to reflect current routine practice in the UK NHS.

The impact of intolerable side effects that led to treatment discontinuation as well as of other common side effects of pharmacological or combined treatments on HRQoL and costs associated with their management was incorporated in the economic analysis. The analysis utilised data from a large large US managed care claims database. The committee acknowledged that surveys of self-reported side effects in people receiving antidepressant medication report much higher prevalence of side effects, however, evidence suggests that only a proportion of those impact on HRQoL and management costs. The committee pointed out that the focus of the economic analysis was the prevalence of side effects with a measurable impact on HRQoL and healthcare resource use and this was more likely to be reflected in side effects recorded through patient claims. Nevertheless, a sensitivity analysis was conducted, which tested a higher prevalence of side effects from antidepressant

treatment, to explore its impact on cost-effectiveness results. No side effects were considered for people receiving non-pharmacological interventions; however, people receiving non-pharmacological treatments for depression are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Therefore, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness. On the other hand, other less common side effects associated with treatment with antidepressants (such as upper gastrointestinal bleeds and falls) were not considered in the economic model. Such side effects result in considerable reduction in HRQoL and high costs for their management; nevertheless, they are relatively rare and therefore their omission is unlikely to have significantly impacted on the model results, although it is acknowledged as a limitation that has potentially overestimated the cost effectiveness of drugs or combined interventions with a drug component relative to other interventions. On balance, the committee considered that the economic results were not affected by the limitations in capturing costs and disutilities associated with side effects of treatment.

Overall conclusions from the guideline economic analysis

In adults with less severe depression, group CBT appeared to be the most cost-effective intervention, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

In adults with more severe depression, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

The results of the analysis were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals (CrI) around the rankings of interventions. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions from the most to the least cost-effective were overall robust under different scenarios explored.

Conclusions from the guideline economic analysis refer mainly to people with depression who are treated in primary care for a new depressive episode; however, they may be relevant to people in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).