



# Effective Health Care Program

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Future Research Needs Paper  
Number 10

## **Future Research Needs for Hematopoietic Stem-Cell Transplantation in the Pediatric Population**



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# *Future Research Needs Paper*

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**Number 10**

## **Future Research Needs for Hematopoietic Stem-Cell Transplantation in the Pediatric Population**

**Identification of Future Research Needs  
From Comparative Effectiveness Review No. 48**

**Prepared for:**

Agency for Healthcare Research and Quality  
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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions.

AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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The following individuals served as members of the Key Informant Panels described in this report. Their contributions were invaluable. They have not reviewed this report and will not be given the opportunity to do so until it is released publicly by AHRQ.

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# Executive Summary

## Background

For many pediatric indications, the use of hematopoietic stem-cell transplantation (HSCT) is not supported by high-quality trial data. In the absence of these data, the comparative effectiveness and harms of HSCT for these indications is uncertain. The Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC) Evidence-based Practice Center (EPC) submitted a draft Comparative Effectiveness Review (CER) on HSCT in the pediatric population to the Agency for Healthcare Research and Quality. The six Key Questions addressed by the review evaluated the comparative effectiveness and/or harms of HSCT and alternative therapies for pediatric patients with (1) malignant solid tumors, (2) inherited metabolic diseases, and (3) autoimmune diseases.

Overall there was a low to moderate strength of evidence for the various diseases and outcomes considered. Evidence consisted largely of case series and case reports. There was a preponderance of small uncontrolled studies, as is often the case in the study of rare diseases. Data synthesis was qualitative. Pooling was not attempted, as the data were not amenable to this approach. An effort was made to identify subgroups based on prognostic factors to see if these subgroups showed patterns of treatment success or failure.

The specific recommendations for future research identified in the draft CER follow.

1. For diseases with adequate patient populations, promote multicenter randomized trials to increase the scientific rigor with which HSCT can be evaluated.
2. Use established registries to standardize the collection of demographic data and data on treatments, and to facilitate the evaluation of comparative harms and benefits of treatments.
3. Recognizing that observational studies, including case series, and case reports will continue to be attractive to investigators, recommendations to improve the usefulness and generalizability of such studies are:
  - Conduct prospective studies with contemporaneous treatments.
  - In both single-arm and comparative studies, use comparable categories for key variables, such as disease, anatomic site, disease stage, and prior treatment.
  - Report survival outcomes consistently, with a clear definition of the survival time—that is, time from diagnosis, time from transplant, or time from recurrence.
  - Consistent harms reporting is essential in facilitating the comparative evaluation of two treatments. Complete reporting of treatment-related mortality, secondary malignancy, serious infections, and veno-occlusive disease should be standard.
  - Make studies comparative when possible.
  - Multivariable regression analyses can be helpful in controlling for potential confounders when sufficient sample sizes can be obtained and should adhere to good modeling practices.
  - Study quality in observational studies should be assessed using guidance developed by Deeks et al.<sup>1</sup>
4. Develop a framework for assessing strength of evidence that is applicable to rare diseases. This should take into account contextual factors related to disease severity, rate of progression, and prognosis that can be used to evaluate the relative risk-benefit ratio of HSCT in clinical decisionmaking

5. For solid tumors, future studies should focus on single diseases and collect detailed information on prognostic factors that may allow for more refined stratification of high-risk categories, which may highlight the patients likely to benefit from HSCT and allow for less uncertainty in the interpretation of results. Followup should be sufficient to assess the impact of HSCT on the development of secondary malignancies and the long-term impact on neurocognitive development and fertility.
6. For pediatric patients with slowly progressive forms of inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms. Trials should use standardized measures of neurocognitive and neurodevelopmental outcomes.
7. For pediatric patients with autoimmune diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefits and harms.

The objective of this Future Research Needs project was to systematically prioritize research gaps in the areas of HSCT for pediatric malignant solid tumors, inherited metabolic diseases, and autoimmune diseases, and to develop a list of research questions to address the prioritized gaps.

In the first stage of this Future Research Needs report, we engaged a group of Key Informants to help develop the approach. (See “Engagement of Stakeholders, Researchers, and Funders” in the full report.) The draft CER that the Key Informants reviewed addressed over 40 diseases, with many diseases having more than one indication for transplant. After reviewing the draft CER, the Key Informants concluded that the Future Research Needs project should be focused on crosscutting evidence gaps that may be pertinent to all or some of these diseases. They stressed that the focus should be on the field as a whole, rather than specific diseases or groups of diseases. Based on these discussions, the crosscutting gaps identified in the draft CER on HSCT in the pediatric population that are pertinent to this project were identified. They are listed below.

One crosscutting evidence gap may be pertinent to all or some of these diseases:

- What are the long-term consequences of HSCT, such as overall survival; functional measures; quality of life; and adverse effects, including infertility and secondary malignancies?

In addition, two crosscutting issues were related to research methods and practice:

- What opportunities and obstacles exist for improving multicenter collaboration, increasing accrual of patients, and systematizing the reporting of outcomes and/or improving the ability to aggregate data collected at individual sites?
- Can a framework be developed to help decisionmakers incorporate contextual factors (the potential for new research, rarity of the disease, etc.) into the interpretation of the strength of the evidence? However, this is a methodological issue, which would require different expertise from that of the technical experts involved and is therefore outside the scope of this Future Research Needs project.

After the completion of the draft CER and in preparation for the Future Research Needs project, a fourth issue emerged:

- Can the long-term adverse effects of HSCT be mitigated by changes in HSCT regimen and/or subsequent interventions? Comparison of specific regimens was outside the scope of the CER due to their evolving nature and difficulties in stratifying small populations



by regimen. But it is well recognized that regimens vary in their potential for long-term adverse effects, so this was listed among the research gaps considered by the group.

## Methods

First, research gaps were identified through the BCBSA TEC draft CER. After the draft report was submitted, the HSCT CER literature search was updated and clinicaltrials.gov was searched to identify any ongoing research studies that might address the evidence gaps. Next, stakeholders were identified. To ensure the clinical relevance of this project, we elicited expert opinion from a group of nine clinical experts (the original Key Informant group) on the approach of this Future Research Needs project. In addition to the clinical experts, we engaged a group of patient advocates and a payer. The discussion with the patient advocates focused on their perspectives on outcomes that are important for patients and families from diagnosis forward. We also engaged a payer, anticipating that payer perspectives might also differ from those of transplant physicians. In the final phase, a combined Key Informant group was formed, comprised of seven members from the original Key Informant panel, one member of the patient advocate group, and one payer representative. This combined Key Informant group was tasked with ranking evidence gaps, as well as generating and ranking Key Questions.

The results of the teleconferences with the patient advocates were shared with the combined Key Informant panel for consideration during the Key Question generation phase. Key Questions for each evidence gap were generated online by the combined Key Informant panel using SurveyMonkey<sup>®</sup>, an online survey tool. The list of Key Questions was then circulated and discussed on the combined Key Informant teleconference. EPC staff compiled a final list, taking the Key Informant comments into consideration and paying particular attention to areas where ongoing efforts might overlap with prioritized gaps.

In selecting criteria for prioritization, we drew on our experience from a previous Future Research Needs project, “Future Research Needs for Comparative Effectiveness of Treatment of Localized Prostate Cancer.” In that project, the Effective Health Care Program Selection Criteria were modified to be applicable to primary research rather than to systematic reviews of original research. The criteria “Current Importance” and “Potential for Significant Health Impact” were used to rank both research gaps and Key Questions; “Feasibility” was added for the Key Questions in this report.

After the stakeholders ranked the gaps and Key Questions, the EPC evaluated potential study designs to address each Key Question. The appropriateness of any one study design to address an evidence gap was evaluated using the following criteria:

- Advantages of the study design for producing a valid result
- Resource use, size, and duration
- Ethical, legal, and social issues
- Availability of data or ability to recruit

The EPC staff relied on this framework as a guide to identifying the least biased study design that was likely to be feasible and affordable.

## Results

Seven research gaps were identified through a combination of the draft HSCT CER and conversations with Key Informants (including a patient advocate). These gaps are crosscutting in that they apply to more than one indication for HSCT.

Through an iterative process, the Key Informant panel members identified and prioritized research gaps. They then generated and prioritized a list of potential research questions to address these gaps. For the assessment of study designs, EPC staff evaluated the appropriateness of a randomized trial, a nonrandomized trial, and a cohort design. The low number of comparative studies in the field highlights the difficulty in completing research. In our analysis, we restricted our discussions to designs that would allow comparisons to be made.

The final prioritized list of research gaps and Key Questions, in order of priority, follows.

### Research Gap Number 1

#### **Mitigation of long-term adverse effects by changes in regimen, including reduced-intensity approaches, and changes in subsequent medical or psychosocial intervention.**

Reason for Gap: Insufficient information (too few studies in the literature)

### Research Question Number 1.1

Can intense psychological support of patients, parents, and siblings prevent development of post-transplant psychological disorders—including post-traumatic stress disorder (PTSD), depression, anxiety, and other adverse psychological outcomes—in surviving and nonsurviving family members?

Population (P)—Pediatric patients undergoing HSCT and their family members

Intervention (I)—Intense psychological support

Comparator (C)—Standard psychological support

Outcomes (O)—Incidence of post-transplant psychological disorders among patients and their family members

Settings (S)—Outpatient (may be delivered inpatient while undergoing HSCT)

### Research Gap Number 2

#### **Role of novel therapies for HSCT in altering short-term adverse effects and long-term effects of these therapies. Such approaches include:**

- a. **Novel cellular therapies (such as natural-killer-cell therapy) and**
- b. **Immunomodulatory therapies (including vaccine therapy).**

Reason for Gap: Insufficient information (too few studies in the literature)

### Research Question 2.1

For pediatric patients receiving a transplant due to cancer, are there interventions that may mitigate immediate and late adverse effects without interfering with the immunotherapeutic effects?

Population (P)—Pediatric patients undergoing HSCT for cancer

Intervention (I)—Novel approaches to HSCT, such as reduced-intensity, cellular, and immunomodulatory therapies

Comparator (C)—Standard approaches to HSCT

Outcomes (O)—Toxicities, antigen-specific immunity, overall survival  
Settings (S)—Inpatient

### Research Question 2.2

For pediatric patients receiving a transplant for noncancer indications, are there interventions that may mitigate short-term and late effects without interfering with the establishment and maintenance of chimerism?

Population (P)—Pediatric patients undergoing HSCT for noncancer indications

Intervention (I)—Novel approaches to HSCT, such as reduced-intensity, cellular, and immunomodulatory therapies

Comparator (C)—Standard approaches to HSCT

Outcomes (O)—Toxicities, antigen-specific immunity, overall survival

Settings (S)—Inpatient

### Research Gap Number 3

**Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT transplantation defined such an approach as including:**

- a. Emotional and psychosocial counseling for the family, with special attention to donor and nondonor siblings,**
- b. Sharing information with caregivers and peers, and**
- c. Providing families tools for navigating the complexities of the medical system and medication management instead of giving only a large amount of information without guidance.**

Reason for Gap: Insufficient information (too few studies in the literature)

### Research Question 3.1

What approaches to integrated care, from diagnosis forward, have the greatest impact on family functioning and the overall health and well-being of families faced with pediatric transplant?

Population (P)—Families (parents and siblings) of pediatric patients undergoing HSCT

Intervention (I)—Organized interventions addressing the needs of the families, including process, medical, psychosocial, and pharmacy needs

Comparator (C)—No organized family intervention

Outcomes (O)—Measures of family functioning, overall health of family members of the transplant patient

Settings (S)—Outpatient

### Research Gap Number 4

**Effectiveness of survivorship planning on long-term comprehensive followup and outcomes.**

Reason for Gap: Insufficient information (too few studies in the literature)

### Research Question 4.1

Does survivorship planning enhance compliance with long-term followup?

Population (P)—Pediatric patients undergoing HSCT

Intervention (I)—A comprehensive care summary and followup plan that summarizes treatment and sets forth standards for future care and post-treatment needs

Comparator (C)—Standard of care

Outcomes (O)—Compliance with long-term followup after HSCT

Settings (S)—Outpatient

#### Research Question 4.2

What are the comparative outcomes for those who participate in long-term survivorship followup versus those who do not?

Population (P)—Pediatric patients undergoing HSCT

Intervention (I)—Organized survivorship/long-term care plan

Comparator (C)—Standard of care

Outcomes (O)—Overall survival and incidence rates of late effects

Settings (S)—Inpatient or outpatient

Within Gap 1, the Key Informants were particularly interested in addressing the impact of post-transplant psychological disorders on pediatric HSCT recipients and families. As many as 41 percent of HSCT survivors may have persistent PTSD symptoms for up to 10 years post-transplant. Further, parents of pediatric transplant recipients also have high levels of PTSD. Addressing this gap would add to the minimal literature specifically addressing the psychosocial needs of pediatric patients and families post-HSCT.

According to the Key Informant panel, Gap 2 concerns the future of transplantation as novel approaches are discovered. They kept the Key Questions broad for the purposes of this report as data are too sparse to focus on one area.

Gap 3 was proposed by the patient advocates and endorsed by the combined panel. As the medical-home model takes shape, families of pediatric HSCT recipients are asking if the model might work for them. With the rising number of affected families, addressing this gap could have a large and beneficial impact on how these children and their families receive care.

Finally, Gap 4 focuses on the specifics of survivorship planning or long-term care planning. Cancer advocacy groups and many cancer centers have taken on the task of helping patients and their families develop and document these plans. At issue is whether the creation of such a formal document affects outcomes. The Institute of Medicine has advocated the implementation of survivorship planning, although they acknowledge that prospective research is needed to confirm or refute the assumption that survivorship planning improves outcomes.

## **Discussion**

The draft HSCT CER addressed more than 40 diseases. Evidence gaps for these diseases are in part due to the fact that we are dealing with rare diseases and the associated difficulty in attaining appropriate sample sizes. Prioritizing research gaps based on findings for specific diseases is problematic. Given the common treatment and other commonalities among families coping with serious and rare diseases, this effort focused on a number of crosscutting research gaps.

In addition to assembling national experts on pediatric HSCT, the EPC engaged a group of patient advocates to discuss treatment outcomes, as well as a payer representative. With the patient advocates, the EPC intended solely to focus on discussing outcomes. While they did provide insight on important patient outcomes, the advocates also broadened the discussion into

other areas. These parents identified challenges in coordinating the followup and care of their children, noting that the comparative effectiveness questions need to go beyond chemotherapy regimen and explore issues such as care coordination and the psychosocial needs of the whole family. These patient advocates provided a valuable unique perspective that resulted in the identification of two additional research gaps and associated research questions.

It should be noted that the Key Informants highlighted research needs that were outside the scope of the original review, such as mitigating harms secondary to treatments, exploration of psychosocial harms for the patients and families, and issues of care coordination. While none of these were within the scope of the CER, the Key Informants agreed about the importance of these issues. Current limitations in the published literature, while not reviewed here, provide a clear opportunity for advancement in the field.

Another notable point, coming from the clinical experts, was the need to understand cancer as a pediatric disease. The clinical experts advocated the separation of research on children's cancer from research on adult cancer, as both the disease and treatment have unique implications for a developing body and mind.

## Conclusions

The following four prioritized evidence gaps and Key Questions were identified.

- 1. Mitigation of long-term adverse effects by changes in regimen, including reduced-intensity approaches, and changes in subsequent medical or psychosocial intervention.**
  - 1.1. Can intense psychological support of patients, parents, and siblings prevent development of post-transplant psychological disorders—including PTSD, depression, anxiety, other adverse psychological outcomes—in surviving and nonsurviving family members?
- 2. Role of novel therapies for HSCT in altering short-term adverse effects and long-term effects of these therapies. Such approaches include:**
  - a. Novel cellular therapies (such as natural-killer-cell therapy) and**
  - b. Immunomodulatory therapies (including vaccine therapy).**
  - 2.1 For pediatric patients receiving a transplant due to cancer, are there interventions that may mitigate immediate and late adverse effects without interfering with the immunotherapeutic effects?
  - 2.2 For pediatric patients receiving a transplant for noncancer indications, are there interventions that may mitigate short-term and late adverse effects without interfering with the establishment and maintenance of chimerism?
- 3. Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT defined such an approach as including:**
  - a. Emotional and psychosocial counseling for the family, with special attention on donor and nondonor siblings,**
  - b. Sharing information with caregivers and peers, and**
  - c. Providing families tools for navigating the complexities of the medical system and medication management instead of giving only a large amount of information without guidance.**

3.1 What approaches to integrated care, from diagnosis forward, have the greatest impact on family functioning and the overall health and well-being of families faced with pediatric transplant?

**4. Effectiveness of survivorship planning on long-term comprehensive followup and outcomes.**

4.1 Does survivorship planning enhance compliance with long-term followup?

4.2 What are the comparative outcomes for those who participate in long-term survivorship followup versus those who do not?

## Reference

1. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27):iii-x, 1-173. PMID 14499048.

# Background

## Clinical Context

For many pediatric indications, the use of hematopoietic stem-cell transplantation (HSCT) is not supported by high-quality trial data. In the absence of these data the comparative effectiveness and harms of HSCT for these indications is uncertain. In February 2011, the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC) submitted a draft comparative effectiveness review (CER) on HSCT in the pediatric population to the Agency for Healthcare Research and Quality (AHRQ).<sup>1</sup> The aims of the review were to evaluate the comparative effectiveness of HSCT versus conventional therapy for the treatment of malignant solid tumors, inherited metabolic diseases, and autoimmune diseases and to assess the comparative harms.

The success of treating some of the hematopoietic pediatric diseases with HSCT has resulted in an increased number of long-term survivors. As improvements in survival have been achieved, there is greater concern with long-term effects, and how adverse effects (i.e., graft-versus-host disease, opportunistic infections, infertility, and secondary malignancies) might be mitigated. The HSCT CER is a broad-based report for all indications where HSCT is applied. The population was pediatric patients, and the indications for transplant varied by disease.

The six Key Questions addressed by the review evaluated the comparative effectiveness or harms of HSCT and alternative therapies for pediatric patients with (1) malignant solid tumors, (2) inherited metabolic diseases, or (3) autoimmune diseases. See Appendix A for the full Key Questions.

Table 1 displays the conclusions for each indication in the draft HSCT CER by the quality of the evidence as determined by the EPC Program-modified GRADE criteria. Definitions of the quality grades low, moderate or high refer to the level of confidence that the body of evidence reflects the true effect. See Appendix B for a list of conclusions by Key Question and disease and Appendix C for diseases where evidence was insufficient to reach a conclusion. These items were presented to stakeholders in preparation of this report. It should be noted that this future research needs project was based on the draft CER, and based on updated literature searches and peer review comments, the conclusions in the final CER could change.

Evidence consisted largely of case series and case reports. There was a preponderance of small, uncontrolled studies, as is often the case in the study of rare diseases. Data synthesis was qualitative. Pooling was not attempted, as the data were not amenable to this approach. An effort was made to identify subgroups based on prognostic factors to see if these subgroups showed patterns of treatment success or failure.

The objective of this future research needs project is to systematically prioritize research gaps in the areas of HSCT for pediatric malignant solid tumors, inherited metabolic disease, and autoimmune disease and to develop a list of research questions to address the prioritized gaps.

**Table 1. Conclusions for each indication in the BCBSA TEC Draft HSCT CER: Single HSCT versus conventional therapy for overall survival**

	Low	Moderate	High
Evidence suggesting comparative benefit of HSCT over conventional therapy	<ul style="list-style-type: none"> <li>Relapsed/refractory Astrocytoma</li> <li>Attenuated MPS II (Hunter's disease)*</li> </ul>		<ul style="list-style-type: none"> <li>Wolman's disease</li> <li>Farber's disease Type 2/3**</li> </ul>
Evidence suggesting no comparative benefit of HSCT over conventional therapy	<ul style="list-style-type: none"> <li>Ewing sarcoma family of tumors</li> <li>Wilms Tumor</li> <li>Newly Diagnosed Glioblastoma Multiforme</li> <li>Niemann-Pick Type A*</li> <li>Niemann-Pick type C*</li> <li>MPS III (Sanfilippo)*</li> <li>Farber's disease type I</li> <li>Juvenile form of GM1*</li> <li>Juvenile Tay-Sachs*</li> </ul>	<ul style="list-style-type: none"> <li>Metastatic Rhabdomyosarcoma</li> <li>Extraocular Retinoblastoma with CNS involvement</li> <li>Gaucher Type III*</li> <li>Severe and attenuated MPS II (Hunters disease)*</li> <li>Infantile ceroid lipofuscinosis*</li> </ul>	
Evidence suggesting comparative harm of HSCT over conventional therapy	<ul style="list-style-type: none"> <li>Nonanaplastic Mixed or Unspecified Ependymoma</li> </ul>		

**Abbreviations:** BCBSA TEC = Blue Cross and Blue Shield Association Technology Evaluation Center; CER = Comparative Effectiveness Review; CNS = central nervous system; GM1 = monosialotetrahexosylganglioside; HSCT = hematopoietic stem-cell transplantation; MPS = mucopolysaccharoidosis

\*Neurocognitive and neurodevelopmental outcome

\*\*Joint mobility outcome

## Evidence Gaps

The draft HSCT CER addressed more than 40 diseases, with many diseases having more than one indication for transplant. These diseases, or the specific indication within these diseases, all are rare. The draft HSCT CER, and thus this future research project, were unusual, in that typically the focus is on one disease with multiple interventions. Here, we focused on one intervention and multiple diseases and disease indications, presenting a challenge for how future research needs are formulated.

The evidence gaps identified in the draft HSCT CER are listed below:

1. For diseases with adequate patient populations, promote multicenter randomized trials to increase the scientific rigor in which HSCT can be evaluated.
2. Use established registries to standardize the collection of demographic data, treatments, and to facilitate the evaluation of comparative harms and benefits of treatments.
3. Recognizing that observational studies, including case series, and case reports will continue to be attractive to investigators, recommendations to improve the usefulness and generalizability of such studies are:
4. Conduct prospective studies with contemporaneous treatments.
  - Patients in both single arm and comparative studies would be comparable in terms of key variables, such as disease, anatomic site, disease stage, and prior treatment.
  - Consistent reporting of survival outcomes, with a clear definition of the survival time, i.e., time from diagnosis, time from transplant or time from recurrence.
  - Consistent harms reporting is essential in facilitating the comparative evaluation two treatments. Complete reporting of treatment related mortality, secondary malignancy, serious infections, and veno-occlusive disease would be standard.



- Make studies comparative when possible.
  - Multivariable regression analyses can be helpful in controlling for potential confounders, when sufficient sample sizes can be obtained, and would adhere to good modeling practices.
  - Guidance for study quality in observational studies has been addressed by Deeks et al.<sup>2</sup>
5. Develop a framework for assessing strength of evidence that is applicable to rare diseases. This would take into account contextual factors related to disease severity, rate of progression, and prognosis that can be used to evaluate the relative risk-benefit ratio of HSCT in clinical decisionmaking.
  6. For solid tumors, future studies would focus on single diseases, and collect detailed information on prognostic factors that may allow for more refined stratification of high-risk categories which may highlight those likely to benefit from HSCT and allowing for less uncertainty in the interpretation of results. Followup would be sufficient to assess the impact of HSCT on the development of secondary malignancies and long-term impact on neurocognitive development and fertility.
  7. For pediatric patients with slowly progressive forms of inherited metabolic diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms. Trials would use standardized measure of neurocognitive and neurodevelopmental outcomes.
  8. For pediatric patients with autoimmune diseases, controlled trials with sufficient followup are needed to evaluate the long-term balance of benefit and harms.

As is detailed in the Methods section, in the first stage of this future research needs report, we engaged a group of key informants to help develop the approach (see section on “Engaging stakeholders, researchers and funders”). In consultation with the key informants, after having reviewed the draft CER they concluded that for this CER which addressed over 40 diseases, with many diseases having more than one indication for transplant, the future research needs project should be focused on crosscutting evidence gaps that may be pertinent to all or some of these diseases. They stressed that the focus should be on the field as a whole, rather than specific diseases or groups of diseases.

Due to these circumstances, the future research needs project focused on crosscutting evidence gaps that may be pertinent to all or some of these diseases. The crosscutting gaps identified in the draft HSCT CER are listed below:

One crosscutting evidence gap may be pertinent to all or some of these diseases.

- What are long-term consequences of HSCT, such as overall survival; functional measures; quality of life; and adverse effects, including infertility and secondary malignancies?

In addition, there are two crosscutting issues related to research methods and practice.

- What are the opportunities and obstacles for improving multicenter collaboration, to increase accrual of patients and systematize reporting of outcomes and/or to improve the ability to aggregate data collected at individual sites?
- Can a framework be developed to help decision makers incorporate contextual factors (such as the potential for new research, rarity of the disease, etc.) into the interpretation of the strength of the evidence? However, for the purposes of this review, we considered it

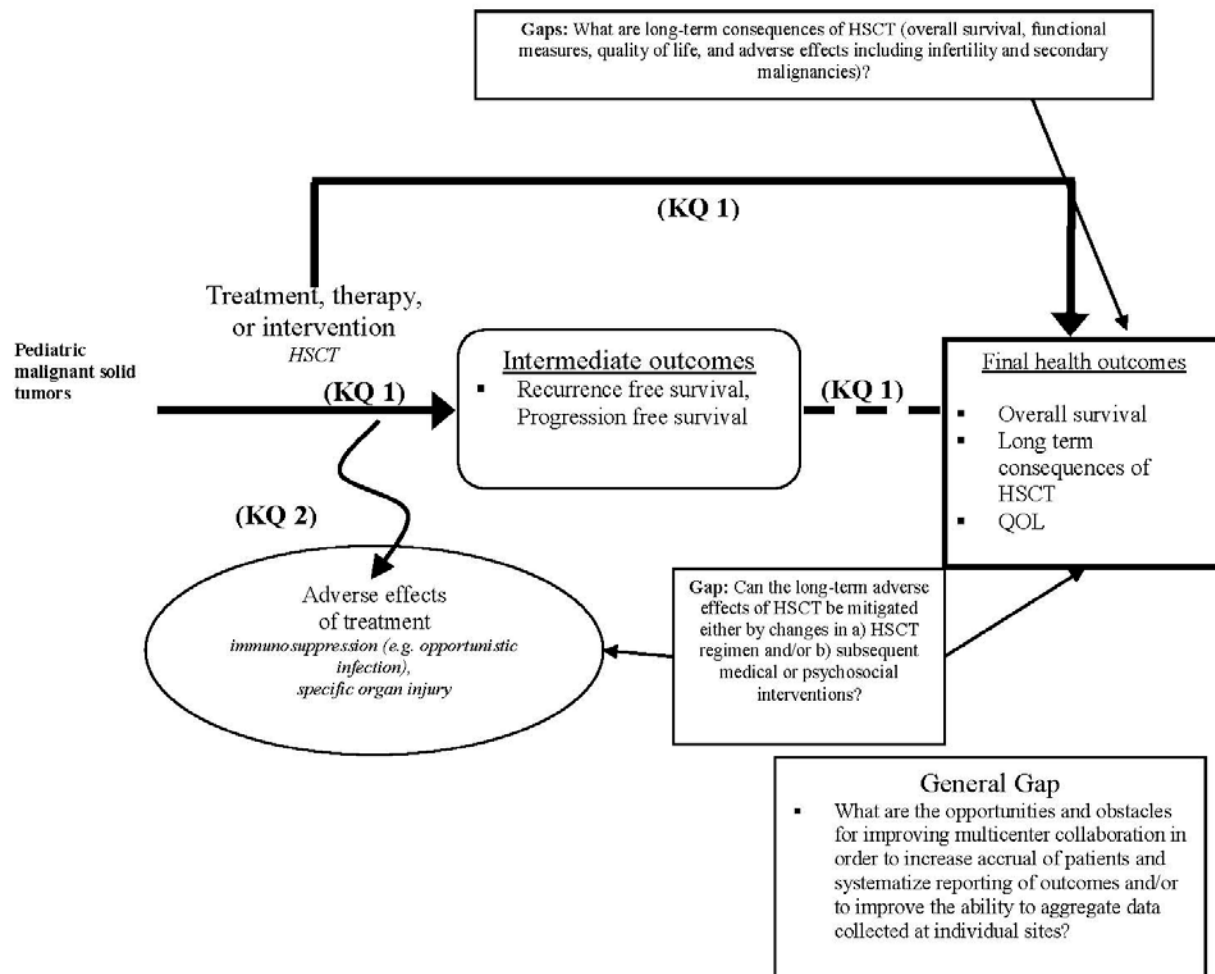
methodological issue, which would draw on other expertise and is therefore outside the scope of this future research project.

In addition, subsequent to the completion of the draft CER, and in preparation for the future research needs project a fourth issue emerged: Can the long-term adverse effects of HSCT be mitigated by changes in HSCT regimen and/or subsequent interventions? Comparison of specific regimens was outside the scope of the CER due to their evolving nature of and difficulties of stratifying small populations by regimen. But, it is well recognized that regimens vary in their potential for long-term adverse effects. Experts involved in the CER considered this issue and agreed that an examination of regimens should remain outside the scope.

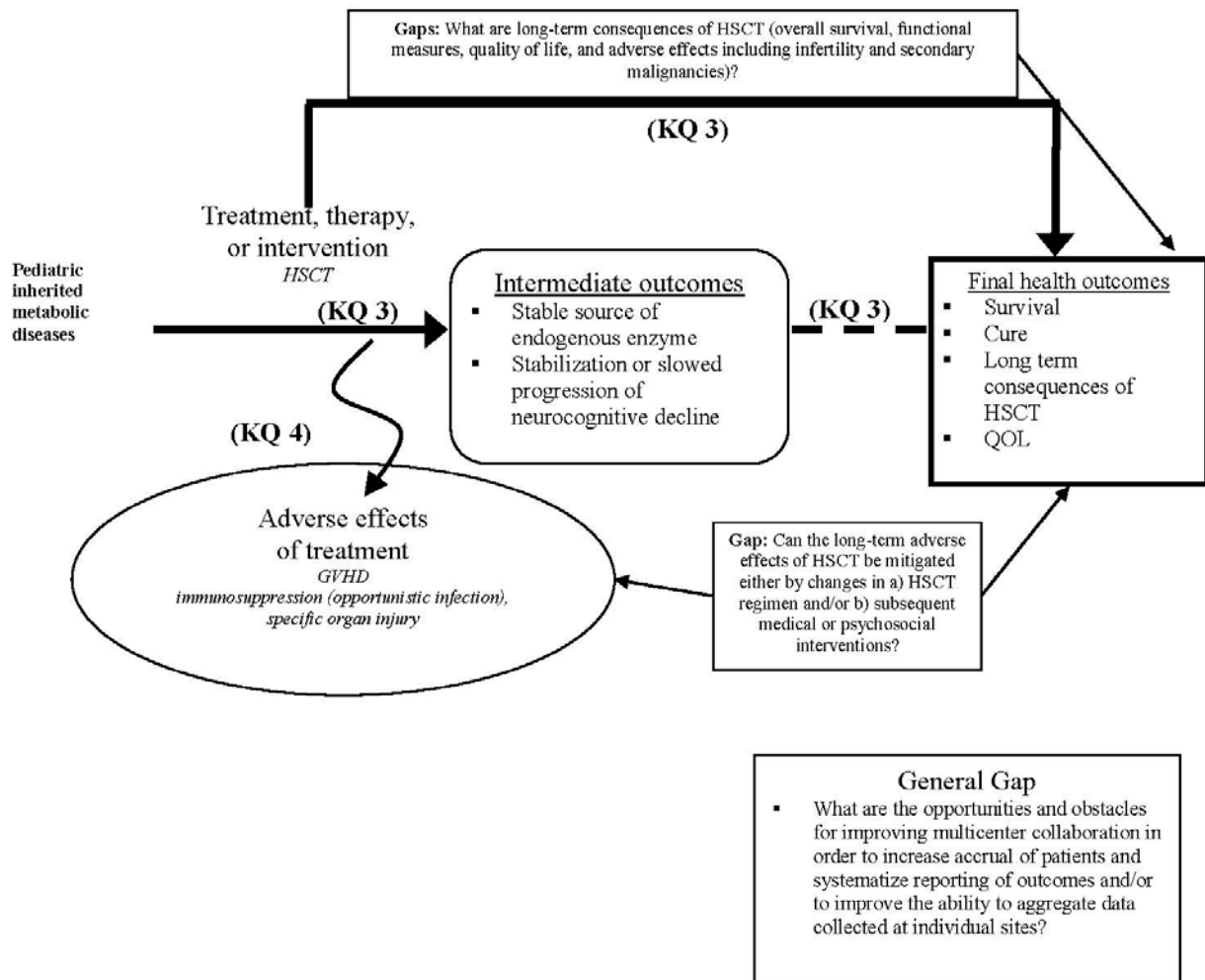
## Analytic Framework

Analytic frameworks are shown in Figures 1, 2, and 3.

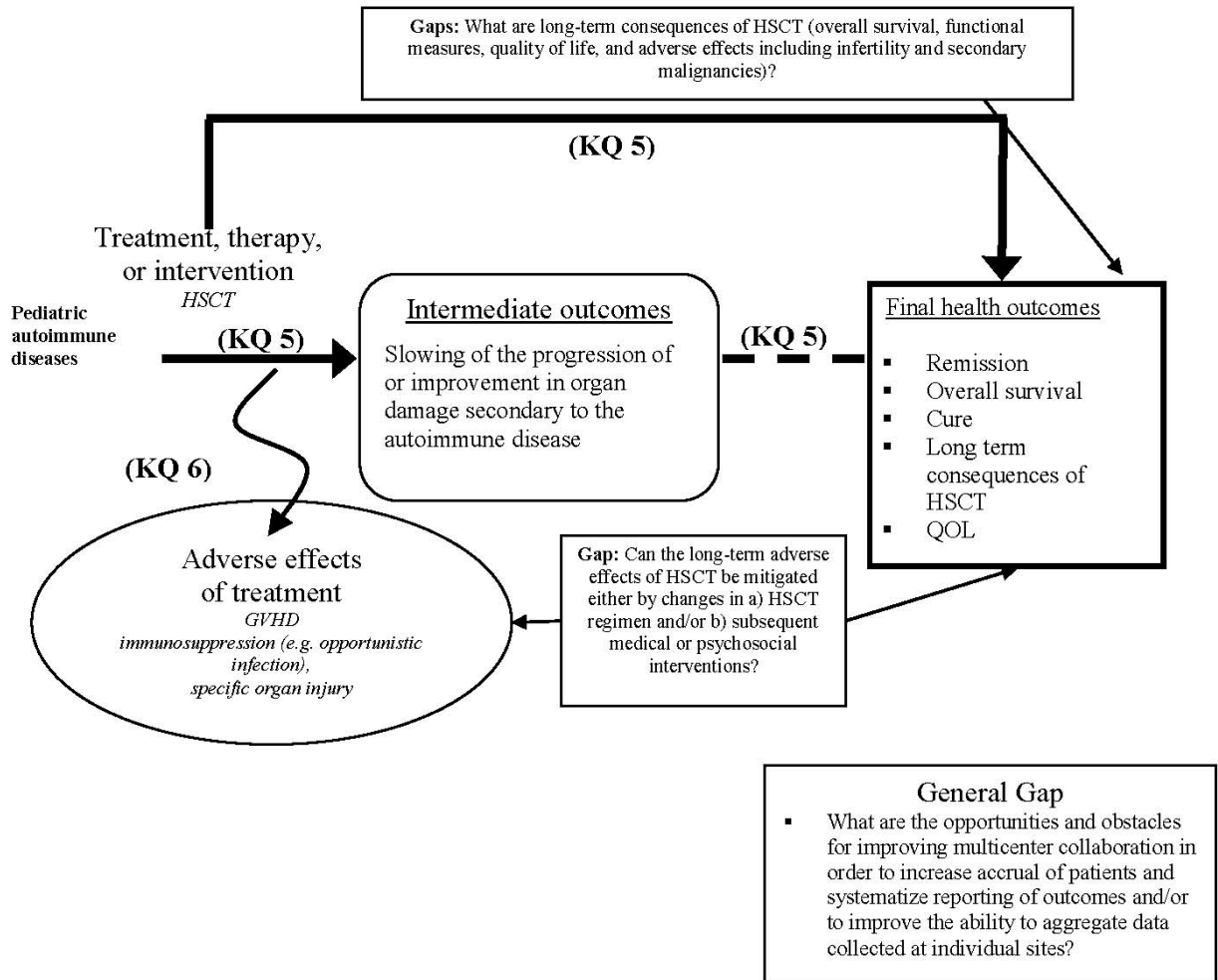
**Figure 1. Analytic framework for HSCT for pediatric malignant solid tumors**



**Figure 2. Analytic framework for HSCT for pediatric inherited metabolic diseases**



**Figure 3. Analytic framework for HSCT for pediatric autoimmune diseases**



## Methods

Figure 4 outlines the process steps of this future research project on HSCT for pediatrics. The details are described in the text.

First, research gaps were identified through the BCBSA TEC draft CER. After the draft report was submitted, the HSCT CER literature search was updated and clinicaltrials.gov was searched to identify any ongoing research studies that might address the evidence gaps. Next, stakeholders were identified and through an iterative process the gaps were shared with and refined by these stakeholders (see section on engagement of stakeholders, researchers and funders). A final group of stakeholders comprised of transplant physicians, one patient advocate and a payer was formed, this group prioritized the refined evidence gaps, and generated Key Questions (see sections on criteria for prioritization, and research question development). Gaps were prioritized through the web using the SurveyMonkey<sup>®</sup> Web site. Finally, the exploration of various research designs was conducted solely by the EPC. Details of these steps follow.

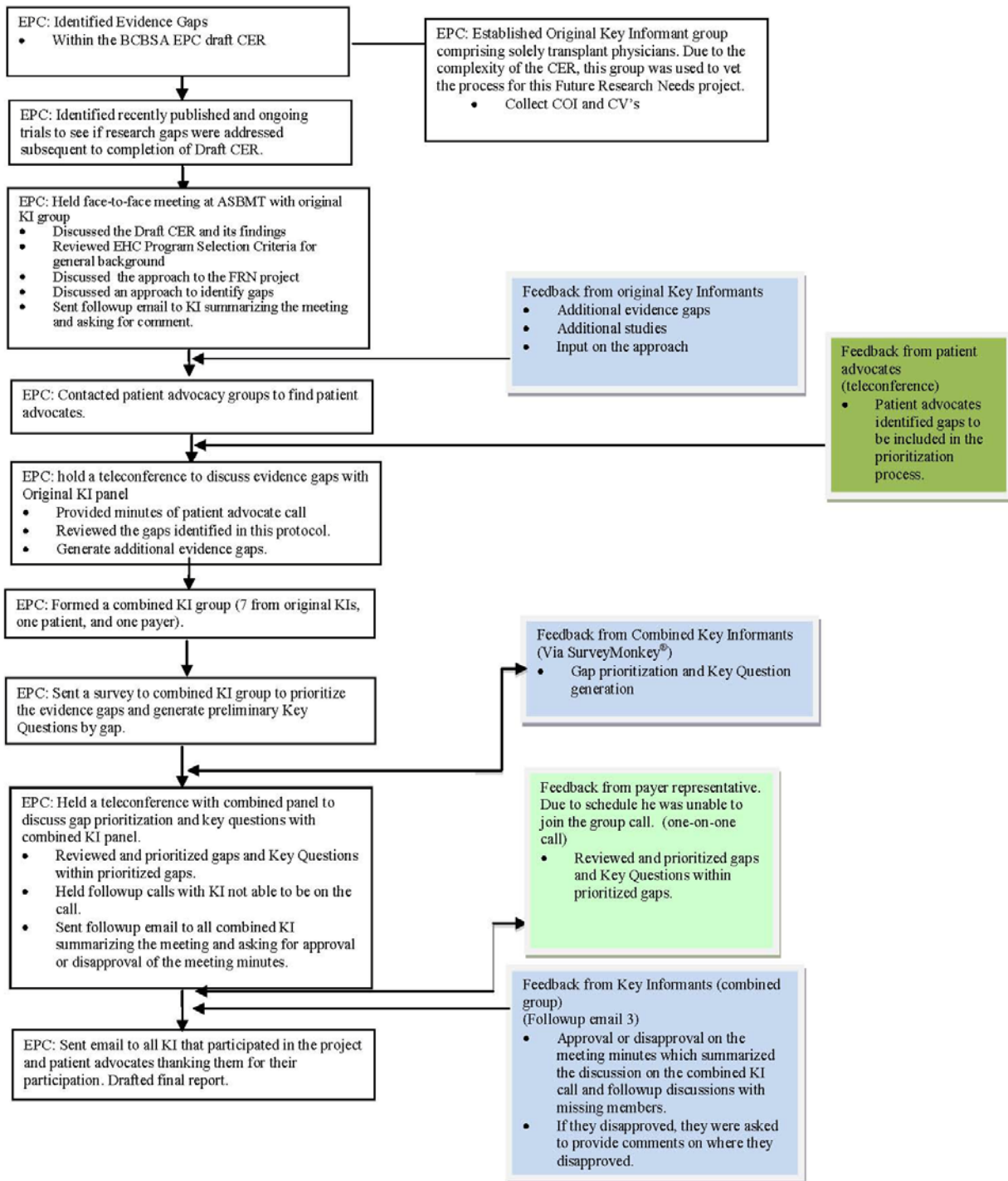
### Identification of Evidence Gaps

A link to the draft HSCT CER and a full list of all diseases and indications reviewed in the draft report were presented to the original group of key informants before the first meeting. Four of these key informants had previously served as key informants and technical expert panel members on the BCBSA TEC HSCT CER. In addition, the CER literature was updated (see Appendix D for the search strings), but few newly published studies were found, as the BCBSA TEC draft CER had been recently completed. Searches of ClinicalTrials.gov identified any ongoing research studies that might address the evidence gaps (Appendix E).

As described above, the following crosscutting gaps identified in the draft HSCT CER, or subsequent to the draft CER in preparation for the future research needs project were the gaps that the original Key Informants believed to be the most relevant to this future research needs report. The following gaps were then presented to additional key informants as is detailed in the engaging stakeholders, researchers and funders section below.

- Can the long-term adverse effects of HSCT be mitigated by changes in HSCT regimen and/or subsequent interventions?
- What are long-term consequences of HSCT (overall survival, functional measures, quality of life, and adverse effects (including infertility and secondary malignancies)?
- What are the opportunities and obstacles for improving multicenter collaboration to increase accrual of patients and systematize reporting of outcomes and/or to improve the ability to aggregate data across sites?

**Figure 4. Outline of the process steps of the future research needs project on HSCT in pediatrics**



**Abbreviations:** ASBMT = American Society of Blood and Marrow Transplantation; BCBSA EPC = Blue Cross and Blue Shield Association Evidence-based Practice Center; CER = Comparative Effectiveness Review; EPC = Evidence-based Practice Center; FRN = Future Research Needs; HSCT = hematopoietic stem-cell transplantation; KI = Key Informant

- Can a framework be developed to help decision makers incorporate contextual factors (such as the potential for new research, rarity of the disease, etc.) into the interpretation of the strength of the evidence. However, for the purposes of this review we considered it methodological issue, which would draw on other expertise and is therefore outside the scope of this future research project.

In the draft HSCT CER, the BCBSA TEC EPC discussed the challenges in grading a body of evidence for a rare disease. However, the examination of methodological issues for systematic review was outside the scope of the present future research needs project. The development of a framework requires a focus on a different body of literature and engagement of different Key Informants, both oriented to methods.

## **Criteria for Prioritization**

In criteria for prioritization, we drew on our experience from a future research project titled Future Research Needs for Localized Prostate Cancer,<sup>3</sup> in which the Effective Health Care (EHC) Program Selection Criteria (see Appendix F) were modified to be applicable to primary research rather than to systematic reviews of original research.<sup>4</sup> They keep the spirit of the EHC criteria but are more succinct and accessible to the Key Informants (Table 2). The criteria were used to prioritize gaps and Key Questions, and, when necessary, proposed studies.

Appropriateness and importance were the main criteria for prioritizing Key Questions, while desirability, feasibility, and potential impact played a larger role when prioritizing the proposed research studies. The modified EHC Program Selection Criteria were distributed to Key Informant panel members each time they were asked to prioritize gaps or Key Questions. Prioritization of study designs was handled by the EPC in accordance with the AHRQ funded methods work under development.<sup>5</sup>

As a group of clinical experts in HSCT in pediatrics, the original Key Informant panel provided insight into how future research agendas and proposed studies to address gaps fit within these prespecified criteria.

**Table 2. Prioritization criteria for research gaps and proposed research studies**

Category	Criterion
<b>Current importance</b>	<ul style="list-style-type: none"> <li>▪ Incorporates both clinical benefits and harms.</li> <li>▪ Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care.</li> <li>▪ Addresses high costs to consumers, patients, health care systems, or payers.</li> <li>▪ Utility of available evidence limited by changes in practice, e.g., disease detection.</li> </ul>
	<ul style="list-style-type: none"> <li>▪ Potential for significant health impact:                             <ul style="list-style-type: none"> <li>○ To improve <u>health outcomes</u>.</li> <li>○ To reduce <u>significant variation</u> related to quality of care.</li> <li>○ To reduce <u>unnecessary burden</u> on those with health-care problems.</li> </ul> </li> <li>▪ Potential for significant economic impact, reducing unnecessary or excessive costs.</li> <li>▪ Potential for evidence-based change.</li> <li>▪ Potential risk from inaction, i.e., lack of evidence for decisionmaking produces unintended harms.</li> <li>▪ Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age).</li> </ul>
	<ul style="list-style-type: none"> <li>• Adds useful new information to existing portfolio of research on topic OR</li> <li>• Validates existing research when body of evidence is scant.</li> </ul>
	<p><i>Factors to be considered:</i></p> <ul style="list-style-type: none"> <li>▪ Interest among researchers.</li> <li>▪ Duration.</li> <li>▪ Cost.</li> <li>▪ Methodological complexity (e.g., do existing methods need to be refined?).</li> <li>▪ Implementation difficulty.</li> <li>▪ Facilitating factors.</li> <li>▪ Potential funders.</li> </ul>

## Methods for Ranking Research Gaps

Research Gaps were ranked via the SurveyMonkey® Web site. Key informants were sent a link to the Web site where they ranked the research gaps from 1 to 7 and generated Key Questions for each gap (Appendix G). The survey allowed each rank to be used only once. Points were assigned to each gap: 1 point for a ranking of seventh, up to 7 points for a ranking of first. The gap with the largest number of points was assigned the highest priority. The comments received from the combined Key Informant panel were reviewed by EPC staff and incorporated where necessary. In addition to the modified EHC Program Selection Criteria, special attention was paid to where Research Gaps overlapped with existing research.

## Engagement of Stakeholders, Researchers, Funders

Central to the methodology of this report was the use of key informants to identify and prioritize evidence gaps. We elicited expert opinion from a group of nine clinical experts (original Key Informant group) with the goal of improving evidence in the area of pediatric HSCT. This original group of Key Informants was comprised of transplant physicians and they were selected to cover the clinical areas in the draft HSCT CER, as well as additional areas important for prioritizing research needs and studies such as ethics and issues of survivorship. Due to the number of disease and disease indications in the CER, this initial group was convened to discuss the best approach for this future research needs project. In recruiting the original Key Informant panel, we contacted Technical Expert Panel (TEP) members from the draft HSCT CER as well as additional clinical experts. This first meeting occurred at the American Society of Blood and Marrow Transplantation (ASBMT) meeting in February, 2011.



For this first meeting and to orient the original Key Informants to the project, they received a link to the BCBSA TEC draft HSCT CER; a list of all diseases addressed in the draft CER matched to its draft CER result; and a list of all new literature and ongoing studies, identified by the disease the study was addressing. Additionally, they received a copy of the modified EHC Program Selection Criteria for background (see Table 2). During the initial face-to-face meeting, the original Key Informants were asked to review and discuss the draft CER, its evidence gaps, and potential approaches for the future research project.

To include a broader array of stakeholder input the original Key Informant panel was supplemented with a group of patient advocates and a payer representative. The advocates were identified through advocacy groups and with the help of one of the original Key Informants. The payer was a representative from a Blue Cross and Blue Shield Plan. The patient advocate group contributed to the evidence gap generation through a separate teleconference (advocate call). The patient advocates were oriented to the project through a discussion of the draft CER and the purpose of the future research needs project. The payer was also engaged in a separate one on one call. We solicited input from a broad array of stakeholders to identify gaps, but then to be in compliance with the Paperwork Reduction Act, the final group that prioritized the gaps, and generated and prioritized Key Questions within gap was a combined panel comprised of seven original key informants, one of the patient advocates and the payer.

The list of evidence gaps was circulated to the combined Key Informant panel for discussion, prioritization and preliminary Key Question development. The combined panel was sent a link to the SurveyMonkey<sup>®</sup> Web site, where they ranked the gaps from 1 to 7 and generated Key Questions for each gap (Appendix G). The comments received from the combined Key Informant panel were reviewed by EPC staff and incorporated where necessary.

A consensus on the important Key Questions for each gap was reached on the combined Key Informant panel teleconference (#2), and confirmed through the two followup calls with the patient advocate and payer who were unable to join the call due to schedule conflicts. Based on this, the EPC staff in consultation with the AHRQ Task Order Officer decided that it would be most appropriate to ask the combined Key Informant panel to approve or disapprove the meeting minutes, but that we would not share a list of the resulting Key Questions. Summaries from the followup interviews were included with the summary comments from the teleconference (#2). These minutes were sent to the combined Key Informant panel for approval or disapproval. Panel members who disapproved were asked to cite their concerns. The comments received from the combined Key Informant panel were reviewed by EPC staff and incorporated where necessary.

To enhance public engagement, AHRQ will solicit broader input on this document by making it available for public input, which may be incorporated and reflected in the final report.

## **Research Question Development and Study Design Considerations**

A teleconference with patient advocates (advocate call) was used to elicit their comments on the outcomes they feel are important for patients and families from diagnosis forward. These comments were shared with the combined KI panel for consideration during the Key Question generation phase. Key Questions for each evidence gap were generated through Survey Monkey<sup>®</sup> by the combined KI panel. The list of Key Questions was circulated and discussed on the combined KI teleconference (#2). EPC staff compiled a final list taking the KI comments into consideration.

As described above, the EPC staff evaluated potential study designs to address each of the Key Questions. This approach is consistent with the guidance under development by AHRQ. The appropriateness of any one study design to address an evidence gap was evaluated using the following criteria:

- Advantages of the study design for producing a valid result;
- Resource use, size, and duration;
- Ethical, legal, and social issues;
- Availability of data or ability to recruit

The EPC staff relied on this framework as a guide during discussions of the least biased study design that was likely to be feasible and affordable. Public comments received after the document is posted will be incorporated into the final report.

# Results

## Research Needs

A total of seven research gaps were identified through a combination of the BCBSA TEC draft HSCT CER and conversations with the key informants (including patient advocates). These gaps are crosscutting in that they apply to more than one indication for HSCT. The gaps are:

- Long-term consequences of HSCT, measured by overall survival, functional measures, quality of life, and adverse effects
- Mitigation of long-term adverse effects by changes in regimen, including reduced intensity approaches, and changes in subsequent medical or psychosocial intervention
- Role of novel therapies for HSCT in altering short-term adverse effects and the long-term effects of these therapies. Such approaches include:
  - novel cellular therapies (such as natural-killer-cell therapy), and
  - immunomodulatory therapies (including vaccine therapy).
- Multicenter collaboration to increase accrual of patients and systematize outcome reporting
- Effectiveness of survivorship planning on long term, comprehensive followup and outcomes
- Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT transplantation defined such an approach as including:
  - emotional and psychosocial counseling for the family with a special attention on donor and nondonor siblings,
  - information to share with caregivers and peers, and
  - tools rather than only a large amount of information for navigating the complexities of the medical system and medication management.
- Uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center

As stated in the Methods section, we attempted to have the Key Informants rank the research gaps and generate Key Questions online prior to a teleconference. Only half of the group responded to the online request. Therefore, on the teleconference, the Key Informants discussed the evidence gaps and appropriate Key Questions. Both the preliminary results based on the five responses and the more complete results based on eight responses elicited after the conference call are found in Appendix H. During the teleconference (#2), the Key Informants discussed the relative importance of each of the seven identified gaps, and then addressed the important Key Questions within each gap. After the teleconference (#2), followup phone calls were completed with two members not on the call, and one additional Key Informant submitted rankings, bringing the total to eight. The rankings from one original Key Informant were never received. The EPC generated the final ranking of research gaps taking all Key Informant comments into account. In the final ranking of the research gaps based on feedback from the key informants on gaps where research was known to be underway were removed from the listing.

The final four research gaps, in priority order are:

1. Mitigation of long-term adverse effects by changes in regimen, including reduced intensity approaches, and changes in subsequent medical or psychosocial intervention.

2. Role of novel therapies for HSCT in altering short-term adverse effects and the long-term effects of these therapies. Such approaches include:
  - a. novel cellular therapies (such as natural-killer-cell therapy), and
  - b. immunomodulatory therapies (including vaccine therapy).
3. Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT transplantation defined such an approach as including:
  - a. emotional and psychosocial counseling for the family with a special attention on donor and nondonor siblings,
  - b. information to share with caregivers and peers, and
  - c. tools rather than only a large amount of information for navigating the complexities of the medical system and medication management.
4. Effectiveness of survivorship planning on long-term, comprehensive followup and outcomes.

Within Gap 1, mitigation of long-term effects by changes in regimen and changes in subsequent medical or psychosocial intervention, the Key Informants were particularly interested in addressing the impact of post-transplant psychological disorders in pediatric HSCT recipients and families. Patient advocates initiated the emphasis on psychosocial support and their view was embraced by all the key informants. Moreover, the matter of changes in regimen was of less interest, as there is ongoing research in the area. It is estimated that as many as 41 percent<sup>6,7</sup> of survivors of HSCT have persistent PTSD symptoms for up to 10 years post-transplant.<sup>8,9</sup> Further, parents of pediatric transplant recipients also have high levels of PTSD.<sup>10</sup> In 2010, DuHamel and colleagues reported that a brief telephone-administered cognitive behavioral therapy intervention for HSCT survivors was effective in reducing illness-related PTSD and general distress.<sup>11</sup> Addressing this gap would add to the minimal literature specifically addressing the psychosocial needs of pediatric patients and families post-HSCT.

Gap 2 addresses ways to reduce the adverse effects of HSCT. Our Key Informant panel believed this to be the future of transplantation as novel approaches are discovered. They kept the Key Questions broad for the purposes of this report, as they felt that data are too sparse to point to one focus area.

Gap 3, impact on outcomes of a “family-centered” approach to transplantation, was proposed by the patient advocates and endorsed by the combined panel. Families of pediatric HSCT recipients are asked to endure a great deal over time and to acquire extraordinary new skills to care for their child. As the medical home model takes shape, families of pediatric HSCT recipients are asking whether the model might work for them. According to the Joint Principles of the Patient-Centered Medical Home,<sup>12</sup> a patient-centered medical home should have a personal physician, physician-directed medical practice, whole person orientation, coordinated care, quality and safety, enhanced access, and adequate payment. The number of autologous transplants in the U.S. has steadily increased since 2000, and allogeneic transplants from unrelated donors surpassed the number of allogeneic transplants from related donors after 2007.<sup>13</sup> With the rising number of affected families, addressing this gap could have a large and beneficial impact on how these children and their families receive care.

Finally, Gap 4 focuses on the specifics of survivorship planning or long-term care planning. Cancer advocacy groups and many cancer centers have taken on the task of aiding patients develop these plans. At issue is whether the creation of such a formal document affects

outcomes. The National Academies Press published a book called *Implementing Cancer Survivorship Care Planning*.<sup>14</sup> They advocate the implementation of survivorship planning, but acknowledged that while it could reasonably be expected that survivorship planning would improve outcomes, prospective research is needed to confirm or refute this assumption. Addressing Gap 4 would begin to answer this question specifically for pediatric patients undergoing HSCT.

Gaps not included in the prioritized list include (1) long-term effects of HSCT measured by overall survival, functional measures, quality of life, and adverse effects; (2) multicenter collaboration to increase accrual of patients and systematize outcome reporting; and (3) uniform reporting of outcome data to allow patient/caregiver comparison of HSCT outcomes by transplant center. These gaps were assigned lower priority than the others not due to their relative importance, but because other groups are working on these issues. First, the Pediatric Blood and Marrow Transplant Consortium (PBMT) is currently working on and has generated multiple Key Questions to specifically target and investigate long-term effects.<sup>15</sup> The Key Informants stated that while multicenter collaboration is encouraged and mechanisms are in place, low levels of funding for pediatric research and pressure to close studies with slow accrual limit a center's ability to engage in such research. Addressing funding streams was outside the scope of this project. Finally, the issue of uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center is being handled by the Center for International Blood and Marrow Transplant Research (CIBMTR).<sup>16</sup> CIBMTR was awarded a contract to administer the Stem Cell Therapeutic Outcomes Database (SCTOD) of the C.W. Bill Young Cell Transplantation Program. The Key Informants discussed that while this database is not perfect, it provides statistics on outcomes from autologous, related and unrelated allogeneic transplants performed by U.S. transplant centers.

As described above, during teleconference #2 the combined Key Informant panel discussed relevant Key Questions for each gap, and followup calls were conducted with members unable to attend the main call. Consensus on the important Key Questions for each gap was achieved. Therefore, no additional ranking of Key Questions was performed.

The final prioritized list of research gaps and Key Questions, in order of priority are:

#### Research Gap Number 1

**Mitigation of long-term adverse effects by changes in regimen, including reduced intensity approaches, and changes in subsequent medical or psychosocial intervention.**

Reason for Gap: insufficient information (too few studies in the literature)

#### Research Question Number 1.1

Can intense psychological support of patient, parents and siblings prevent development of post-transplant psychological disorders (including PTSD, depression, anxiety, other adverse psychological outcomes) in "surviving" and "nonsurviving" family members?

Population (P) – family members of and pediatric patients undergoing HSCT

Intervention (I) – intense psychological support

Comparator (C) – standard psychological support

Outcomes (O) – incidence of post-transplant psychological disorders among patients and their family members

Settings (S) – outpatient (may be delivered inpatient while undergoing HSCT)

## Research Gap Number 2

**Role of novel therapies for HSCT in altering short-term adverse effects and the long-term effects of these therapies. Such approaches include:**

- a. novel cellular therapies (such as natural killer-cell therapy), and**
- b. immunomodulatory therapies (including vaccine therapy).**

Reason for Gap: insufficient information (too few studies in the literature)

### Research Question 2.1

For pediatric patients receiving a transplant due to cancer: Are there interventions that may mitigate immediate and late adverse effects without interfering with the immunotherapeutic effects?

Population (P) – pediatric patients undergoing HSCT for cancer

Intervention (I) – novel approaches to HSCT such as reduced intensity, cellular and immunomodulatory therapies.

Comparator (C) – standard approaches to HSCT

Outcomes (O) – toxicities, antigen-specific immunity, overall survival

Settings (S) – inpatient

### Research Question 2.2

For pediatric patients receiving a transplant for noncancer indications: Are there interventions that may mitigate immediate and late adverse effects without interfering with the establishment and maintenance of chimerism?

Population (P) – pediatric patients undergoing HSCT for noncancer indications

Intervention (I) – novel approaches to HSCT such as reduced intensity, cellular and immunomodulatory therapies.

Comparator (C) – standard approaches to HSCT

Outcomes (O) – toxicities, antigen-specific immunity, overall survival

Settings (S) – inpatient

## Research Gap Number 3

**Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT transplantation defined such an approach as including:**

- a. emotional and psychosocial counseling for the family with a special attention on donor and nondonor siblings,**
- b. information to share with caregivers and peers, and**
- c. provision of tools rather than only a large amount of information for navigating the complexities of the medical system and medication management.**

Reason for Gap: insufficient information (too few studies in the literature)

### Research Question 3.1

What approaches to integrated care, from diagnosis forward, have the greatest impact in family functioning and overall health and well-being for families faced with pediatric transplant?

Population (P) – families (parents and siblings) of pediatric patients undergoing HSCT  
Intervention (I) – organized interventions addressing the needs of the families including process, medical, psychosocial, pharmacy.  
Comparator (C) – no organized family intervention  
Outcomes (O) – measures of family functioning, overall health of family members of the transplant patient.  
Settings (S) – outpatient

#### Research Gap Number 4

#### **Effectiveness of survivorship planning on long term, comprehensive followup and outcomes.**

Reason for Gap: insufficient information (too few studies in the literature)

#### Research Question 4.1

Does survivorship planning enhance compliance with long-term followup?

Population (P) – pediatric patients undergoing HSCT  
Intervention (I) – A comprehensive care summary and followup plan that summarizes treatment and sets forth standards for future care and post-treatment needs.  
Comparator (C) – standard of care  
Outcomes (O) – compliance with long-term followup after HSCT  
Settings (S) – outpatient

#### Research Question 4.2

What are the comparative outcomes for those that participate in long-term survivorship followup versus those who do not?

Population (P) – pediatric patients undergoing HSCT  
Intervention (I) – organized survivorship/long-term care plan  
Comparator (C) – standard of care  
Outcomes (O) – overall survival and incidence rates of late effects  
Settings (S) – in- or outpatient

The specific research projects to address each gap and Key Question are described in more detail in the following section. For the assessment of study designs we evaluated the appropriateness of a randomized trial, a nonrandomized trial, and a prospective cohort. The low number of comparative studies in the field highlights the difficulty in completing research. However, in our analysis of the appropriate study designs, we felt it would be important to restrict our discussions to designs where comparisons could be made. While a retrospective design with a control group can offer comparison and we have used that suggestion below, in general, the research questions focus on new interventions for which there are limited existing data.

#### Research Question Number 1.1

Can intense psychological support of patients, parents and siblings prevent development of post-transplant psychological disorders (including PTSD, depression, anxiety, other adverse psychological outcomes) in surviving and nonsurviving family members? (Table 3)

**Table 3. Study design evaluations for research question 1.1**

Study Design Considerations	Randomized Trial	Nonrandomized Comparative Study	Prospective Cohort
<u>Description of design</u>	<p>Individual participants <i>randomly</i> assigned to intense psychological support or no support for a period following transplant.</p> <p>Centers could be the unit of analysis and randomized to provide intense psychological support or usual care after transplantation. A disadvantage of this over individual patient randomization is that outcomes for patients from a given center are not independent and other aspects of care may help account for differences in outcomes.</p>	<p>Individual participants assigned by nonrandom process to intense psychological support or no support for a period following transplant.</p> <p>Individual centers are assigned to provide intense psychological support or usual care after transplantation. A disadvantage of this over individual patient randomization is that outcomes for patients from a given center are not independent and other aspects of care may help account for differences in outcomes.</p>	<p>Individuals participants at centers offering intense psychological support can elect to receive the support or not. Data are collected on psychological health pretransplant, and continued data collection and monitoring of the development of post-transplant psychological disorders up to a specified time post-transplant.</p>
<u>Resource Use, Size and Duration</u>	<p>Likely to require substantial resources to recruit and treat the patients and their families. The outcome is common so fewer patients are needed to see a difference between groups and patients with varied indications for transplant could be combined in the same study.</p> <p>For studies of centers recruitment of sufficient number of practices willing to be randomized can be a constraint, so sample size considerations may continue to be an issue.</p>	<p>Lower resource use than randomized studies, but will require resources to ensure monitoring of the protocol. Recruitment of sufficient number of centers may still be difficult.</p>	<p>Low resource use compared with alternatives, other than data collection of intent and outcomes. Psychological services in this design will be provided by the centers. Involvement from multiple centers will be necessary to recruit enough patients.</p>
<u>Ethical, Legal and Social Issues:</u>	<p>Ethical issues are minimal as the effectiveness of the intervention in this population is uncertain, and usual care is the comparator. The enrollment/consent process for children in research can be a challenge.</p>	<p>Ethical and legal issues are similar.</p>	<p>No major ethical or legal issues other than the enrollment and consent process for children in research can be a challenge.</p>



**Table 3. Study design evaluations for research question 1.1 (continued)**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Prospective Cohort</b>
<u>Availability of data or ability to recruit:</u>	Recruitment is a challenge as the numbers of patients at any one center is small. Therefore it will require a multicenter study. As the intervention is non-drug randomization may not offer as large a barrier as in a drug trial. However there may be social stigmas associated with psychological services.	Recruitment may face the same challenges although the elimination of randomization may be beneficial as for example their physician may choose the group they enter. However there may be social stigmas associated with psychological services.	No major challenges to recruitment other than the multicenter nature of the study.
<u>Advantages of study design for producing a valid result:</u>	The design is feasible although may take a relatively long time. It should produce the most valid results.	While this design may be more acceptable within the patient community, it will produce less valid results and is therefore less efficient than a randomized design.	Strong potential for confounding, and crossover may occur. The design offers good generalizability, because it replicates a real world environment.

The study design evaluations for research questions 2.1 and 2.2 were combined as they would require the same design and face similar challenges (Table 4).

Research Question 2.1

For pediatric patients receiving a transplant for cancer: Are there interventions that may mitigate immediate and late adverse effects without interfering with the immunotherapeutic effects?

Research Question 2.2

For pediatric patients receiving a transplant for noncancer indications: Are there interventions that may mitigate immediate and late adverse effects without interfering with the establishment and maintenance of chimerism?

**Table 4. Study design evaluations for research questions 2.1 and 2.2**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Retrospective Cohort</b>
<u>Description of design</u>	Individual participants randomly assigned to receive a novel therapy or standard of care. Patients are followed post-transplant; data collected on toxicities (short-term) and late-effects.	Individual participants assigned by nonrandom process to receive a novel therapy or standard of care. Patients are followed post-transplant; data collected on toxicities (short-term) and late-effects.	Patients who have been treated with novel therapies (exposed) and standard of care (non-exposed) post-transplant.
<u>Resource Use, Size and Duration</u>	Likely to require substantial resources to recruit and follow patients. The short-term effects and late toxicities are a mix of rare and common. However, multicenter studies would be employed to recruit patients in a timely manner due to the small number of patients at any one center.	Lower resource use than randomized studies, but will require resources to ensure monitoring of the protocol. Recruitment of sufficient number of patients may still be difficult.	Using an existing dataset is far less resource intensive than generating new data. But, there may be costs associated with using the data.

**Table 4. Study design evaluations for research questions 2.1 and 2.2 (continued)**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Retrospective Cohort</b>
<u>Ethical, Legal and Social Issues:</u>	Substantial ethical issues as the effectiveness of the interventions is uncertain. Enrollment/consent process for children in research can be challenging.	Ethical and legal issues are similar but reduced in a scenario where allocation is not randomized. The enrollment and consent process for children in research can be a challenge.	No major ethical or legal issues.
<u>Availability of data or ability to recruit:</u>	Recruitment may be slow and numbers at any one center are small. Therefore it will require a multicenter study.	Recruitment may face the same challenges, although the elimination of randomization may be beneficial for example their physician may choose the group they enter.	No major challenges other than negotiating with those who control the data.
<u>Advantages of study design for producing a valid result:</u>	The design is feasible and would be likely to produce the most valid results, as important characteristics such as indication for treatment should be balanced between the two groups.	Lack of randomization will reduce the validity of the results. While this design may be more acceptable within the patient community, it will produce less-valid results and is therefore less efficient than a randomized design.	Strong potential for confounding, if using a database like CIBMTR where all transplants are to be reported, although there is lower likelihood of biased reporting. Patient selection for novel therapies may be a significant concern. A retrospective design is a good way to generate hypotheses for the design of a focused RCT for novel therapies.

Research Question 3.1

What approaches to integrated care, from diagnosis forward, have the greatest impact in family functioning and overall health and well-being for families faced with pediatric transplant? (Table 5)

**Table 5. Study design evaluations for research question 3.1**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Prospective Cohort</b>
<u>Description of design</u>	Randomize patients and their families to be enrolled in a medical home or receive usual care. Data on measures of family functioning, health of family members and overall family well-being.	Assign patients and their families in a non-random way to be enrolled in a medical home or receive usual care. Data on measures of family functioning, health of family members and overall family well-being.	Families of patients who will undergo HSCT will be enrolled in a cohort; data on all interventions at intake and ongoing psychosocial care that the families received from diagnosis through a pre-defined post-transplant period will be recorded, as well as measures of family functioning, individual health of family members, and overall family well-being.

**Table 5. Study design evaluations for research question 3.1 (continued)**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Prospective Cohort</b>
<u>Resource Use, Size and Duration</u>	The study outcomes are common so fewer families are needed to see a difference between groups and patients with varied indications for transplant could be combined in the same study. Patients would need to be followed for a pre-defined period post-transplant.	Resource use would be similar to randomized trial.	Resources needed are substantial to enroll and follow multiple family members.
<u>Ethical, Legal and Social Issues:</u>	Ethical issues are minimal as the effectiveness of the interventions is uncertain. The enrollment and consent process for children in research can be a challenge.	Ethical and legal issues are similar but reduced in a scenario where allocation is not randomized. The enrollment and consent process for children in research can be a challenge.	No major ethical or legal issues other than the enrollment and consent process for children in research.
<u>Availability of data or ability to recruit:</u>	Recruitment may be slow and numbers at any one center are small. Therefore it will require a multicenter study.	Recruitment may face the same challenges. Although the elimination of randomization may be beneficial as for example their physician may choose the group they enter.	Since a treatment is not being assigned, this design is more acceptable than an RCT. However, multiple family members are asked to engage in a research process to measure very personal issues.
<u>Advantages of study design for producing a valid result:</u>	The design is feasible and would be likely to produce the most valid results, as important characteristics such as indication for treatment should be balanced between the two groups.	Lack of randomization will reduce the validity of the results. While this design may be more acceptable within the patient community, it will produce less valid results and is therefore less efficient than a randomized design.	Strong potential for confounding. However, since the design is prospective, data to account for potential confounding factors can be collected. This work will generate hypotheses for the design of focused RCTs.

Research Question 4.1

Does survivorship planning enhance compliance with long-term followup? (Table 6)

**Table 6. Study design evaluations for research question 4.1**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Retrospective Cohort</b>
<u>Description of design</u>	Individual participants randomly assigned to receive specific survivorship plan or to receive standard instructions for followup. Patients are followed post-transplant; data collected on compliance with followup.	Individual participants assigned in a non-random way to receive specific survivorship plan or to receive standard instructions for followup. Patients are followed post-transplant; data collected on compliance with followup.	Patients who have been treated and received a long-term care or survivorship plan (exposed) and standard of care (nonexposed) are enrolled.
<u>Resource Use, Size and Duration</u>	Likely to require substantial resources to recruit and follow the patients. Due to the rarity of transplant patients would need to be recruited from multiple centers.	Lower resource use than randomized studies, but will require resources to ensure monitoring of the protocol. Recruitment of sufficient number of patients may require multiple centers.	Using an existing dataset is far less resource intensive than generating new data. But, there may be costs associated with using the data. And, a dataset that includes information survivorship planning may not exist.
<u>Ethical, Legal and Social Issues:</u>	Ethical issues are moderate as the effectiveness of the intervention is uncertain, but the perception may be that important family care is being withheld from the control group. The enrollment and consent process for children in research can be a challenge.	Ethical and legal issues are similar but reduced in a scenario where allocation is not randomized. The enrollment and consent process for children in research can be a challenge.	No major ethical or legal issues.
<u>Availability of data or ability to recruit:</u>	Recruitment may be slow and numbers at any one center are small. Therefore it will require a multi-center study, and families may not want to be randomized as they perceive the medical home model to be beneficial.	Recruitment may face the same challenges although the elimination of randomization may be beneficial as for example their physician may choose the group they enter.	No major challenges other than negotiating with those who control the data, if available.
<u>Advantages of study design for producing a valid result:</u>	The design would be likely to produce the most valid results as important characteristics, such as indication for treatment, should be balanced between the two groups. However, it may not be feasible to recruit adequate numbers of families.	Lack of randomization will reduce the validity of the results. While it may be more acceptable within the patient community it will produce less valid results and is therefore less efficient than a randomized design.	Strong potential for confounding, if using a database like CIBMTR where all transplants are to be reported, but there is lower likelihood of biased reporting. Accounting for patient grouping by center will be important in the analysis as survivorship planning is likely to be offered to all patients at one center or not. While the results may be less valid than for an RCT, this may be a more feasible way to approach the question.

Research Question 4.2

What are the comparative outcomes for those that participate in long-term survivorship followup versus those who do not? (Table 7)

**Table 7. Study design evaluations for research question 4.2**

<b>Study Design Considerations</b>	<b>Randomized Trial</b>	<b>Nonrandomized Comparative Study</b>	<b>Retrospective Case-Control</b>	<b>Retrospective Cohort</b>
<u>Description of design</u>	Within centers not offering survivorship planning, Individual patients randomly assigned to receive specific survivorship plan or to receive standard instructions for followup. Patients are followed post-transplant; data collected on overall survival, incidence of late-effects and quality of life.	Individual patients are assigned (based on current practice of their center) to have survivorship care planning or not. Patients are followed post-transplant; data collected on overall survival, incidence of late-effects and quality of life.	Patients who have been treated and developed late effects (cases) or did not develop late effects (non-case) are included. Data are collected retrospectively on whether survivorship planning was provided to the patients post-transplant.	Patients who have been treated and received a long-term care or survivorship plan (exposed) and standard of care (non-exposed) are included.
<u>Resource Use, Size and Duration</u>	Likely to require substantial resources to recruit and follow the patients. Patients will need to be followed for at least 5 years for enough events to occur to enable a comparison and to measure quality of life after immediate post-transplant effects and regimen have ended.	Lower resource use than randomized studies, but will require resources to ensure monitoring of the protocol. Patients will need to be followed for at least 5 years for enough events to occur to enable a comparison and to measure quality of life after immediate post-transplant effects and regimen have ended.	Using an existing dataset is far less resource intensive than generating new data. But, there may be costs associated with using the data. And, a dataset that includes information on survivorship planning may not exist. Also, may not be enough cases who had survivorship planning to measure the impact.	Using an existing dataset is far less resource intensive than generating new data. But, there may be costs associated with using the data. And, a dataset that includes information on whether survivorship planning was executed may not exist.
<u>Ethical, Legal and Social Issues:</u>	Ethical issues are minimal as the effectiveness of the intervention is uncertain. The enrollment and consent process for children in research can be a challenge, but in this case as no treatment is given, it should be easier.	Ethical and legal issues are similar but reduced in a scenario where allocation is not randomized. The enrollment and consent process for children in research can be a challenge, but in this case as no treatment is given, it should be easier.	No major ethical or legal issues.	No major ethical or legal issues.

**Table 7. Study design evaluations for research question 4.2 (continued)**

Study Design Considerations	Randomized Trial	Nonrandomized Comparative Study	Retrospective Case-Control	Retrospective Cohort
<u>Availability of data or ability to recruit:</u>	Recruitment may be slow and numbers at any one center are small; therefore, it will require a multicenter study. Randomization may present a barrier if survivorship planning is perceived as a beneficial service by the patient and their family.	Recruitment may face the same challenges, although the elimination of randomization may be beneficial.	No major challenges other than negotiating with those who control the data.	No major challenges other than negotiating with those who control the data.
<u>Advantages of study design for producing a valid result:</u>	The design would be likely to produce the most valid results, as important characteristics such as indication for treatment should be balanced between the two groups.	Lack of randomization will reduce the validity of the results. While it may be more acceptable within the patient community, it will produce less valid results and is therefore less efficient than a randomized design. In addition, the elimination of randomization will not overcome the limited number of patients available for analysis.	Strong potential for confounding, if using a database like CIBMTR where all transplants are to be reported, but there is lower likelihood of biased reporting. Controlling for the center will be important in the analysis as survivorship planning is likely to be offered to all patients at one center or not. While the results may be less valid than if an RCT were used, this may be a more feasible way to approach the question.	Strong potential for confounding, if using a database like CIBMTR where all transplants are to be reported, but there is lower likelihood of biased reporting. Controlling for the center will be important in the analysis as survivorship planning is likely to be offered to all patients at one center or not. While the results may be less valid than if an RCT were used, this may be a more feasible way to approach the question.

## Discussion

In the pediatric population, HSCT is used to treat a wide variety of diseases, both malignant and nonmalignant. The success of treating many of the pediatric diseases with HSCT has resulted in an increased number of long-term survivors. The draft HSCT CER addressed over 40 diseases. Evidence gaps for these diseases are in part due to the fact that we are dealing with rare diseases and the associated difficulty attaining appropriate sample sizes. Prioritizing research gaps based on findings for specific diseases is problematic, as the results may appear to favor one disease over another. Given the common treatment and other commonalities among families coping with serious and rare diseases, important, crosscutting research gaps were identified.

Inherent in the scope of the draft HSCT CER were challenges in developing the future research needs report. As noted, crosscutting issues came to the center of the future research needs project. Engaging key informants who could speak to each of the diverse diseases addressed in the draft CER was infeasible. Therefore our outreach to key informants proceeded in several phases. The first focus was on HSCT specialists, then engaging patient advocates, and the health plan perspective. Initiated by the patients but embraced by all key informants were issues of family support and survivorship that were not addressed in the draft CER but were clearly important to incorporate in this follow-on future research needs report. Another inherent challenge was the difficulty of proposing study designs suitable for rare diseases. Not addressed here but of importance to systematic evaluation of evidence is the development of a framework to help decision makers incorporate contextual factors into the interpretation of the strength of evidence.

The discussion among the patient advocates highlighted the importance of appreciating the family unit and the consequences of HSCT for the family as a whole. The patient advocate discussion coalesced around themes central to concept of a patient-centered medical home. They envisioned a care setting that could provide the continuity of support to families through the continuum of disease and survivorship. The continuum includes diagnosis, treatment, transition from treatment center back to the community and long-term followup. For example, the complex pharmacologic regimens patient require, particularly shortly after transplant, require an advanced level of planning and organization from these families.

The patient advocates requested the provision of simple tools to plan medication administration, as well as periodic updates on research on the disease and treatment. The long-term impact of the disease and its treatment should be recognized. Even for children who do well with treatment, routine ongoing monitoring can require upwards of 10 to 15 specialty appointments per year. The time it takes to coordinate these appointments and manage the information flow between the various physicians is challenging, and gaining cooperation from adolescent patients may also be taxing. Thus comparative effectiveness of HSCT needs to be considered in the context of the psychosocial components of the family within the healthcare delivery system.

Another dimension for the family is the impact on siblings. The ability to be or not be a donor may have emotional toll on both the sibling and the patient. Further, if a transplant fails the donor may be faced with additional feelings of responsibility for the continued care of their sibling. Both donor and non-donor siblings of HSCT recipients have their own needs during and post-transplant. Their health is intrinsic to the overall health of the family.

The patient advocates provided a valuable, unique perspective that resulted in the identification of two additional research gaps and associated research questions. Both of these

gaps were assigned high priority by the combined clinical, patient, and payer panel; and they are included in the prioritized recommendations.

It should be noted that the key informants highlighted research needs that were outside the scope of the original review such as mitigating harms secondary to treatments, exploration of psychosocial harms for the patients and families and issues of care coordination. While none of these were within the scope of the draft CER there was agreement among the key informants as to the importance of these issues that current limitations in the published literature, while not reviewed here, provide clear opportunity for advancement in the field.

Another notable point, from the clinical experts, was understanding cancer as a pediatric disease. The clinical experts advocated the separation of research on children's cancer from that for adults. Although the diseases may appear to be similar, the implications of both the disease and treatment on a developing body and mind have unique implications.



## Conclusions

This future research project was built from the draft HSCT CER. We used key informants to identify and prioritize evidence gaps. Due to the complexity and the large number of diseases in the draft HSCT CER we focused on crosscutting evidence gaps and Key Questions. The results of this process are the following four prioritized evidence gaps and Key Question:

### Research Gap Number 1

**Mitigation of long-term adverse effects by changes in regimen, including reduced intensity approaches, and changes in subsequent medical or psychosocial intervention.**

#### Research Question Number 1.1

Can intense psychological support of patient, parents and siblings prevent development of post-transplant psychological disorders (including PTSD, depression, anxiety, other adverse psychological outcomes) in surviving and nonsurviving family members?

### Research Gap Number 2

**Role of novel therapies for HSCT in altering short-term adverse effects and the long-term effects of these therapies. Such approaches include:**

- a. **novel cellular therapies (such as natural-killer-cell therapy), and**
- b. **immunomodulatory therapies (including vaccine therapy).**

#### Research Question 2.1

For pediatric patients receiving a transplant due to cancer: Are there interventions that may mitigate immediate and late adverse effects without interfering with the immunotherapeutic effects?

#### Research Question 2.2

For pediatric patients receiving a transplant for noncancer indications: Are there interventions that may mitigate immediate and late adverse effects without interfering with the establishment and maintenance of chimerism?

### Research Gap Number 3

**Impact on outcomes of a “family-centered” approach to transplantation. Advocates of children who have undergone HSCT defined such an approach as including:**

- a. **emotional and psychosocial counseling for the family with a special attention on donor and non-donor siblings,**
- b. **information to share with caregivers and peers, and**
- c. **provision of tools rather than only a large amount of information for navigating the complexities of the medical system and medication management.**

#### Research Question 3.1

What approaches to integrated care, from diagnosis forward, have the greatest impact in family functioning and overall health and well-being for families faced with pediatric transplant?

Research Gap Number 4

**Effectiveness of survivorship planning on long term, comprehensive followup and outcomes.**

Research Question 4.1

Does survivorship planning enhance compliance with long-term followup?

Research Question 4.2

What are the comparative outcomes for those that participate in long-term survivorship followup versus those who do not?

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## Acronyms

AHSCR	Autologous hematopoietic stem cell rescue
AHSCT	Autologous hematopoietic stem cell treatment
ASCR	Autologous stem cell rescue
CR	Complete remission
CSF	Cerebrospinal fluid
DOD	Dead of disease
EFS	Event-free survival
FU	Followup
HDCT	High-dose chemotherapy
HSCT	Hematopoietic stem cell treatment
OS	Overall survival
PBSCT	Peripheral blood stem-cell treatment
RBFS	Retinoblastoma-free survival
RFS	Relapse-free survival
SCT	Stem cell treatment
TRM	Treatment-related mortality

# Appendix A. Key Questions From Comparative Effectiveness of HSCT for Pediatrics

**Key Question 1.** For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?

**Key Question 2.** For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long term consequences of HSCT, and impaired quality of life?

**Key Question 3.** For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), substrate reduction with iminosugars, and chaperones regarding overall survival, cure, long-term consequences of HSCT, and quality of life?

**Key Question 4.** For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, enzyme-replacement therapy (ERT), substrate reduction with iminosugars, and chaperones regarding adverse effects of treatment, long term consequences of HSCT, and impaired quality of life?

**Key Question 5.** For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, target biologic therapies, and low dose chemotherapy regarding overall survival, cure, and remission?

**Key Question 6.** For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, target biologic therapies, and low dose chemotherapy regarding adverse effects of treatment, long term consequences of HSCT, and impaired quality of life?

# Appendix B. Conclusions From Draft Comparative Effectiveness Review of HSCT

## Malignant Solid Tumors (Key Questions 1 and 2)

### Evidence Suggesting Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for recurrent/progressive anaplastic astrocytoma. The evidence suggests clinical superiority of HSCT over conventional therapy on overall survival. Results from one historic comparison report 5 year survival of 40 percent for HSCT treated pediatric patients (n=10) compared with 0 percent for those treated with conventional therapy. The strength of the body of evidence is low.

### Evidence Suggesting Comparative Harm of HSCT Over Conventional Therapy.

- For single HSCT for nonanaplastic mixed or unspecified ependymoma. The evidence suggests a comparative harm of HSCT over conventional therapy on overall survival, due to higher treatment related mortality. The strength of the body of evidence is low.

### Evidence Suggesting No Comparative Benefit of HSCT Over Conventional Therapy.

- For single HSCT for extraocular retinoblastoma with CNS involvement and for metastatic rhabdomyosarcoma. The evidence suggests no comparative benefit of HSCT over conventional therapy on overall survival. The strength of the body of evidence is moderate.
- For single HSCT for high-risk Ewings sarcoma family of tumors, high-risk relapsed Wilm's tumor, and one type of glial tumor (newly diagnosed glioblastoma multiforme). The evidence suggests no comparative benefit of HSCT over conventional therapy on overall survival. The strength of the body of evidence is low.

### Insufficient Evidence

- For tandem HSCT versus single HSCT for high-risk Ewings sarcoma family of tumors, neuroblastoma, central nervous system embryonal tumors, and germ cell tumors. The strength of evidence is insufficient to draw conclusions on overall survival.
- For single HSCT versus conventional therapy for central nervous system embryonal tumors, high-risk rhabdomyosarcoma of mixed stages, congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, allogeneic transplantation of metastatic rhabdomyosarcoma, extraocular retinoblastoma with no CNS involvement, trilateral retinoblastoma, and five types of glial tumor (newly diagnosed anaplastic astrocytoma, anaplastic ependymoma and choroid plexus carcinoma and recurrent/progressive glioblastoma multiforme, and nonanaplastic, mixed or unspecified ependymoma). The strength of evidence is insufficient to draw conclusions on overall survival.

## Nonmalignant Diseases: Inherited Metabolic Diseases (Key Questions 3 and 4)

The inherited metabolic diseases were split into three categories for this review. Rapidly progressive disease was defined as progression to death within 10 years; the outcome of interest

is overall survival. Slowly progressive disease was defined as progression to death of 10 years or greater; the outcomes of interest are neurocognitive and neurodevelopmental measures. Diseases that have both rapidly and slowly progressive forms of disease where outcomes are overall survival and neurocognitive and neurodevelopmental measures respectively.

## **Rapidly Progressive Diseases**

### Evidence Suggesting Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for Wolman's disease. The natural history of this disease death occurs by approximately by 6 months of age. Of five cases reported in the evidence three patients are alive at 4-11 years followup, with normal function and attending school. The strength of the body of evidence is high.

### Evidence Suggesting No Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for Niemann-Pick Type A. The evidence suggests no benefit of HSCT compared with symptom management or disease natural history. One case has been reported and was alive but with neurocognitive and neurodevelopmental decline at age 2.7 years. The strength of the body of evidence is low.

### Insufficient Evidence

- The strength of the body of evidence is insufficient to draw conclusions on the comparative benefit of single HSCT compared with symptom management on overall survival for mucopolidosis II (I-cell disease).

### No Evidence Found

- There was no evidence on single HSCT for Gauche disease type 2, cystinosis and infantile free sialic acid disease.

## **Slowly Progressive Diseases**

### Evidence Suggesting Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for the attenuated form of MPS II (Hunter's disease). The evidence suggests benefit of HSCT compared with enzyme replacement therapy with respect to neurocognitive and neurodevelopmental measures. Three of five transplanted patients were reported to have stable neurocognitive and neurodevelopmental measures at 2-13 years followup. The strength of the body of evidence is low.

### Evidence Suggesting No Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for both severe and attenuated MPS II (Hunters disease). The evidence suggests no benefit of HSCT compared with enzyme replacement therapy with respect to neurocognitive and neurodevelopmental outcomes. Neurodevelopmental outcomes appear similar for both HSCT and enzyme replacement therapy for the severe and attenuated forms of MPS II both offering some benefit. For the severe form of the disease neither HSCT nor ERT appear to offer a benefit relative to disease natural history. The strength of the body of evidence is moderate.
- For single HSCT for Gaucher Type III. The evidence suggests no benefit for HSCT compared with enzyme replacement therapy with respect to neurocognitive outcomes.

Five of eight transplanted patients and seven of nine ERT patients showed stable neurocognitive scores at 1-10 years followup and 2-5 years followup, respectively. The strength of the body of evidence is moderate.

- For single HSCT for Niemann-Pick type C, MPS III (Sanfilippo). The evidence suggests no benefit for HSCT compared with symptom management, substrate reduction therapy or disease natural history. Results in transplanted patients show continued neurocognitive and neurodevelopmental decline. The strength of the body of evidence is low.

#### Insufficient Evidence

- The strength of the body of evidence is insufficient to draw conclusions on the comparative benefit of single HSCT compared with symptom management and or disease natural history with respect to neurocognitive and neurodevelopmental outcomes for MPS IV (Morquio syndrome) and aspartylglucosaminuria.

#### No Evidence Found

- There was no evidence on single HSCT for Fabry's disease,  $\beta$ -mannosidosis, mucopolipidosis III or IV, glycogen storage disease type II (Pompe disease), Salla disease, and adrenomyeloneuropathy.

## **Disease With Both Rapidly and Slowly Progressive Forms**

#### Evidence Suggesting Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for Farber's disease Type 2/3. The evidence suggests a benefit for HSCT compared with symptom management or disease natural history. All five patients transplanted with type 2/3 showing a reduction in number of subcutaneous nodules and number of joints with limited range of motion at 0.7-1.3 years of followup. The strength of the body of evidence is high.

#### Evidence Suggesting No Comparative Benefit of HSCT Over Conventional Therapy

- For single HSCT for infantile ceroid lipofuscinosis. The evidence suggests no benefit for HSCT compared with symptom management or disease natural history with respect to neurocognitive outcomes. All three transplanted pediatric patients had neurocognitive decline and were hypotonic and spastic at 2-4 years followup. The strength of the body of evidence is moderate
- For single HSCT for Farber's disease type I (overall survival), juvenile form of GM<sub>1</sub> (neurocognitive and neurodevelopmental), juvenile Tay-Sachs (neurocognitive and neurodevelopmental). The evidence suggests no benefit for HSCT compared with symptom management or disease natural history with respect to overall survival and/or neurocognitive and neurodevelopmental outcomes. Pediatric patients treated with HSCT showed similar decline and development to comparator patients. The strength of the body of evidence is low.

#### Insufficient Evidence

- The strength of the body of evidence is insufficient to draw conclusions on the comparative benefit of single HSCT compared with symptom management and or disease natural history with respect to overall survival and/or neurocognitive and



neurodevelopmental measures for galactosialidosis (type unspecified) and Sandhoff disease (type unspecified).

No Evidence Found

- There was no evidence on single HSCT for infantile GM<sub>1</sub> gangliosidosis, infantile Tay-Sachs and juvenile ceroid lipofuscinosis.

## **Autoimmune Diseases (Key Questions 5 and 6)**

**Insufficient Evidence.** The strength of evidence is insufficient to draw conclusions about the comparative effects of single HSCT and conventional therapy or disease natural history. In some diseases there is evidence that periods of drug free remission can be achieved. However, for all evaluated autoimmune diseases evidence was insufficient to evaluate the balance of long term benefits and harms. The autoimmune diseases evaluated in this report were: Type 1 diabetes mellitus, and severe/refractory systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, evans syndrome, autoimmune hemolytic anemia and autoimmune cytopenia.

## Appendix C. Conclusions for Which There Was Insufficient Evidence

**Insufficient Evidence.** Rhabdomyosarcoma of mixed stages, Congenital alveolar rhabdomyosarcoma, Cranial parameningeal rhabdomyosarcoma with metastasis, Allogeneic transplantation of metastatic rhabdomyosarcoma, Germ cell tumor, Central Nervous System Embryonal Tumors, Newly diagnosed anaplastic astrocytoma, Anaplastic ependymoma, Choroid plexus carcinoma, Recurrent/progressive glioblastoma multiforme, Nonanaplastic mixed or unspecified ependymoma, Ewing sarcoma family of tumors Tandem versus Single, Neuroblastoma Tandem versus Single, Mucopolipidosis II (I-cell disease), MPS IV (Morquio syndrome)\*, aspartylglucosaminuria\*

**No Evidence Found.** Gauchers disease type 2, cystinosis, infantile free sialic acid disease, Fabry's disease,  $\beta$ -mannosidosis, mucopolipidosis III or IV, glycogen storage disease type II (Pompe disease), Salla disease, adrenomyeloneuropathy, galactosialidosis (type unspecified) and Sandhoff disease (type unspecified), infantile GM1 gangliosidosis, infantile Tay-Sachs, juvenile ceroid lipofuscinosis, Type 1 diabetes mellitus, and severe/refractory systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, evans syndrome, autoimmune hemolytic anemia and autoimmune cytopenia.

# Appendix D. Search Strategy for Recently Published and Ongoing Studies

The search strategy was the same one as was used in the BCBSA TEC HSCT CER with dates starting 10/09/09 through January 2011.

**All Child: 0-18 years=3709**

**#107 Search #104 AND #106**

**#106 Search "Humans"[Mesh]**

**#104 Search #102 AND #103**

**#103 Search #55 OR #88 OR #90 OR #101**

**#102 Search #45 OR #47**

**#101 Search "Fabry Disease" OR "Fabry's disease" OR "Farber Lipogranulomatosis" OR "Fabry Disease" OR "Fabry's disease" OR "Farber Lipogranulomatosis" OR Gangliosidos\* OR "Sandhoff Disease" OR "sandhoff's disease" OR "Gaucher Disease" OR "gaucher's disease" OR "Niemann-Pick Disease\*" OR "Tay-Sachs Disease" OR Aspartylglucosaminuria OR "beta-Mannosidosis" OR Mucopolidos\* OR "Wolman Disease" OR "Ceroid Lipofuscinos\*" OR "Ceroid-Lipofuscinos\*" OR galactosialidosis OR Cystinosis OR "Sialic Acid Storage Disease" OR "salla disease" OR "peroxisomal storage disorder\*" OR adrenomyeloneuropath\* OR "immune cytopenia"**

**#90 Search "Ewing's Sarcoma" OR "Wilms Tumor" OR Rhabdomyosarcoma\* OR Retinoblastoma\* OR Medulloblastoma\* OR PNET OR "Primitive Neuroectodermal Tumor\*" OR Astrocytoma\* OR Mucopolysaccharidos\* OR Sphingolipidos\* OR "Lysosomal Storage Disease\*" OR "Glycogen Storage Disease\*" OR "Niemann-Pick Disease\*" OR Adrenoleukodystrophy OR "Juvenile Rheumatoid Arthritis" OR "Systemic Lupus Erythematosus" OR SLE OR Scleroderma OR "Crohn Disease" OR "Crohn's disease" OR "Autoimmune Disease"**

**#88 Search (((((((("Mucopolysaccharidoses"[Mesh] OR "Sphingolipidoses"[Mesh]) OR "Lysosomal Storage Diseases"[Mesh]) OR "Glycogen Storage Disease"[Mesh]) OR "Niemann-Pick Diseases"[Mesh]) OR "Adrenoleukodystrophy"[Mesh]) OR "Arthritis, Juvenile Rheumatoid"[Mesh]) OR "Lupus Erythematosus, Systemic"[Mesh]) OR "Scleroderma, Systemic"[Mesh]) OR "Crohn Disease"[Mesh]) OR "Autoimmune Diseases"[Mesh]**

**#55 Search (((("Sarcoma, Ewing's"[Mesh] OR "Wilms Tumor"[Mesh]) OR "Rhabdomyosarcoma"[Mesh]) OR "Retinoblastoma"[Mesh]) OR "Medulloblastoma"[Mesh]) OR "Neuroectodermal Tumors, Primitive"[Mesh]) OR "Astrocytoma"[Mesh]**

**#47 Search "stem cell\*" OR "bone marrow"**

**#45 Search "Bone Marrow Transplantation"[Mesh] OR ("Hematopoietic Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Stem Cell Transplantation"[Mesh])**

**Additional searching was done to obtain information on comparators in the following diseases:**

#### **Diabetes**

- #15 Search (#10 AND #13) NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12**
- #14 Search (#10 AND #13) NOT #5**
- #13 Search "Immunosuppression"[Mesh] OR immunomodulation OR immunosuppressant OR immunosuppressive OR "immune modulation" OR "immune suppression"**
- #10 Search "Diabetes Mellitus, Type 1"[Mesh] OR ("type 1" AND (diabetes OR diabetic OR DM)) OR "juvenile diabetes"**
- #5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant\*" OR "stem cell support" OR "stem cell transplant\*"**

#### **Other Autoimmune Diseases**

- #23 Search (#20 AND #13) NOT #5 AND (severe OR refractory OR "poor prognosis") Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12**
- #22 Search (#20 AND #13) NOT #5 Limits: Humans, Clinical Trial, Editorial, Practice Guideline, Randomized Controlled Trial, Case Reports, Comparative Study, Controlled Clinical Trial, Guideline, English, All Infant: birth-23 months, All Child: 0-18 years, Publication Date from 1995/10/01 to 2010/07/12**
- #21 Search (#20 AND #13) NOT #5**
- #20 Search ("Arthritis, Juvenile Rheumatoid"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh]) OR "Scleroderma, Systemic"[Mesh] OR "Crohn Disease"[Mesh]**
- #13 Search "Immunosuppression"[Mesh] OR immunomodulation OR immunosuppressant OR immunosuppressive OR "immune modulation" OR "immune suppression"**
- #5 Search "Bone Marrow Transplantation"[Mesh] OR ("Stem Cell Transplantation"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh]) OR "bone marrow transplant\*" OR "stem cell support" OR "stem cell transplant\*"**

**Appendix Table D1. List of recently published studies**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>MEDULLOBLASTOMA</b>	Aihara Y, Tsuruta T, Kawamata T, Kanno H. Double high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation for primary disseminated medulloblastoma: a report of 3 cases. J Pediatr Hematol Oncol 2010 32(2):e70-4.	To describe the toxic and tumor response of 3 pediatric medulloblastoma cases after undergoing double HDCT.	Case report	3 cases FU: 9, 40, and 41 mo	Resection of main tumor mass, craniospinal radiation therapy, 4-5 course conventional therapy with 2 courses of HDCT with PBSCT.	Response, toxicity	2 patients were in complete remission 40 and 41 months after second HDCT. 1 patient relapsed after 9 months after second HDCT. Hepatic veno-occlusive disease in case 2 after second HDCT.
<b>MEDULLOBLASTOMA</b>	Johnston DL, Keene D, Bartels U, Carret A-S. Medulloblastoma in children under the age of three years: A retrospective Canadian review. J. Neuro-Oncol. 2009 94(1):51-56.	To review the outcome of children less than 36 months of age diagnosed with medulloblastoma.	Retrospective review	96 cases of medulloblastoma. 12 received HDCT with stem cell transplant 1990-2005 (stem cell transplant occurred in 2 patients 1995-2000, and 10 cases in 2000-2005)	12 patients received HDCT with stem cell transplantation. Retrospective review does not provide further treatment details for these patients	OS	Of the 12 patients that received stem cell transplant 7 were alive at last follow up. This compared with 74 patients who did not receive stem cell transplant with 27 alive at last follow up (p=.15).

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>NEUROBLASTOMA</b>	Sung KW, Ahn HS, Cho B, Choi YM, Ch. Efficacy of tandem high-dose chemotherapy and autologous stem cell rescue in patients over 1 year of age with stage 4 neuroblastoma: the Korean Society of Pediatric Hematology-Oncology experience over 6 years (2000-2005). J Korean Med Sci 2010 25(5):691-7.	To determine the efficacy of tandem HDCT/ASCR in patients with newly diagnosed stage 4 neuroblastoma compared with single HDCT/ASCR.	Prospective cohort study	141 patients, 71 single, 71 tandem 6/2000-12/2005 FU: median 56 months (24-88 months)	Maximal tumor resection when possible followed by local radiotherapy, induction chemotherapy, HDCT/ASCR	EFS, RFS	10 TRM were reported in the single group and 8 in the tandem group. The probability of 5-yr EFS after diagnosis was higher in the tandem group than in the single group (51.2%±12.4% vs. 31.3%±11.5%, P=0.030). When the analysis was confined to 123 patients who proceeded to HDCT/ASCR as assigned at diagnosis, the probability of 5-yr RFS after the first HDCT was higher in the tandem group than in the single group with borderline significance (59.7±13.5% vs. 41.6±14.5%, P=0.099). (C) However, the difference became significant when the analysis was confined to only patients who were not in CR prior to the first HDCT (55.7±17.0% vs. 0%, P=0.012). Multivariate analyses including the prognostic factors at diagnosis for EFS revealed that tandem HDCT /ASCR treatment was the only independent favorable prognostic factor associated with the EFS (hazard ratio 0.16, 95%

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
							confidence interval 0.03-0.91, P=0.039)
<b>CENTRAL NERVOUS SYSTEM TUMORS</b>	Sands SA, Oberg JA, Gardner SL, Whiteley J. Neuropsychological functioning of children treated with intensive chemotherapy followed by myeloablative consolidation chemotherapy and autologous hematopoietic cell rescue for newly diagnosed CNS tumors: An analysis of the head start II survivors. <i>Pediatr. Blood Cancer</i> 2010 54(3):429-436.	To evaluate the neuropsychological late effects among survivors treated on the Head Start II protocol (included medulloblastoma, sPNET, ependymoma, pineoblastoma, glioblastoma multiforme, AT/RT/, Glioma, astrocytoma, choroid plexus tumor	Prospective cohort	51 patients with malignant brain tumor who underwent ASCT had baseline testing, 26 survivors received post-testing at 2-years 1997-2003 FU: post test at 2 years from baseline assessment	Maximum safe resection of primary tumor, multiple cycles of induction chemotherapy, myeloablative chemotherapy with ASCT.	Neuropsychological assessment in domains of: intelligence, perceptual-motor and receptive vocabulary, academic achievement, learning and memory, social-emotional and behavioral functioning	The mean interval between T1 and T2 testing was 2.75 years (SD=1.4). Comparison of mean MDI, FSIQ, VIQ, and PIQ change scores remained stable over the followup period (P=0.76, d=0.07; P=.95, d=0.01; P=0.20, d=0.35, respectively). Specifically, the mean Overall Intelligence (MDI or FSIQ) changed score increased 1.05 points, while mean VIQ change score declined 0.38 points. Although not statistically significant, PIQ was negatively impacted (mean change score loss of 5.5 IQ points over 3 years). Comparison of social-emotional and behavioral change scores were within normal limits and not statistically significant for either internalizing (P=0.22, d=0.17) or externalizing behaviors (P=0.14, d=0.99); however, both scores increased (internalizing=+3.20; externalizing=+7.80).

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>RETINOBLASTOMA</b>	Dimaras H, Heon E, Budning A, Doyle JJ. Retinoblastoma CSF metastasis cured by multimodality chemotherapy without radiation. <i>Ophthalmic Genet</i> 2009 30(3):121-6.	To reported a patient retinoblastoma with CSF metastasis who was cured by consolidation therapy and ASCR.	Case-report	1 patient FU: 7.8 years post transplant	7-cycle high-dose chemotherapy with autologous cord blood stem cell transplant	Survival	Patient is in remission 8.3 years after diagnosis and 7.8 years post-transplant
<b>RETINOBLASTOMA</b>	Dunkel IJ, Chan HS, Jubran R, Chantada. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. <i>Pediatr Blood Cancer</i> 2010 55(1):149-52.	To determine if HDCT with ASCR might be associated with a better chance of survival than conventional therapy.	Case series	8 pediatric patients with metastatic unilateral or bilateral retinoblastoma 10/2000-1/2006 FU: 3-101 mo	Induction chemotherapy followed by HDCT/ASCR. 2/3 patients received RT post-ASCR	EFS	1 patient died of toxicity at 3 months follow up. 5 patients were DOD at 5-21 months follow up, and 2 patients had EFS of 40 and 101 months.
<b>RETINOBLASTOMA</b>	Dunkel IJ, Khakoo Y, Kernan NA, Gershon. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. <i>Pediatr Blood Cancer</i> 2010 55(1):55-9.	To determine the survival outcomes of stage 4a retinoblastoma patients following treatment with HDCT/ASCR	Case series	15 pediatric patients with stage 4a retinoblastoma 2/1993-12/2006 FU 103 months median (24-202 months)	Induction chemotherapy followed by HDCT in 13/15 patients, AHSCR, and post-AHSCR radio therapy in 7/15 patients	Retinoblastoma-free survival	10 patients remain free of retinoblastoma in first remission. 5- year RBFS is 67% (38-85%, 95% CI) 5 year EFS is 59% (31-79%, 95% CI)



**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>RETINOBLASTOMA</b>	Dunkel IJ, Jubran RF, Gururangan S, Cha. Trilateral retinoblastoma: potentially curable with intensive chemotherapy. <i>Pediatr Blood Cancer</i> 2010 54(3):384-7.	To determine the role of high-dose chemotherapy for patients with trilateral retinoblastoma which has been lethal in virtually all reported cases.	Multi-center retrospective review	13 pediatric patients with trilateral retinoblastoma 5/1997-10/2005 FU: median of 77 months (36-104 months)	Induction chemotherapy, 9 patients received HDCT followed by ASCR, 4 patients had post-ASCR radiotherapy	OS EFS	Median overall survival was 19 months. 5 patients were alive at last follow up (104 months). The 5-year overall survival was 38% (14-63%, 95% CI). The 5- year EFS for patients with M-0 disease was 57% (17-84%, 95% CI) and in M-1+ patients was 17% (1—52%, 95% CI). Four of the seven patients who received a high-dose thiotepa-based regimen are event-free survivors versus one of the three who received a high-dose melphalan-based regimen.
<b>RETINOBLASTOMA</b>	Chantada GL, Fandino AC, Guitter MR. Results of a prospective study for the treatment of unilateral retinoblastoma. <i>Pediatr Blood Cancer</i> 2010 55(1):60-6.	To improve the outcome of patients with metastatic disease at diagnosis or relapse by the introduction of consolidation with high-dose chemotherapy and autologous stem-cell rescue.	Prospective non-randomized study	4 treatment groups: ASCR group for overt extraocular disease N=2 January 2002-June 2008 FU: 5 year	Neoadjuvant therapy followed by surgery and HDCT/ASCR	EFS	For patients with overt extraocular disease both patients died of progressive disease. One patient was only given palliative treatment and the other patient was DOD at 5 mo.

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>EWING TUMOR</b>	Burdach S, Thiel U, Schoniger M, Haase R. Total body MRI-governed involved compartment irradiation combined with high-dose chemotherapy and stem cell rescue improves long-term survival in Ewing tumor patients with multiple primary bone metastases. Bone Marrow Transplant 2010 45(3):483-9.	To examine the role of total body magnetic resonance imaging (TB-MRI), involved compartment irradiation (ICI), and high dose chemotherapy (HDCT) followed by stem cell rescue (SCR) in patients with high-risk Ewing tumors with multiple primary bone metastases.	Case-series	11 patients with HSCT and 26 historic control patients without TB-MRI, ICI, and HSCT with SCR 1995-2000 FU: .5-14 years	Induction chemotherapy followed by local intensification with ICI, and HDCT with SCR.	OS	The overall survival of these 11 pediatric patients was 6 months to 14 years with a median OS of 6 months. Three patients were dead from complication. Two of these patients had treatment related secondary-malignancies, and one liposarcoma. At 5 years, the survival of the 11 treatment patients was 45% compared with 8% in the historic controls.

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>EWING TUMOR</b>	Diaz MA, Lassaletta A, Perez A, Sevilla. High-dose busulfan and melphalan as conditioning regimen for autologous peripheral blood progenitor cell transplantation in high-risk ewing sarcoma patients: a long-term followup single-center study. <i>Pediatr Hematol Oncol</i> 2010 27(4):272-82.	To analyze the outcome and identify risk factors associated to progression free survival.	Retrospective case-series	46 1995 – 2009 FU: median fu of 2 years (2 months – 7 years)	HDCT with SCR	PFS TRM Univariate/ multivariate analysis of risk factors	The best response at 3 months posttransplant was complete remission in 33 patients (70%), partial remission in 1 patient (2%) and stable disease in 13 patients (28%). The PFS was 56% ± 4 with a median follow up of 92 months for survivors (6-168 months). Female gender, higher Lansky score, localized disease at diagnosis, CR status at time of transplant , and CR after transplant were associated with higher PFS. 3 patients died of transplant-related complications (1 engraftment syndrome, 1 septic shock with multiorgan failure, and 1 fungal infection). Probability of TRM was 6%±3% at 1 year.

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>EWING TUMOR</b>	Ilari I, De Ioris MA, Milano GM, Pessolano. Toxicity of high-dose chemotherapy with etoposide, thiotepa and CY in treating poor-prognosis Ewing's sarcoma family tumors: The experience of the Bambino Gesù Children's Hospital. Bone Marrow Transplant. 2010 45(8):1274-1280.	To describe the experience with HDCT in poor-prognosis ESFT treated in a single pediatric hospital in Italy.	Retrospective case-series	26 1998 – 2007 FU: median 37 months (13 – 129 months)	HDCT and SCT with or without surgery and radiotherapy	OS EFS Toxicity	The 7-year OS and EFS were 59% (35-76%, 95% CI) and 49% (26-69%, 95% CI) respectively. Relapse occurred in nine (38%) of patients. No toxic deaths occurred in HSCT patients.

**Appendix Table D1. List of recently published studies (continued)**

Research Gap	Study	Study Objective	Research Design	Sample Size; Years; Followup	Treatment(s)	Outcomes	Summary Results
<b>EWING TUMOR</b>	Ladenstein R, Potschger U, Le Deley, MC, W. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol 2010 28(20):3284-91.	To improve the prognosis of patients with primary disseminated multifocal Ewing sarcomas with a dose-intense treatment concept.	Randomized phase III trial	281 patients (.4 – 49 years) 1999 – 2005 FU: median 3.8 years	Patients treated with or without PBSCR, radiation therapy, and or surgery	EFS OS TRM Multivariate analysis of risk factors	The 3-year EFS was 27%±3% and OS was 34%±4%. Median survival time was 1.6 years for all patients. Three patients died within the first 100 days after HDCT. 1 patient died of acute respiratory distress syndrome and two as a result of severe VOD and septicemia. 3 patients died of digestive tract late radiation toxicity 1 to 1.5 years after HDCT. 1 patient died as a result of post-allograft toxicity which was performed by clinician choice. Age ≥14, ≥ single lesion, bone marrow metastases, primary tumor volume ≥ 200ml, and lung metastases were significantly associated with an increased hazard ratio in a multivariate model.

**Abbreviations:** AHSCR: Autologous hematopoietic stem cell rescue; AHSCT: Autologous hematopoietic stem cell treatment; ASCR: Autologous stem cell rescue; CR: Complete remission; CSF: Cerebrospinal fluid; DOD: Dead of disease; EFS: Event-free survival; FU: Follow up; HDCT: High-dose chemotherapy; HSCT: Hematopoietic stem cell treatment; OS: Overall survival; PBSCT: Peripheral blood stem cell treatment; RBFS: Retinoblastoma free survival; RFS: Relapse free survival; SCT: Stem cell treatment; TRM: Treatment-related mortality

## Appendix E. Ongoing Studies

**Appendix Table E1. List of ongoing studies**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>EWING SARCOMA</b>	Phase 3, Open Label, Multi-centre, Randomized Controlled International Study in Ewing Sarcoma; University Hospital Münster, NCT00987636	To examine whether high dose chemotherapy using busulfan-melphalan with autologous stem cell reinfusion, compared with standard chemotherapy, improves event-free survival in patients with localized Ewing sarcoma and unfavorable histological response or tumor volume>200ml. To examine whether the addition of high dose chemotherapy using treosulfan-melphalan followed by autologous stem cell reinfusion to eight cycles of standard adjuvant chemotherapy, compared with eight cycles of standard adjuvant chemotherapy alone, improves event-free survival in patients with primary disseminated disease.	Efficacy Study	1383 10/2009-3/2018 Germany FU: 6.5, 8.5 years	HSCT compared with standard chemotherapy	Event free survival Overall survival Safety and toxicity Quality of life	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

<b>Research Gap</b>	<b>Study</b>	<b>Study Objective (group by this)</b>	<b>Research Design</b>	<b>Sample size; Years; Location; Followup</b>	<b>Treatment(s)</b>	<b>Outcomes</b>	<b>Status</b>
<b>EWING SARCOMA</b>	Combination Chemotherapy With or Without Peripheral Stem Cell Transplantation, Radiation Therapy, and/or Surgery in Treating Patients With Ewing's Sarcoma; University Hospitals, Leicester, NCT00020566	To study different combination chemotherapy regimens to see how well they work when given with or without peripheral stem cell transplantation, radiation therapy, and/or surgery in treating patients with Ewing's sarcoma.	Treatment Study	1200 2/2001-12/2011 United Kingdom Patients are followed every 3 months for 4 years, every 6 months for 1 year, and then periodically thereafter.	chemotherapy with or without peripheral stem cell transplantation, radiation and/or surgery	Event free survival Overall survival	This study has been suspended.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>WILMS TUMOR</b>	Chemotherapy Followed by Surgery and Radiation Therapy With or Without Stem Cell Transplant in Treating Patients With Relapsed or Refractory Wilms' Tumor or Clear Cell Sarcoma of the Kidney; Children's Cancer and Leukemia Group, United Kingdom, Ireland, NCT00025103	To determine survival rates of patients with relapsed or refractory Wilms' tumor or clear cell sarcoma of the kidney treated with chemotherapy followed by surgical resection and adjuvant radiotherapy with or without autologous stem cell rescue. To determine the efficacy and toxicity of these regimens in these patients. To determine prognostic variables in patients treated with these regimens.	Treatment Study	75 5/2001-11/2008 United Kingdom, Ireland Patients are followed every 8 weeks for 1 year, every 12 weeks for 1 year, and then every 6 months thereafter.	Chemotherapy followed by surgery and radiation, with or without HSCT	Overall Survival Toxicity Prognostic variables	This study is ongoing, but not recruiting participants.



**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>RETINOBLASTOMA</b>	Combination Chemotherapy, Autologous Stem Cell Transplant, and/or Radiation Therapy in Treating Young Patients With Extraocular Retinoblastoma; Children's Oncology Group, United States, NCT00554788	To study the side effects and how well giving combination chemotherapy together with autologous stem cell transplant and/or radiation therapy works in treating young patients with extraocular retinoblastoma.	Treatment Study	60 2/2008-2/2014 United States FU: Not reported	HDC, and HSCT and/or radiotherapy	Event-free survival Response Rate Toxicity	This study is currently recruiting participants.
<b>NEUROBLASTOMA</b>	Comparing Two Different Myeloablation Therapies in Treating Young Patients Who Are Undergoing a Stem Cell Transplant for High-Risk Neuroblastoma; Children's Oncology Group, United States, NCT00567567	To compare EFS and tumor response of tandem HDC/HSCT and single HDC/HSCT	Treatment Study	495 11/2007-3/2011 United States FU: Not reported	tandem HDC/HSCT compared with single HDC/HSCT	Event-free survival Response after induction therapy Incidence rate of local recurrence Duration of $\geq$ grade 3 neutropenia during course one Duration of $\geq$ grade 3 thrombocytopenia during course one Response rate after two courses of induction therapy	This study is currently recruiting participants.
<b>GERM CELL TUMORS</b>	High-dose Chemotherapy for Poor-prognosis Relapsed Germ-Cell Tumors; M.D. Anderson Cancer Center; Fred Hutchinson Cancer Research Center, Texas & Washington, NCT00936936	To learn if bevacizumab, when given in combination with 2 cycles of high-dose chemotherapy, can help to control germ-cell tumors.	Safety/Efficacy Study	25 6/2009-6/2014 United States FU: 2 years	2 cycles of HDCT/SCT	2-year Event-Free Survival	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>HIGH RISK SOLID TUMORS</b>	Tandem Peripheral Blood Stem Cell (PBSC) Rescue for High Risk Solid Tumors; Children's Memorial Hospital, Chicago, NCT00179816	To study the feasibility and toxicity of tandem rescue with peripheral blood cells following HDC as consolidation in pediatric patients with high risk solid tumors	Safety/Efficacy Study	12 4/1999-9/2012 United States FU: Annually until end of study	HDCT with tandem PBSCR	Toxicity DFS Stem cell dose to time of engraftment	This study is currently recruiting participants.
<b>HIGH RISK CNS TUMORS</b>	Stem Cell Transplant for High Risk Central Nervous System (CNS) Tumors; Children's Memorial Hospital, Chicago, NCT00179803	To determine if a stem cell transplant in patients with newly diagnosed high risk CNS tumors (glioblastoma multiforme [GBM], high grade astrocytoma, pineoblastoma, rhabdoid tumor, supratentorial primitive neuroectodermal tumor [PNET]) increases overall survival.	Safety/Efficacy Study	50 3/1998 – 1/2008 United States FU: Not reported	HDCT with tandem SCR	OS PFS Adverse Events	This study is ongoing, but not recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

<b>Research Gap</b>	<b>Study</b>	<b>Study Objective (group by this)</b>	<b>Research Design</b>	<b>Sample size; Years; Location; Followup</b>	<b>Treatment(s)</b>	<b>Outcomes</b>	<b>Status</b>
<b>GLIOBLASTOMA MULTIFORME AND BRAIN STEM TUMORS</b>	Chemotherapy Followed by Bone Marrow or Peripheral Stem Cell Transplantation in Treating Patients With Glioblastoma Multiforme or Brain Stem Tumors; New York University School of Medicine, New York, NCT00002619	To study the effectiveness of chemotherapy followed by autologous bone marrow or peripheral stem cell transplantation in treating patients with glioblastoma multiforme or brain stem tumors.	Phase II treatment study	60 (ages 6 to 59 years) 9/1994 - End date not provided United States FU: Not reported	HDCT with autologous bone or peripheral stem cell transplant	OS PFS Time to progression /recurrence Toxicity	This study is ongoing, but not recruiting participants.
<b>NEWLY DIAGNOSED/ RELAPSED SOLID TUMORS</b>	Busulfan, Melphalan, Topotecan Hydrochloride, and a Stem Cell Transplant in Treating Patients With Newly Diagnosed or Relapsed Solid Tumor; City of Hope Medical Center, California, NCT00638898	To study how well giving busulfan, melphalan, and topotecan hydrochloride together with a stem cell transplant works in treating patients with newly diagnosed or relapsed solid tumor.	Efficacy Study	25 patients 12/2006 – 4/2011 United States FU: 1 year	HDCT with ASCR	OS DFS Engraftment incidence Pharmacokinetics and pharmacodynamics of topotecan hydrochloride and busulfan	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>BRAIN AND CNS TUMORS, GERM CELL TUMORS</b>	High-Dose Chemotherapy With or Without Total-Body Irradiation Followed by Autologous Stem Cell Transplant in Treating Patients With Hematologic Cancer or Solid Tumors; Roswell Park Cancer Institute, New York, NCT00536601	To study different high-dose chemotherapy regimens with or without total-body irradiation to compare how well they work when given before autologous stem cell transplant in treating patients with hematologic cancer or solid tumors.	Phase II/III Treatment Study	530 6/2006 – 4/2024 United States FU: 10 years	HDCT with ASCR with or without TBI	PFS OS Toxicity Tumor response Efficacy	This study is currently recruiting participants.
<b>GLIOBLASTOMA MULTIFORME AND GLIOSARCOMA</b>	Temozolomide, Carmustine, O6-Benzylguanine, Radiation Therapy, and an Autologous Stem Cell Transplant in Treating Patients With Newly Diagnosed Glioblastoma Multiforme or Gliosarcoma; Fred Hutchinson Cancer Research Center, Washington, NCT00669669	To study the best dose of carmustine and temozolomide when given together with radiation therapy, carmustine, O6-benzylguanine, and an autologous stem cell transplant in treating patients with newly diagnosed glioblastoma multiforme or gliosarcoma.	Safety/Efficacy Study	30 7/2006 – 2/2017 United States FU: 15 years	Radiotherapy followed by HDCT and PBSCR	Toxicity Development of replication competent retrovirus or leukemia Tumor response Time to progression Chemoprotection (temozolomide dose) Duration of response Gene transfer efficiency and in vivo gene marking in peripheral blood and marrow	This study is currently recruiting participants.
<b>INHERITED METABOLIC DISEASE (adrenoleukodystrophy, metachromatic leukodystrophy, globoid)</b>	Stem Cell Transplant for Inborn Errors of Metabolism; Masonic Cancer Center, University of	To determine the safety and engraftment of donor hematopoietic	Efficacy Study	134 1/1995 – 6/2010 United States FU: 3 years	Surgery, chemotherapy and HSCT	OS Change in neuropsychometric function Toxicity Engraftment	This study is ongoing, but not recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
cell leukodystrophy, Gaucher's disease, fucosidosis, Wolman's disease, Niemann-Pick disease, Batten disease, GM1 gangliosidosis, Tay-Sachs disease, and Sandhoff disease)	Minnesota, Minnesota, NCT00176904	cells using this conditioning regimen in patients undergoing a hematopoietic (blood forming) cell transplant for an inherited metabolic storage disease.				GVHD Pharmacokinetic parameters	
<b>TYPE 1 DIABETES MELLITUS</b>	Autologous Transplantation of Mesenchymal Stem Cells for Treatment of Patients With Onset of Type 1 Diabetes; Third Military Medical University, Chongqing, NCT01157403	To study the safety and efficacy of autologous bone marrow mesenchymal stem cells in treatment of newly diagnosed patients with T1DM.	Safety/Efficacy Study	80 7/2010 – 8/2012 China FU: 2 years	Autologous bone marrow mesenchymal stem cell IV (2.5 x 10 <sup>6</sup> cell/kg body weight)	C-peptide release test	This study is currently recruiting participants.
<b>TYPE 1 DIABETES MELLITUS</b>	Autologous Hematopoietic Stem Cell Transplantation for Early Onset Type 1 Diabetes; Shanghai Jiao Tong University School of Medicine, NCT00807651	To evaluate whether stem cell transplantation is safe when chemotherapy and immunotherapy are used in combination and if it has immune resetting effect that may halt the immune attack to pancreas islets and thus preserve the body's own insulin production.	Safety/Efficacy Study	30 2/2008 – 2/2013 China FU: 3 years	HSC with cyclophosphamide and rabbit antithymocyte globulin IV	Exogenous insulin dose Anti-GAD titers C-peptide level HbA1c level	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>TYPE 1 DIABETES MELLITUS</b>	Hematopoietic Stem Cell Transplantation in Type 1 Diabetes Mellitus; Hospital Universitario Dr. Jose E. Gonzalez, Mexico, NCT01121029	To determine if autologous nonmyeloablative hematopoietic stem cell transplantation is able to induce prolonged and significant increases of C-peptide levels associated with absence of or reduction of daily insulin.	Safety/Efficacy Study	15 (2-35 years of age) 5/2010 – 3/2011 Mexico FU: 1 year	Nonmyeloablative conditioning followed by IV PBSCT	C-peptide level HbA1c level	This study is currently recruiting participants.
<b>TYPE 1 DIABETES MELLITUS</b>	Safety and Efficacy Study of Autologous Stem Cell Transplantation for Early Onset Type I Diabetes Mellitus; University of Sao Paulo, Brazil, NCT00315133	To evaluate the effect of inactivation of the immune system with chemotherapy and immunotherapy and infusion of bone marrow stem cells in early onset type 1 diabetes mellitus.	Safety/Efficacy Study	24 (12 to 35 years of age) 12/2003 – 12/2012 Brazil FU: 1 year	High dose immunosuppression with cyclophosphamide and rabbit antithymocyte globulin and PBSCT	Exogenous insulin dose C-peptide level Hemoglobin A1c Quality of life measures Anti-GAD titers Immunogenic reconstitution parameters	This study is currently recruiting participants.
<b>TYPE 1 DIABETES MELLITUS</b>	Safety and Efficacy of Autologous Adipose-Derived Stem Cell Transplantation in Patients With Type 1 Diabetes; Adistem Ltd, Philippines, NCT00703599	To study whether intravenous administration of autologous adipose stem cells is safe and beneficial in patients with type 1 diabetes.	Safety/Efficacy Study	30 11/2007 – 12/2009 Philippines FU: 4 years	Autologous adipose derived stem cell transplant	Lowering of insulin-dependence and hyperglycemic medication dosage HbA1C level C-peptide level Quality of life measures Kidney, liver and other hematological functioning parameters	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>SYSTEMIC LUPUS ERYTHEMATOSUS</b>	Cyclophosphamide and rATG/Rituximab in Patients With Systemic Lupus Erythematosus; Northwestern University, Chicago, NCT00278538	To produce a normal immune system that will no longer attack body. The study purpose is to examine whether this treatment will result in improvement in the lupus disease.	Safety/Efficacy Study	40 (16 to 60 years) 8/2005 – 8/2013 United States FU: 5 years	AHSCT	OS of patients who achieve and maintain remission post transplant	This study is currently recruiting participants.
<b>SYSTEMIC LUPUS ERYTHEMATOSUS</b>	Mesenchymal Stem Cells Transplantation for Refractory Systemic Lupus Erythematosus (SLE); Nanjing Medical University, Jiangsu, China , NCT00698191	To explore a new approach to treat patients with a medical condition known as systemic lupus erythematosus (SLE) who have been resistant to previous treatments using a new population of cells with capability to restore a normal immune system that will no longer attack the body.	Safety/Efficacy Study	20 (15 to 70 years) 3/2007 – 12/2012 China FU: 2 years	Cyclophosphamide administered before allogeneic bone marrow derived mesenchymal stem cell transplant (106 cells/kg body weight)	Systemic Lupus Erythematosus Disease Activity Index Lupus serology (ANA, dsDNA, C3, C4) Renal function (GFR, BUN, urinalysis) Percentage of systemic T regulatory population	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>SYSTEMIC SCLEROSIS</b>	Allogeneic Mesenchymal Stem Cells Transplantation for Systemic Sclerosis (SSc); The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, Jiangsu, China, NCT00962923	To explore safety and efficacy of allogeneic mesenchymal stem cells transplantation (MSCT) to treat patients with diagnosis of systemic sclerosis(SSc) who have been resistant to multiple standard treatments.	Treatment Study	20 (15 to 65 years) 8/2009 – 12/2011 China FU: Not Reported	Allogeneic mesenchymal stem cells will be infused intravenously (single dose, 10 <sup>6</sup> cells/kg body weight).	mRSS score, HRQOL score, SF-36 score Remission for organ function, VC, DLCO, PAP, serum albumin, serum creatinine, weight loss, 24h proteinuria SSc Serology(ATA,ACA,ANA,anti-ssDNA,anti-dsDNA,IgM,IgG,and IgA, compliment C3 and C4 Change of peripheral blood B and T cells	This study is currently recruiting participants.
<b>SYSTEMIC SCLEROSIS</b>	Pilot Study of Total Body Irradiation in Combination With Cyclophosphamide, Anti-thymocyte Globulin, and Autologous CD34-Selected Peripheral Blood Stem Cell Transplantation in Children With Refractory Autoimmune Disorders; Fred Hutchinson Cancer Research Center, Seattle, Washington, NCT00010335	To determine the safety and long term complication of TBI combined with PBSC for refractory autoimmune disorders. To determine the efficacy, engraftment rate, and reconstitution of immunity in these patients.	Safety/Efficacy Study	20 11/2000 – 12/2020 United States FU: 10 years	Stem cell transplantation along with irradiation and the drugs anti-thymocyte globulin, cyclophosphamide, and filgrastim	Mortality Immune reconstruction Engraftment Efficacy Late-effects	This study is ongoing, but not recruiting participants.



**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>CHRON'S DISEASE</b>	Autologous Stem Cell Transplantation for Crohn's Disease; Duke University, Miltenyi Biotec GmbH, Durham, North Carolina , NCT00692939	To evaluate the safety and effectiveness of administering high-dose chemotherapy followed by infusion of autologous CD34-selected peripheral blood stem cells (PBSC) in pediatric and young adult patients with severe Crohn's disease.	Safety/Efficacy Study	10 (5 to 25 years) 4/2005 – 12/2014 United States FU: 5 years	High-dose immunotherapy followed by infusion of autologous CD34-selected peripheral blood stem cells	Evaluate the safety of administering high-dose immunotherapy followed by infusion of autologous CD34-selected peripheral blood stem cells Pace of neutrophil and platelet recovery after the administration using ablative therapy and infusion of autologous CD34-selected PBSCs Pace of reconstitution of immunity Long-term complications, such as sterility, endocrinopathy, and growth failure Immune function/profile Describe the effects of this therapy on the clinical manifestations of Crohn's Disease	This study is currently recruiting participants.
<b>CHRON'S DISEASE</b>	Hematopoietic Stem Cell Support in Patients With Severe Crohn's Disease. Northwestern University, Chicago, Illinois, NCT00278577	To determine the safety and efficacy of immune ablation with stem cell support on the treatment of Crohn's Disease.	Safety/Efficacy Study	50 (up to 60 years) 4/2001 – 4/2011 United States FU: 5 years	Immune Ablation and Hematopoietic Stem Cell Support	CDAI - If the index worsens by 50 points for more than 4 weeks, the disease will be considered progressive; if it improves by 70 points for more than four weeks, it will be considered improved; otherwise it will be considered stable	This study is ongoing, but not recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>SOCIAL SUPPORT (SARCOMA, NEUROBLASTOMA)</b>	A Web-Based Stem Cell Transplant Support System or Standard Care in Young Patients Undergoing Stem Cell Transplant and Their Families; Tufts Medical Center Cancer Center, United States, NCT00782145	To study a web-based stem cell transplant support system to see how well it works compared with standard care in families of young patients undergoing a stem cell transplant.	Support Intervention Study	200 children w/ accompanying parent undergoing HSCT (all transplant types) 6/2008 – 12/2010 United States FU: 3, 6, 9, 12 mo testing after baseline	Web-based information and social support intervention with analysis of quality-of-life (Child Health Ratings Inventory) at baseline 3, 6, 9 and 12 months and Patient Health Questionnaire (PHQ-9) at baseline and 6 months. Parent completes measures for family and individual coping, social support, process of care and Internet use.	To evaluate the ability of a Web-based Hematopoietic Stem Cell Transplantation (HSCT-) Comprehensive Health Enhancement Support System (HSCT-CHESS) to mitigate the impact of a child's HSCT on the health-related quality of life, family functioning, knowledge, skills, and processes of care of the accompanying parent. To explore the potential mechanisms of action of HSCT-CHESS in improving outcomes in these parents, in terms of parental activation, social support and/or coping skills. To explore the impact of HSCT-CHESS on the health-related quality of life of the pediatric HSCT patient, as reported by the parent and child.	This study is currently recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>FUNGAL INFECTION</b>	Voriconazole Compared With Itraconazole in Preventing Fungal Infections in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation; Jonsson Comprehensive Cancer Center, California, NCT00079222	To study voriconazole to see how well it works compared with itraconazole in preventing fungal infections in patients who are undergoing allogeneic hematopoietic stem cell transplantation.	Supportive care intervention	150 (75 per arm) 1/2004 – End date not reported United States FU 180 days post transplant	Arm I: Beginning after allogeneic hematopoietic stem cell transplantation (AHSCT), patients receive voriconazole IV twice daily on days 1-14 and then orally* twice daily on days 15-100. Arm II: Beginning after AHSCT, patients receive itraconazole IV twice daily on days 1-2, once daily on days 3-14, and then orally* twice daily on days 15-100.	Toxicity Infection Safety	This study is ongoing, but not recruiting participants.

**Appendix Table E1. List of ongoing studies (continued)**

Research Gap	Study	Study Objective (group by this)	Research Design	Sample size; Years; Location; Followup	Treatment(s)	Outcomes	Status
<b>GENETIC RISK FOR SECONDARY MALIGNANCY</b>	Genetic Susceptibility and Risk of Second Cancers in Patients Who Have Undergone Stem Cell Transplant for Cancer; Vanderbilt-Ingram Cancer Center, Tennessee, NCT00949052	To study genetic susceptibility and risk of second cancers in patients who have undergone stem cell transplant for cancer.	Observational study	1000 (800 patients without secondary malignancy and 200 with secondary malignancy) 1/2009-1/2014 United States FU: Not reported	Observational study	Genetic susceptibility to the carcinogenic effects of radiotherapy, tobacco, and UV light and risk of second malignant neoplasms. Radiation sensitivity in B-cell lymphoblastoid cells Allelic variants of genes involved in xenobiotics metabolism, DNA repair, and provision of nucleotide pool of patients with secondary malignancy compared with their first-degree relatives and patients without secondary malignancy Role of potentially carcinogenic environmental exposures (tobacco and sun light) pre- and post-HSCT in the risk of secondary malignancy	This study is currently recruiting participants.
<b>LYSATE-PULSED DENDRITIC VACCINE FOR HIGH-RISK SOLID TUMORS</b>	A Pilot Study of Tumor Cell Vaccine for High-risk Solid Tumor Patients Following Stem Cell Transplantation; University of Michigan Cancer Center, Michigan, NCT00405327	To investigate a tumor lysate-pulsed dendritic cell vaccine for immune augmentation after stem-cell transplantation for pediatric patients with high-risk solid tumors	Safety/Efficacy study	30 patients (up to 30 years of age) 6/2006 - 12/2013 United States FU: 3 years	HSCT with tumor lysate-pulsed dendritic cell vaccine	Rate of immune response of this immunotherapy treatment To correlate and characterize the immune response to the clinical response. To define immunologic endpoints that can serve as surrogates of clinical response.	This study is ongoing, but not recruiting participants.

**Abbreviations:** AHSCR: Autologous hematopoietic stem cell rescue; AHSCT: Autologous hematopoietic stem cell treatment; ASCR: Autologous stem cell rescue; CR: Complete remission; CSF: Cerebrospinal fluid; DOD: Dead of disease; EFS: Event-free survival; FU: Follow up; HDCT: High-dose chemotherapy; HSCT: Hematopoietic stem cell treatment; OS: Overall survival; PBSCT: Peripheral blood stem cell treatment; RBFS: Retinoblastoma free survival; RFS: Relapse free survival; SCT: Stem cell treatment; TRM: Treatment-related mortality

# Appendix F. Effective Health Care Program Selection Criteria

## Appropriateness

- Represents a health care drug, intervention, device, technology or health care system/setting available (or soon to be available) in the U.S.
- Relevant to 1013 enrollees (Medicare, Medicaid, S-CHIP, other federal health care programs)
- Represents one of the priority conditions designated by the Department of Health and Human Services

## Importance

- Represents a significant disease burden, large proportion or priority population
- Is of high public interest; affects health care decision-making, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular
- Was nominated/strongly supported by one or more stakeholder groups
- Represent important uncertainty for decision-makers
- Incorporates issues around both clinical benefits and potential clinical harms
- Represents important variation in clinical care, or controversy in what constitutes appropriate clinical care
- Represent high costs due to common use, to high unit costs, or to high associated costs to consumers, to patients, to health care systems, or to payers

## Desirability of new research/duplication

- Would not be redundant (the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)

## Feasibility

- Effectively uses existing research and knowledge by considering adequacy of research for conducting a systematic review, and newly available evidence

## Potential Impact

- Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups.

# Appendix G. Tool Used To Solicit KI Research Gap Ratings and Key Questions Via SurveyMonkey<sup>®</sup> (June 16, 2011)

[Distributed to combined KI group after the first set of conference calls, one with original KI group and one with patient advocates]

HSCT FRN  
Exit this survey

## HSCT Future Research Needs: Gap Prioritization and Key Question Survey

Thank you for taking the time to answer the questions on this survey. We will collect the responses and get back to you shortly with the results at our next meeting.

\*

Please enter your name:

Please enter your name:

\*

Please rate each of the quality gaps on a scale of one to seven. With a score of one signifying most importance and seven least importance. Each score may only be used once.

	1	2	3	4	5	6	7
Long term consequences of HSCT, measured by overall survival, functional measures, quality of life, and adverse effects	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mitigation of long term effects by changes in regimen and changes in subsequent medical or psychosocial intervention	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Role of novel approaches to HSCT in altering short-term adverse effects such approaches include: reduced intensity approaches, novel cellular therapies (such as natural killer-cell therapy) and immunomodulatory therapies (including vaccine therapy)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Multicenter collaboration to increase accrual of patient and systematizing outcome reporting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Effectiveness of survivorship planning on long term, comprehensive followup	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Impact on outcomes of a 'family-centered' approach to transplantation (Advocates of children who have undergone HSCT transplantation defined such an approach as including: emotional and psychosocial counseling for the family with a special attention on donor and non-donor siblings, information to share with caregivers and peers, and tools rather than only a large amount of information for navigating the complexities of the medical system and medication management)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

\*

**Please specify key questions for each of the quality gaps above. Key questions will be used to guide future primary research efforts.**

Please specify key questions for each of the quality gaps above. Key questions will be used to guide future primary research efforts. Long term consequences of HSCT, measured by overall survival, functional measures, quality of life, and adverse effects

Mitigation of long term effects by changes in regimen and changes in subsequent medical or psychosocial intervention

Role of novel approaches to HSCT in altering short-term adverse effects such approaches include: reduced intensity approaches, novel cellular therapies (such as natural killer-cell therapy) and immunomodulatory therapies (including vaccine therapy)

Multicenter collaboration to increase accrual of patient and systematizing outcome reporting

Effectiveness of survivorship planning on long term, comprehensive followup

Impact on outcomes of a 'family-centered' approach to transplantation (Advocates of children who have undergone HSCT transplantation defined such an approach as including: emotional and psychosocial counseling for the family with a special attention on donor and non-donor siblings, information to share with caregivers and peers, and tools rather than only a large amount of information for navigating the complexities of the medical system and medication management)

Uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center

Done

# Appendix H. Research Gap Rankings

**Appendix Table H1. Initial research gap rankings (five KI members)**

Gap:	Ranking # (Total Points of 35):
Long term consequences of HSCT, measured by overall survival, functional measures, quality of life, and adverse effects	<b>3 (25/35)</b>
Mitigation of long term effects by changes in regimen and changes in subsequent medical or psychosocial intervention	<b>1 (30/35)</b>
Role of novel approaches to HSCT in altering short-term adverse effects such approaches include: reduced intensity approaches, novel cellular therapies (such as natural killer-cell therapy) and immunomodulatory therapies (including vaccine therapy)	<b>2 (26/35)</b>
Multicenter collaboration to increase accrual of patient and systematizing outcome reporting	<b>5 (15/35)</b>
Effectiveness of survivorship planning on long-term, comprehensive followup	<b>6 (14/35)</b>
Impact on outcomes of a 'family-centered' approach to transplantation (Advocates of children who have undergone HSCT transplantation defined such an approach as including: emotional and psychosocial counseling for the family with a special attention on donor and non-donor siblings, information to share with caregivers and peers, and tools rather than only a large amount of information for navigating the complexities of the medical system and medication management)	<b>4 (17/35)</b>
Uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center	<b>7 (13/35)</b>



**Appendix Table H2. Final list of research gap rank (from eight KI members)**

<b>Gap:</b>	<b>Ranking # (Total Points of 56):</b>
Long term consequences of HSCT, measured by overall survival, functional measures, quality of life, and adverse effects	<b>1 (41/56)</b>
Mitigation of long term effects by changes in regimen and changes in subsequent medical or psychosocial intervention	<b>1 (41/56)</b>
Role of novel approaches to HSCT in altering short-term adverse effects such approaches include: reduced intensity approaches, novel cellular therapies (such as natural killer-cell therapy) and immunomodulatory therapies (including vaccine therapy)	<b>2 (34/56)</b>
Multicenter collaboration to increase accrual of patient and systematizing outcome reporting	<b>3 (31/56)</b>
Effectiveness of survivorship planning on long term, comprehensive followup	<b>4 (24/56)</b>
Impact on outcomes of a 'family-centered' approach to transplantation (Advocates of children who have undergone HSCT transplantation defined such an approach as including: emotional and psychosocial counseling for the family with a special attention on donor and non-donor siblings, information to share with caregivers and peers, and tools rather than only a large amount of information for navigating the complexities of the medical system and medication management)	<b>3 (31/56)</b>
Uniform reporting of outcome data to allow patient comparison of HSCT outcomes by transplant center	<b>5 (22/56)</b>