Guidelines for Defining Standard Episode for Hematopoietic Stem Cell Transplantation
Patient Care Within the Context of Clinical Trials

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Abstract
The Patient Protection and Affordable Care Act requires that healthcare insurers cover routine patient costs associated with participating in clinical trials for cancer and other life-threatening diseases. There is a need to better define ‘routine costs’ within the context of hematopoietic stem cell transplantation (HSCT) clinical trials. This white paper presents guidance on behalf of the American Society for Blood and Marrow Transplantation for defining a standard HSCT episode and delineates components that may be considered as routine patient costs versus clinical research costs. The guidelines will assist investigators, trial sponsors and transplant centers in planning for clinical trials that are conducted as a part of the HSCT episode and will inform payers who provide coverage for transplantation.
Background
Clinical research and clinical trials are critical to improving patient survival and outcomes after hematopoietic stem cell transplantation (HSCT). HSCT is a complex procedure that includes several phases of care from the pre-transplant workup to long-term post-transplant followup. Within these episodes there are multiple opportunities for clinical trials to evaluate novel therapies and improve HSCT procedures. Examples include, but are not limited to, investigations of newer conditioning regimens, graft manipulation, supplemental cellular therapies, and interventions to prevent or treat post-transplant complications. However, it can be challenging to differentiate routine standard care as part of the HSCT episode from care that is provided as part of a clinical trial.

With implementation of the Patient Protection and Affordable Care Act (ACA) healthcare insurers are prohibited from denying participation in an approved clinical trial for cancer or other life-threatening disease. Now payers must cover routine patient costs associated with participating in these clinical trials. However, to assure appropriate payment for costs associated with clinical trials involving HSCT, we need to know what constitutes routine patient care costs versus clinical research costs in such trials. There is a need to better define a standard episode for HSCT in order to guide patients, healthcare providers, transplant centers and payers about components of transplant care that may be considered routine and standard versus those that may be considered investigational.

The American Society for Blood and Marrow Transplantation (ASBMT) established a Task Force comprising of experts in HSCT including transplant clinical trials, payers and patient advocates. The Task Force presents this white paper as consensus guidelines for defining a standard HSCT episode (that is, routine patient care) and delineates components that should be considered as clinical research costs. It will assist transplant centers in planning for clinical trials that are conducted as a part of the HSCT episode and will inform payers who provide coverage for transplantation.

Clinical Trial Coverage under the Affordable Care Act
The ACA provision for cancer clinical trial coverage went into effect in January 2014 (www.healthcare.gov and www.dol.gov/ebsa/healthreform). In essence, it is designed to provide a greater opportunity for clinical trial participation for patients with cancer or other life-threatening diseases and prohibits health plans or insurance issuers from denying coverage or
discriminating on the basis of participation in an approved clinical trial. An “approved” clinical trial is defined as a phase I, II, III or IV trial for the prevention, detection or treatment of cancer or other life-threatening disease or condition (“life-threatening disease or condition” is one from which the likelihood of death is probable unless the course of the disease or condition is interrupted). It includes federally funded trials, trials conducted under an investigational new drug application reviewed by the Food and Drug Administration (FDA), or drug trials exempt from having an investigational new drug application. The law directs payers to cover routine patient costs associated with participation in a clinical trial.

The statute provides a broad definition of “routine patient costs”, and includes items and services consistent with the coverage provided in the health plan that typically would be covered for a qualified individual who is not enrolled in a clinical trial. Excluded from the definition of routine patient costs are (1) costs of the investigational item, device, or service itself, (2) costs of items and services that are provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient, and (3) costs of a service that is clearly inconsistent with widely accepted and established standards of care for a particular diagnosis.

Given the non-specificity of this definition, trial sponsors, transplant centers and payers are encouraged to work together using the framework provided in this document to determine routine patient care and costs associated with patient participation in a clinical trial before the trial is opened for enrollment. Transplant centers will also need to educate patients considering participation in a clinical trial to ensure they understand coverage for the trial based on their health plan. In addition, more and clearer guidance on the definition of routine patient care costs from federal authorities in charge of implementing the ACA would be helpful to patients, trial sponsors, transplant centers and payers.

**Guiding Principles**

The Task Force recognizes the complexity of clinical trials performed as part of HSCT. General guidelines are presented in this document and individual clinical trials will need to be reviewed to determine standard care vs. research. General guiding principles that were considered in the development of recommendations are as follows:
- General guidance is presented as it is not possible to envision and incorporate all HSCT clinical trial scenarios. Each clinical trial will need individual assessment of what constitutes standard clinical care versus research.
- Guidelines will need to be reviewed and updated periodically so that they are reflective of the state of the art research being conducted in HSCT.
- Guidelines focus on research conducted as a part of the autologous or allogeneic HSCT episode. This paper does not provide guidance on clinical trials of cellular therapies or other clinical interventions that do not include HSCT (see below for definition of HSCT).
- Phase I, II, III and IV clinical trials for the prevention, detection or treatment of cancer and life-threatening diseases as defined under the ACA are considered; for example, these guidelines do not apply to research that is conducted using existing data (e.g., retrospective or registry studies).
- The clinical trial protocol and the study’s stated hypotheses, aims and endpoints should be used as a reference to guide and inform coverage decisions.
- The guidelines apply to a reasonable period of time post-transplantation when the majority of a patient’s post-transplant care can be expected to occur at the transplant center. However, clinical trials may include interventions or assessments that extend beyond this time period. Investigators, transplant centers and study sponsors should delineate care that is considered standard versus investigational for the duration of the study.
- There exists considerable variation in the models and coverage of care for long-term transplant survivors. Patients may continue to be followed at the transplant center long-term for routine followup or for the management of transplant related complications (e.g., chronic graft-versus-host disease) at some centers. Clinical trials in this population will need to be reviewed individually to determine what may be considered as routine care and what components may be research.
- It is not uncommon that currently available drugs are used for off label indications in the setting of HSCT either to treat or prevent complications (e.g., use of palifermin to prevent mucositis for allogeneic recipients or use of anti-tumor necrosis factor agents to treat steroid refractory graft-versus-host disease). Outside of clinical trials that are specifically investigating such agents, we view that this utilization should be considered as part of covered benefits.
- Clinical trials may compare transplant with non-transplant therapies. These guidelines can be applied to the transplant component of such clinical trials.
The Task Force considered situations such as new or emerging indications for which transplantation is not considered as standard therapy. Some examples include investigation of transplantation for autoimmune diseases such as multiple sclerosis, systemic sclerosis, inflammatory bowel disease and systemic lupus erythematos or for a new prognostic (e.g., molecular) marker that may adversely impact survival in patients with diseases that are considered as standard indications for transplantation (e.g., acute myeloid leukemia). HSCT may be considered as the application of routine therapy to a new or emerging indication in such circumstances and not the development of an entirely new treatment. Alternatively, clinical trials may focus on HSCT approaches that are routinely used in clinical practice and considered as standard of care. An example is a phase III clinical trial comparing two commonly used conditioning regimens, where the majority of clinical care provided under the trial may be considered as standard of care. Although it was beyond our scope to envision all HSCT clinical trial scenarios, the Task Force generally recommends a similar approach for defining a standard HSCT episode for HSCT clinical trials (e.g., the HSCT procedure itself and the associated usual pre- and post-transplant care may be considered as routine care in clinical trials that are evaluating new or emerging indications, comparison of two transplant regimens or a transplant and non-transplant treatment, and investigations of supportive care interventions). However and as noted above, each clinical trial will need to be evaluated individually and study investigators, transplant centers, trial sponsors and payers are encouraged to engage early in the trial development process to address the issue of standard versus investigational, where it is relevant. All interested parties should be aware that the interpretation of the definitions of routine patient costs and coverage determinations for clinical trial services may vary between insurance carriers.

Investigators and transplant centers routinely undertake the process of identifying standard versus investigational portions of a trial during the contractual and budgeting stage and some Institutional Review Boards may request this information to be submitted as part of their review procedure. The Task Force encourages investigators to also specify in study protocols these components of the trial that may be considered standard of care or investigational.

**Definition of HSCT Episode**
Standard definitions of HSCT patient care episode that have been proposed by the ASBMT and the National Marrow Donor Program (NMDP) have been followed (Table 1).
Phases of HSCT Episode
For the purposes of payer coverage, the HSCT episode is frequently divided into several phases. These include:

- Evaluation phase: This phase includes services required to assess and evaluate whether a patient, and in the case of allogeneic HSCT the donor, are suitable for the transplantation procedure. It may also include evaluations to assess whether a transplant is an appropriate treatment option for the patient.

- Pre-transplant care phase: This phase involves care provided from the time a patient is identified as a candidate for HSCT and includes all related care until the initiation of conditioning regimen.

- Transplant event phase: This phase usually starts from the day of starting conditioning regimen and it can last from 30 to 120 days post-transplant. This phase covers the hematopoietic stem cell infusion and the transplant hospitalization and also typically includes graft procurement, stem cell mobilization and processing. In some situations, this phase can extend for a longer period of time (e.g., tandem transplantation for germ cell tumors or multiple myeloma). This phase also includes any clinic visits associated with providing care to patients receiving an outpatient transplant.

- Followup care phase: This phase starts on completion of the transplant event phase and can extend until the patient is discharged from routine transplant center followup care.

Of note, there may be a gap between the evaluation phase and the pre-transplant care phase, especially for diseases where a transplant is not required immediately (e.g., myelodysplastic syndromes or myelofibrosis) and in situations where the patient may need more therapy before a transplant can proceed.

Definition of Standard HSCT Episode
Table 2 presents the phases of an HSCT episode and the components within each phase that may be considered as standard clinical care for HSCT recipients. To assist with the interpretation of these guidelines, some examples based on ongoing Blood and Marrow Clinical Trials Network (BMT CTN) clinical trials are presented in Table 3.
References
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Hematopoietic stem cell infusion (HSCI)</td>
<td>Infusion of a product (bone marrow, peripheral blood stem cells, cord blood) that contains hematopoietic progenitor cells (HPCs), often characterized by CD34 expression.</td>
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<td>Hematopoietic stem cell transplantation (HSCT)</td>
<td>An episode of care starting with a preparative regimen and continuing through HSCI and recovery.</td>
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<td>Allogeneic HSCT</td>
<td>HSCI using products collected from a donor and usually following a preparative regimen. Donors may be a biological relative of the recipient or anonymous and unrelated.</td>
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<td>Syngeneic HSCT</td>
<td>HSCI using products collected from an identical sibling.</td>
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<tr>
<td>Autologous HSCT</td>
<td>HSCI using products collected from the recipient before myeloablative chemotherapy.</td>
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<td>Tandem transplantation</td>
<td>The patient receives a second preparative regimen, along with HPCs collected during the initial mobilization. Both transplantations are planned in advance and typically are performed a few weeks to a few months apart.</td>
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<td>Donor cellular infusion (DCI)</td>
<td>An infusion of cells from an allogeneic donor typically given after HSCT. Types of cells used for DCI include, but are not limited to, the following: Lymphocytes/T cells (donor lymphocyte infusion), Peripheral blood mononuclear cells (both stimulated and unstimulated), Dendritic cells from the original donor, or Mesenchymal cells.</td>
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<td>Supplemental infusion</td>
<td>An infusion of cells given before clinical day 0 (day of HSCT) for any reason other than to produce engraftment. An infusion of supplemental cells is often given in conjunction with a preparative regimen for HSCT.</td>
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<td>Re-transplantation</td>
<td>HSCT after undergoing a previous transplantation.</td>
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<td>Subsequent (boost) infusion</td>
<td>Subsequent transfusion of allogeneic or autologous HPCs.</td>
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<td>Treatment phase</td>
<td>Examples of components considered part of standard HSCT episode</td>
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| Evaluation phase (Transplant consultation and evaluation) | - Transplant consultation  
- HLA typing of related and, if applicable, unrelated donors and/or umbilical cord blood unit(s) | - Evaluations that are not a part of standard care and are performed to determine eligibility for a clinical trial |
| Pre-transplant care phase (Pre-transplant workup) | - Evaluation of disease status (e.g., bone marrow biopsy, CT scan, serum protein electrophoresis)  
- Evaluation of organ function (e.g., liver function tests, echocardiogram, pulmonary function tests)  
- Psychosocial assessment  
- Other evaluations to determine recipient suitability (e.g., consultation with a specialist, additional tests to evaluate abnormal findings)  
- Assessments to determine related or unrelated donor suitability and eligibility | - Evaluations that are not a part of standard care and are performed to determine eligibility for a clinical trial  
- Evaluations that are not a part of routine care and are performed specifically to meet the requirements of a clinical trial |
| Transplant event phase (From start of conditioning regimen to 30-120 days post-transplantation) | - Mobilization and collection of peripheral blood or bone marrow HPCs  
- Conditioning regimen chemotherapy and/or radiation therapy  
- Hospitalization and/or outpatient visits associated with administration of conditioning regimen  
- Infusion of bone marrow, peripheral blood or umbilical cord blood HPCs  
- Hospitalization and/or outpatient post-transplant supportive care  
- Management of HSCT related complications | - Drug administered under FDA’s investigational new drug application  
- Cellular therapy product administered under FDA’s investigational new drug application  
- Evaluations that are not a part of routine care and are performed specifically to meet the requirements of a clinical trial |
| Followup care phase (Extends through discharge from transplant center) | - Hospitalization or outpatient supportive care  
- Management of HSCT related complications | - Evaluations that are not a part of routine care and are performed specifically to meet the requirements of a clinical trial |
Table 3: Examples to provide guidance on implementing definition of standard HSCT episode of care in the context of a clinical trial

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Evaluation phase</th>
<th>Pre-transplant care phase</th>
<th>Transplant event phase</th>
<th>Followup care phase</th>
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<tr>
<td>BMT CTN 0601 Study</td>
<td>Standard care - Transplant consultation&lt;br&gt;- HLA typing of unrelated donors</td>
<td>Standard care - Evaluation of disease status and organ function, psychosocial assessments and any other evaluations performed by the center to determine recipient and donor suitability for transplantation</td>
<td>Standard care - Collection of donor bone marrow&lt;br&gt;- Conditioning regimen chemotherapy specified in the clinical trial protocol&lt;br&gt;- Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplant supportive care&lt;br&gt;- GVHD prophylaxis regimen specified in the clinical trial protocol&lt;br&gt;- Patient visits and clinic assessments that are routine care&lt;br&gt;- Management of HSCT related complications</td>
<td>Standard care - Hospitalization or outpatient supportive care&lt;br&gt;- Management of HSCT related complications</td>
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<tr>
<td>Design: Phase II&lt;br&gt;Title: Unrelated donor reduced intensity bone marrow transplant for children with severe sickle cell disease&lt;br&gt;Type: Testing efficacy and toxicity of an established transplant technique for a new indication</td>
<td>Research - None</td>
<td>Research - Center effort associated with registering and enrolling patient on the trial</td>
<td>Research - Center effort associated with performing HRQOL assessments&lt;br&gt;- Center effort associated with performing endpoint and adverse event assessment and reporting</td>
<td>Research - Center effort associated with performing HRQOL assessments&lt;br&gt;- Center effort associated with performing adverse event assessment and reporting for the duration of the study (2 years)</td>
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<tr>
<td>BMT CTN 0901 Study</td>
<td>Standard care - Transplant consultation&lt;br&gt;- HLA typing of related and, if applicable, unrelated donors</td>
<td>Standard care - Evaluation of disease status and organ function, psychosocial assessments and any other evaluations</td>
<td>Standard care - Mobilization and collection of donor PBSCs or collection of donor bone marrow&lt;br&gt;- Conditioning regimen</td>
<td>Standard care - Hospitalization or outpatient supportive care&lt;br&gt;- Management of HSCT related complications</td>
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<tr>
<td>Design: Phase III&lt;br&gt;Title: A randomized, phase III study of allogeneic stem cell transplantation</td>
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<tr>
<td>- None</td>
<td>- Center effort associated with registering and enrolling patient on the trial</td>
<td>- Blood samples for future research</td>
<td>- Center effort associated with performing HRQOL assessments</td>
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<tr>
<td>BMT CTN 1203 Study</td>
<td>Standard care</td>
<td>Standard care</td>
<td>Standard care</td>
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<tr>
<td>Design: Phase II</td>
<td>- Transplant consultation</td>
<td>- Evaluation of disease status and organ function, psychosocial assessments and any other evaluations performed by the center to determine recipient and donor suitability</td>
<td>- Mobilization and collection of donor PBSCs</td>
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<tr>
<td>Title: A multi-center phase II trial randomizing novel approaches for GVHD prevention compared to contemporary controls (patients randomized to Tac/MTX/bortezomib vs. Tac/MTX/maraviroc vs.</td>
<td>- HLA typing of related and, if applicable, unrelated donors</td>
<td>- Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol</td>
<td>- Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplant supportive care</td>
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<tr>
<td>Standard care</td>
<td>Standard care</td>
<td>Standard care</td>
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<tr>
<td>- Transplant consultation</td>
<td>- Evaluation of disease status and organ function, psychosocial assessments and any other evaluations performed by the center to determine recipient and donor suitability</td>
<td>- Mobilization and collection of donor PBSCs</td>
<td>- Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplant supportive care</td>
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<tr>
<td>- HLA typing of related and, if applicable, unrelated donors</td>
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<td>- Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol</td>
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</table>
| Tac/MMF/Cy)  | Type: Testing novel approaches to prevent or reduce post-transplant complications | post-transplant supportive care  
- Tac, MTX, Cy and MMF for GVHD prophylaxis  
- Patient visits and clinic assessments that are routine care  
- Management of HSCT related complications |  
Research  
- None | Research  
- Center effort associated with registering and enrolling patient on the trial | Research  
- Bortezomib and maraviroc for GVHD prophylaxis  
- Blood samples for future research  
- Center effort associated with performing endpoint and adverse event assessment and reporting | Research  
- Center effort associated with performing adverse event assessment and reporting for the duration of the study (2 years) |

BMT CTN – Blood and Marrow Transplant Clinical Trials Network; Cy – cyclophosphamide; GVHD – graft-versus-host disease; HLA – human leukocyte antigens; HRQOL – health related quality of life; MMF – mycophenolate mofetil; MTX – methotrexate; PBSCs – peripheral blood stem cells; Tac – tacrolimus;