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Guideline

Guidelines for Defining and Implementing Standard Episode of Care for Hematopoietic Stem Cell Transplantation within the Context of Clinical Trials



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A B S T R A C T

The Patient Protection and Affordable Care Act requires that health care 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 research costs. The guidelines will assist investigators, trial sponsors, and transplantation 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.

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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 pretransplantation workup to long-term post-transplantation follow-up. 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-transplantation complications. However, it can be challenging to differentiate routine 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) health care insurers are prohibited from denying patients' 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 to guide patients, health care providers, transplantation centers, and payers about components of transplantation care that may be considered routine versus those that may be considered investigational. Martin et al. have recently provided a perspective on coverage of costs associated with patient participation in cancer clinical trials [1].

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The American Society for Blood and Marrow Transplantation (ASBMT) established a task force comprising experts in HSCT, including transplantation 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 may be considered clinical research costs. It will assist transplantation 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 ACA

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 (IND) application reviewed by the Food and Drug Administration (FDA), or drug trials exempt from having an IND 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.

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 routine care versus research. The following guiding principles were considered in the development of these recommendations:

- Clinical trials are critical to advancing the field of HSCT and for improving patient outcomes. Care for HSCT recipients should ideally be provided on well-designed and high-impact clinical trials.
- General guidance is presented as it is not possible to envision and incorporate all HSCT clinical trial scenarios. Each clinical trial will need an individual assessment of what constitutes routine 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 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).

- The terms *standard care* or *routine care* can create ambiguity for the purposes of defining coverage as the “standard” can change over time or vary among transplantation centers. Instead, *reasonable and medically necessary* is a better term to describe items and services that are required for the direct clinical management of the patient [1]. However, to be consistent with the terminology included in the ACA, we have used the term *routine care* in this manuscript.
- 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 (eg, 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 after transplantation when the majority of a patient’s post-transplantation care can be expected to occur at the transplantation center. However, clinical trials may include interventions or assessments that extend beyond this time period. Investigators, transplantation 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 transplantation survivors. At some centers, patients may continue to be followed at the transplantation center long-term for routine follow-up or for the management of transplantation-related complications (eg, chronic graft-versus-host disease). 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 for currently available drugs to be used for off-label indications in HSCT recipients. For example, graft-versus-host disease in allogeneic HSCT recipients is not an FDA-approved indication for most drugs that are commonly used for the prevention or treatment of this complication. Other examples include use of palifermin to prevent mucositis for allogeneic recipients or use of antitumor 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 transplantation with non-transplantation therapies. These guidelines can be applied to the transplantation component of such clinical trials.

SPECIAL CONSIDERATIONS FOR HSCT CLINICAL TRIAL COVERAGE

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

Table 1
Recommended Procedure Terms for HSCT Patient Care Episode (from LeMaistre et al. [2])

Term	Definition
HSCI	Infusion of a product (bone marrow, peripheral blood stem cells, cord blood) that contains HPCs, often characterized by CD34 expression.
HSCT	An episode of care starting with a preparative regimen and continuing through HSCI and recovery.
Allogeneic HSCT	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.
Syngeneic HSCT	HSCI using products collected from an identical sibling.
Autologous HSCT	HSCI using products collected from the recipient before myeloablative chemotherapy.
Tandem transplantation	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.
DCI	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 lymphocytes/T cells (donor lymphocyte infusion), peripheral blood mononuclear cells (both stimulated and unstimulated), dendritic cells from the original donor, or mesenchymal cells.
Supplemental infusion	An infusion of cells given before clinical day 0 (day of HSCT) for any reason other than to produce engraftment.
Retransplantation	HSCT after undergoing a previous transplantation.
Subsequent (boost) infusion	Subsequent transfusion of allogeneic or autologous HPCs.

HSCI indicates hematopoietic stem cell infusion; HPC, hematopoietic progenitor cells; DCI, donor cell infusion.

bowel disease, and systemic lupus erythematosus, or for a new prognostic marker that may adversely affect survival in patients with diseases that are considered as standard indication for transplantation (eg, new molecular marker for 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 2 commonly used conditioning regimens, where the majority of clinical care provided under the trial may be considered as routine 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 (eg, the HSCT procedure itself and the associated usual pre- and post-transplantation care may be considered as routine care in clinical trials that are evaluating new or emerging indications, comparison of 2 transplantation regimens, or a transplantation and non-transplantation treatment, and investigations of supportive care interventions). However and as noted above, each clinical trial will need to be evaluated individually and study investigators, transplantation centers, trial sponsors, and payers are encouraged to engage early in the trial development process to address the issue of routine 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 among insurance providers and by region. For example, a clinical

Table 2
Guidelines for Defining Standard HSCT Episode of Care

Treatment Phase	Examples of Components Considered Part of Standard HSCT Episode	Examples of Components Considered Research
Evaluation (Transplantation consultation and evaluation)	<ul style="list-style-type: none"> - Transplantation consultation - HLA typing of related and, if applicable, unrelated donors and/or umbilical cord blood unit(s) 	<ul style="list-style-type: none"> - Evaluations that are not part of routine care and are performed specifically to determine eligibility or to meet the requirements for a clinical trial
Pretransplantation care (Pretransplantation workup)	<ul style="list-style-type: none"> - Evaluation of disease status (eg, bone marrow biopsy, CT scan, serum protein electrophoresis) - Evaluation of organ function (eg, liver function tests, echocardiogram, pulmonary function tests) - Psychosocial assessment - Other evaluations to determine recipient suitability (eg, consultation with a specialist, additional tests to evaluate abnormal findings) - Assessments to determine related or unrelated donor suitability and eligibility 	<ul style="list-style-type: none"> - Evaluations that are not part of routine care and are performed specifically to determine eligibility or to meet the requirements for a clinical trial
Transplantation event (From start of conditioning regimen to 30-120 d after transplantation)	<ul style="list-style-type: none"> - 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-transplantation supportive care - Management of HSCT-related complications 	<ul style="list-style-type: none"> - Drug administered under FDA's IND application - Cellular therapy product administered under FDA's IND application - Evaluations that are not part of routine care and are performed specifically to meet the requirements of a clinical trial
Follow-up care phase (Extends through discharge from transplantation center)	<ul style="list-style-type: none"> - Hospitalization or outpatient supportive care - Management of HSCT-related complications 	<ul style="list-style-type: none"> - Evaluations that are not a part of routine care and are performed specifically to meet the requirements of a clinical trial

CT indicates computed tomography.

Table 3
Examples to Provide Guidance on Implementing Definition of Standard HSCT Episode of Care in the Context of a Clinical Trial

Clinical Trial	Evaluation Phase	Pretransplantation Care Phase	Transplantation Event Phase	Follow-Up Care Phase
<p>BMT CTN 0601 <i>Design:</i> Phase II <i>Title:</i> Unrelated donor reduced-intensity bone marrow transplantation for children with severe sickle cell disease <i>Type:</i> Testing efficacy and toxicity of an established transplantation technique for a new indication</p>	<p>Routine care - Transplantation consultation - HLA typing of unrelated donors</p> <p>Research - None</p>	<p>Routine 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</p> <p>Research - Center effort associated with registering and enrolling patient on the trial</p>	<p>Routine care - Collection of donor bone marrow - Conditioning regimen chemotherapy specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - GVHD prophylaxis regimen specified in the clinical trial protocol - Patient visits and clinic assessments that are routine care - Management of HSCT-related complications</p> <p>Research - Center effort associated with performing HRQOL assessments - Center effort associated with performing endpoint and adverse event assessment and reporting</p>	<p>Routine care - Hospitalization or outpatient supportive care - Evaluation and management of HSCT-related complications, including GVHD and late effects</p> <p>Research - Center effort associated with performing HRQOL assessments - Center effort associated with performing adverse event assessment and reporting for the duration of the study (2 yr)</p>
<p>BMT CTN 0901 <i>Design:</i> Phase III <i>Title:</i> A randomized, phase III study of allogeneic stem cell transplantation comparing regimen intensity in patients with myelodysplastic syndrome or acute myeloid leukemia <i>Type:</i> Comparing standard transplantation treatment regimens</p>	<p>Routine care - Transplantation consultation - HLA typing of related and, if applicable, unrelated donors</p> <p>Research - None</p>	<p>Routine care - Evaluation of disease status and organ function, psychosocial assessments and any other evaluations performed by the center to determine recipient and donor suitability</p> <p>Research - Center effort associated with registering and enrolling patient on the trial</p>	<p>Routine care - Mobilization and collection of donor PBSCs or collection of donor bone marrow - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - GVHD prophylaxis regimen specified in the clinical trial protocol - Patient visits and clinic assessments that are routine care - Management of HSCT-related complications</p> <p>Research - Blood samples for future research - Center effort associated with performing HRQOL assessments - Center effort associated with performing endpoint and adverse event assessment and reporting</p>	<p>Routine care - Hospitalization or outpatient supportive care - Evaluation and management of HSCT-related complications including GVHD and late effects</p> <p>Research - Center effort associated with performing HRQOL assessments - Center effort associated with performing endpoint and adverse event assessment and reporting for the duration of the study (4 yr)</p>

<p>BMT CTN 1203 Design: Phase II Title: A multicenter phase II trial randomizing novel approaches for GVHD prevention compared to contemporary controls (patients randomized to Tac/MTX/bortezomib versus Tac/MTX/maraviroc versus Tac/MMF/Cy) Type: Testing novel approaches to prevent or reduce post-transplantation complications</p>	<p>Routine care - Transplantation consultation - HLA typing of related and, if applicable, unrelated donors</p>	<p>Routine care - Evaluation of disease status and organ function, psychosocial assessments, and any other evaluations performed by the center to determine recipient and donor suitability</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Hospitalization or outpatient supportive care - Evaluation and management of HSCCT related complications including GVHD and late effects</p>
<p>Routine care - Evaluation of disease status and organ function, psychosocial assessments, and any other evaluations performed by the center to determine recipient and donor suitability</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Hospitalization or outpatient supportive care - Evaluation and management of HSCCT related complications including GVHD and late effects</p>
<p>Routine care - Evaluation of disease status and organ function, psychosocial assessments, and any other evaluations performed by the center to determine recipient and donor suitability</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Mobilization and collection of donor PBSCs - Conditioning regimen chemotherapy and TBI specified in the clinical trial protocol - Hospitalization and/or outpatient visits associated with administration of conditioning regimen and post-transplantation supportive care - Tac, MTX, Cy and MMF for GVHD prophylaxis - Patient visits and clinic assessments that are routine care - Management of HSCCT-related complications</p>	<p>Routine care - Hospitalization or outpatient supportive care - Evaluation and management of HSCCT related complications including GVHD and late effects</p>

BMT CTN indicates Blood and Marrow Transplant Clinical Trials Network; GVHD, graft-versus-host disease; HRQOL, health related quality of life; PBSC, peripheral blood stem cells; TBI, total body irradiation; Tac, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil; Cy, cyclophosphamide.

trial that may not be covered under the ACA definition may be covered through another state law. Alternatively, federal or state regulations and coverage mechanisms may determine clinical trial coverage for transplantation. For example, a state Medicaid program may limit clinical trial participation to transplantation centers within the state. Another example is coverage for transplantation for myelodysplastic syndromes by Centers for Medicare and Medicaid Services under its Coverage with Evidence Development mechanism.

A scenario that deserves special mention is when a federal agency or another regulatory body mandates that the HSCT procedure or certain components of the HSCT procedure be performed on a clinical trial protocol for additional data collection or for other regulatory purposes. An example is the IND application through the FDA for a multicenter access and distribution protocol for unlicensed cryopreserved umbilical cord blood units, which provides access to these units for patients in the United States through the National Marrow Donor Program. The FDA may grant an exemption to allow cost recovery for a drug (including biological products) that is being provided under an IND application. An example for this mechanism is the use of a well-proven therapy in a new population or through a modification of an established approved therapy such that the FDA allows the patient's insurance provider to be billed for its costs (eg, collection of CD34 selected peripheral blood stem cells in pediatric donors or using a new technology). The Centers for Medicare and Medicaid Services Coverage with Evidence Development mechanism for providing coverage for myelodysplastic syndromes is another example of when a federal agency has mandated further data collection under a clinical trial protocol before it can provide a definitive coverage decision. Hence, in appropriate situations where the HSCT procedure or its components are performed under an investigational mandate (eg, IND or Investigational Device Exemption application through the FDA), the procedure and/or pre- and post-transplantation care may be considered routine patient care. However, in these situations, payers would not be expected to cover the costs of services and care that is not "routine" and not used in direct clinical management of the patient (eg, data collection and analysis for the examples listed above).

Investigators and transplantation centers routinely undertake the process of identifying routine 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 routine care or investigational. Transplantation programs are also encouraged to establish center-specific guidelines, as needed. Outlining the center specific approaches may aid in building consensus with payers and help in the planning of clinical trials.

We encourage transplantation centers to engage payers as early as possible in the transplantation evaluation process for a patient as coverage determination for the HSCT procedure can take time, especially when care is being provided within the context of a complex clinical trial.

Trial sponsors, transplantation 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. Transplantation 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, transplantation centers, and payers.

DEFINITION OF HSCT EPISODE

Standard definitions of *HSCT patient care episode* that have been proposed by the ASBMT and the National Marrow Donor Program are presented in Table 1 [2].

PHASES OF HSCT EPISODE

For the purposes of payer coverage, the HSCT episode is frequently divided into several phases, as follows.

Evaluation

The evaluation 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 transplantation is an appropriate treatment option for the patient.

Pretransplantation Care

The pretransplantation care 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.

Transplantation Event

The transplantation event phase usually starts from the day of starting conditioning regimen and it can last from 30 to 120 days after transplantation. This phase covers the hematopoietic stem cell infusion and the transplantation hospitalization, and it also typically includes graft procurement, stem cell mobilization, and processing. In some situations, this phase can extend for a longer period of time (eg, 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 transplantation.

Follow-Up Care

The follow-up care phase starts on completion of the transplantation event phase and can extend until the patient is discharged from routine transplantation center follow-up care.

Of note, there may be a gap between the evaluation phase and the pretransplantation care phase, especially for diseases where a transplantation is not required immediately (eg, myelodysplastic syndromes or myelofibrosis) and in situations where the patient may need more therapy before a transplantation can proceed. Also, some services may be included in different phases depending on payer and institutional preference (eg, donor search or umbilical cord blood acquisition costs may be considered in the pretransplantation care phase, the transplantation event phase, or as an item that is invoiced separately).

The phases described above reflect payer perspective for coverage of the HSCT episode. Patients need routine long-term follow-up care after the “HSCT episode” has been completed. Some examples of such care include assessments for disease status, evaluation and management of chronic graft-versus-host disease, providing post-transplantation

vaccinations and screening, and evaluation and treatment of late complications. Such long-term follow-up care for transplantation recipients should be considered routine care and not investigational.

Definition of Phases of HSCT Episode

Table 2 presents the phases of an HSCT episode and the components within each phase that may be considered as routine clinical care for HSCT recipients. To assist with the interpretation of these guidelines, some examples based on ongoing Blood and Marrow Clinical Trials Network clinical trials are presented in Table 3.

PUBLIC COMMENTS

The draft white paper was circulated to the ASBMT membership for public comments. Based on comments provided by several individuals, this final draft clarifies that HSCT recipients need follow-up for screening, prevention, and management of late complications of transplantation and this long-term care should be considered as routine care. Several commenters suggested that we provide additional guidance on HSCT that are performed under a clinical trial to fulfill regulatory requirements but where the HSCT procedure would be considered as routine care; the final draft has clarified and provides several examples to address this comment. Other commenters requested that specific examples of clinical trial scenarios be provided (eg, which T cell depletion methods are routine care versus research); the task force felt that such detailed guidance on specific transplantation technologies and care practices was beyond the scope of this white paper. In response to other comments, we have emphasized that care for HSCT recipients should ideally be provided under clinical trials. There were comments that discussed the influence of HSCT clinical trials on quality and costs, the “value” of transplantation as a treatment, and certain payer issues around clinical trials coverage (eg, role of reinsurers in determining coverage); these issues were considered by the task force to be beyond the scope of this white paper. However, we believe that the guidance provided in this paper will facilitate further conversations about these important issues. One commenter voiced reservations about our recommendation that HSCT not be considered as development of an entirely new treatment in cases of new or emerging indications. The task force had considerable debate on this issue and ultimately decided to take the stated approach due to several factors. Some examples include the lack of specific federal guidance on how to define *routine care* under the ACA, the nuances of defining a “new” indication for transplantation, and the analogy of using HSCT as “off-label” therapy in such circumstances. A separate initiative from this task force will be providing guidance on indications for transplantation.

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REFERENCES

- Martin PJ, Davenport-Ennis N, Petrelli NJ, et al. Responsibility for costs associated with clinical trials. *J Clin Oncol*. 2014;32:3357-3359.
- LeMaistre CF, Farnia S, Crawford S, et al. Standardization of terminology for episodes of hematopoietic stem cell patient transplant care. *Biol Blood Marrow Transplant*. 2013;19:851-857.