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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.



## 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 statue 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