January 23, 2015

Tamara S. Syrek Jensen, J.D.
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services

Re: Formal Request for Reconsideration of NCD 110.8.1 – Stem Cell Transplantation

Ms. Syrek Jensen:

The American Society for Blood and Marrow Transplantation (ASBMT) is an international professional membership association of more than 2,000 physicians, investigators and other healthcare professionals promoting blood and marrow transplantation and cellular therapy research, education, scholarly publication and clinical standards. Be The Match®, operated by the National Marrow Donor Program® (NMDP), manages the largest and most diverse marrow registry in the world through a competed contract overseen by the Health Resources and Services Administration (HRSA). The NMDP also operates the Office of Patient Services. Through this congressionally-established office, the NMDP helps patients navigate the complexities of the health care system generally and insurance coverage more specifically. The Center for International Blood and Marrow Transplant Research (CIBMTR) under contract to HRSA and, with additional support from the National Institutes of Health, collects data on the use and outcomes of the vast majority of hematopoietic stem cell transplantations (HSCT) performed in the United States.

Summary of Request

During the last several years, more and more Medicare beneficiaries have contacted us trying to find a way to access HSCT after having been told Medicare will not cover the procedure***. At the request of our member physicians and transplant centers, we are formally asking CMS to reconsider the current NCD and expand the scope of coverage for HSCT.***

The need for finding a more effective pathway toward coverage for HSCT is urgent. Every week, physicians and our patient advocates hear from patients and their families from across the country who can no longer access HSCT once they turn 65 years old and become Medicare beneficiaries. Since time to transplant is a critical determinant of the success of a transplant, a delay or permanent barrier to transplant can lead to relapse and even death.

Based upon information from SEER and other clinical resources, we estimate that more than 2,000 Medicare beneficiaries who need a transplant are unable to access one each year because of the lack of clarity in the national coverage policies. Based on discussion with our network transplant centers, it has become clear that expanded coverage guidance is critical to beneficiaries in need of transplantation.

Clinical Summary

HSCT is an established standard therapy for patients with a variety of blood cancers, inherited genetic disorders such as sickle cell anemia and thalassemia, immunodeficiency syndromes and aplastic anemia. HSCT is the only therapy offering the potential for cure for patients with blood cancers who relapse after

initial chemotherapy. Advances in care have led to marked improvements in outcomes across all populations and HSCT is now being used as part of front line therapy for patients at high risk of relapse to afford a greater chance for cure. These advances have also allowed treatment of older patients, many of whom now have outcomes similar to younger patients. Men and women at age 70 typically have a median remaining life expectancy of 12 and 16 years, respectively, indicating a significant lost number of average life years if not provided with curative treatment options[1]. The remaining life expectancy of Medicare beneficiaries, together with the potential to cure the blood cancers that occur most commonly in this age group, support the need to ensure access to HSCT.

Current NCD

The NCD for Stem Cell Transplantation (110.8.1) explicitly covers allogeneic transplantation for patients with leukemia/aplastic anemia, severe combined immunodeficiency disease (SCID), Wiskott-Aldrich, and, under Coverage with Evidence Development (CED), Myelodysplastic Syndromes (MDS). Allogeneic HSCT is currently non-covered for the indication of multiple myeloma. For autologous transplant, coverage is available for patients with some types of acute leukemia, resistant non-Hodgkin's lymphomas, advanced Hodgkin's lymphoma, multiple myeloma and primary amyloid light chain (AL) amyloidosis. Non-covered indications include acute leukemia (not in remission), chronic granulocytic leukemia, solid tumors other than neuroblastoma, tandem transplantation for multiple myeloma, and non-primary AL amyloidosis.

This list leaves many clinical indications in the administrative state of being neither covered nor non-covered. For lack of better terminology, we refer to these indications as having 'silent' coverage status.

Reconsideration of the Current NCD

We are asking CMS for reconsideration and expansion of the current NCD. Specifically, we are asking for expansion or clarification of coverage in two ways:

- Explicit coverage of 'silent indications'
- Reconsideration of the negative coverage status for Multiple Myeloma

Sickle Cell Disease, Myelofibrosis, and **Lymphoma** (silent for allogeneic HSCT) are three examples of disease indications where HSCT has been shown to be effective therapy for many patients and for which coverage is currently unclear. Each of these indications is routinely approved for HSCT by the commercial payer population. We have partnered with transplant and non-transplant physician experts to develop a current summary of the medical literature and clinical research in these disease areas; these summaries are submitted alongside this letter. In addition to preventing patients from receiving the treatment they need to combat their illness, the lack of CMS coverage impedes the enrollment of patients in clinical trials evaluating innovative approaches to perform transplantation with less morbidity and better outcomes. This is a particular problem in SCD, where a high percentage of patients

[1] http://www.ncbi.nlm.nih.gov/pubmed/11386931 Reference in NCCN Clinical Guidelines for Senior Oncology. Attachment 1.

participate in governmental payer health care coverage plans. Medicare beneficiaries are thus underrepresented in important clinical trials about the diseases they face.

In addition to the indications highlighted, we ask that CMS establish coverage or a mechanism for prospective approval of treatment for **rare and life-threatening indications**, such as Langerhan Cell Histiocytosis, for HSCT. The minimal numbers of these indications each year make it extremely difficult to establish prospective studies that meet the clinical trial coverage guidelines as detailed in the Affordable Care Act. However, the rationale for transplantation with curative intent is the same and beneficiaries will be subject to the same identified access barriers without coverage guidance.

Finally, the knowledge and treatment of **Multiple Myeloma** has changed since the applicable NCD decision in 2000. We ask CMS to reconsider its negative coverage determination and allow for the use of HSCT for multiple myeloma in certain treatment conditions, such as planned tandem autologous transplantation and/or use of a second autologous transplant as consolidation after relapse. The European Society for Blood and Marrow Transplantation (EBMT) identifies allogeneic HSCT as a viable clinical option for some patients with multiple myeloma in its 2012 clinical handbook. Autologous HSCT is listed as standard of care with many centers performing tandem transplantation as standard of care based on large retrospective analysis from Europe and Little Rock. The Freytes et al study utilizes CIBMTR data to compare outcomes among patients treated with a second autologous transplant or an allogeneic transplant after relapse. Long-term survival rates (60 months) was poor in patients that received an allogeneic transplant. However, on multivariate analysis there has been a significant improvement in outcomes after 2004. We believe this provides preliminary evidence that either of these options should be available for treatment option deliberation by physicians for individual patients.

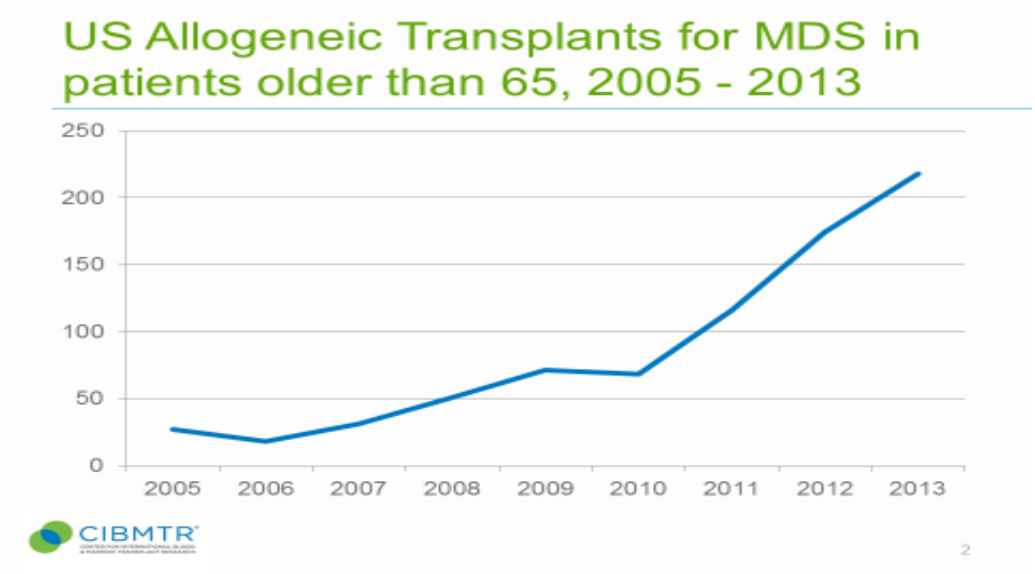
Beneficiary Access Barriers

Based on data collected from CIBMTR, the Medicare beneficiary population appears to be underutilizing HSCT as a treatment option for these silent coverage status indications. A separate analysis of the FY2103 Medicare Inpatient data files confirm that Medicare beneficiaries receive HSCT for silent status indications in very low numbers. Because age alone is not a factor in determining eligibility for HSCT, we believe that the reason for underutilization is most likely linked to their status as Medicare beneficiaries. Please reference our previously submitted summary of this issue for a more detailed explanation of these issues (NMDP/ASBMT letter dated January 12, 2015).

LCDs Do Not Provide Equitable Access

We acknowledge that it may be possible to seek LCDs from each MAC for each of these indications. However, the resource burden placed on our relatively small organizations to do this for each MAC is substantial and would need to be revisited each time a contractor changes. More importantly, our history with LCDs for MDS has demonstrated that seeking individual decisions by the contractors is not a mechanism that allows us to provide equitable care to our patients.

Prior to the establishment of the CED for MDS, one MAC (NGS) had issued a draft LCD for MDS and another had indicated informally that they would not deny claims with the relevant set of diagnoses. The remainder of the MACs indicated they did not have an interest in issuing a LCD, leaving a substantial portion of the country without clarity or access. After the opening of the MDS CED, the numbers of HSCT performed for MDS in the Medicare beneficiary population quickly grew and leveled out at the expected annual levels based on incidence and clinical eligibility-based estimates (~275/year). The CED study was approved in 2010.



Considerations for HSCT Coverage

The Appendix to this request provides information about the CIBMTR and the Stem Cell Therapeutic Outcome Database (SCTOD). Briefly, the SCTOD was created as a part of the HRSA-sponsored C.W. Bill Young Cell Transplantation Program (the Program), which was established by the Stem Cell Therapeutic and Research Act of 2005 (Public Law 109-129). CIBMTR is a joint venture of the NMDP and the Medical College of Wisconsin that provides an outcomes registry and conducts authoritative research in the HSCT field. The CIBMTR has become the international leader in transplant research and data collection and has held the contract from HRSA to operate the SCTOD since 2006. The Congress specifically created the SCTOD to track all allogeneic transplants with the goal of protecting patients and improving patient outcomes. The goals of CIBMTR are in strong alignment with CMS's identified goals for

beneficiary coverage. CIBMTR currently conducts a study evaluating outcomes in patients with MDS that qualifies under CED.

The Foundation for Accreditation in Cellular Therapy (FACT) is the only accrediting organization that has experience addressing all quality aspects of cellular therapy treatments: clinical care, donor management, cell collection, cell processing, cell storage and banking, cell transportation, cell administration, cell selection, and cell release. FACT accreditation is required by the Cancer Cooperative Groups for participation in studies involving HSCT and FACT is approved as an accrediting organization by the United States Health Resources Services and Administration (HRSA) for the C.W. Bill Young Cord Blood Transplantation Program. The 6th edition for the FACT standards, which will be effective May 30, 2015, includes a new standard *that transplant centers submit all transplant data – both autologous and allogeneic – to the CIBMTR for the purposes of the outcomes registry.* Currently, over 90% of U.S. transplant centers are FACT accredited.

In considering how best to provide access to HSCT for Medicare beneficiaries, we note the following:

- HSCT is unusual in its resource-intensity, its variety of applicable clinical indications and the relatively low number of patients receiving transplant annually, particularly in the Medicare beneficiary population. It is generally the only curative therapy for patients with transplantable indications and, as such, is considered the standard of care.
- The transplant community has an established and robust mechanism for data collection, standard reporting, research and quality monitoring that can provide data on beneficiary outcomes. We believe this will provide assurance to CMS that its resource investment is being closely monitored.
- Data submission is currently required for every allogeneic transplant provided in the United States. Reporting of autologous transplant data is currently voluntary, though CIBMTR estimates it receives data on approximately 80% of all completed autologous HSCTs. A CMS requirement to report data on autologous transplants in beneficiaries could improve this reporting rate substantially.

We believe the federally mandated data collection efforts of CIBMTR provide the platform to capture continued outcomes data for Medicare beneficiaries undergoing HSCT, while concurrently allowing beneficiary access to treatment. We believe utilization of the CIBMTR outcomes registry to inform coverage policy is the most efficient and effective way to leverage the existing federal investment.

Summary

This is a formal request for reconsideration of NCD 110.8.1 – Stem Cell Transplantation. We thank CMS for their time and consideration of this matter. Please contact Stephanie Farnia (NMDP) at 612-884-8640 or sfarnia@nmdp.org with any questions.

Sincerely,

[sent via email]

Sergio Giralt, MD	President, ASBMT
Michael Boo, JD	Chief Strategy Officer, NMDP

Appendix: Center for International Blood and Marrow Transplant Research

The Center for International Blood and Marrow Transplant Research (CIBMTR) collaborates with the global scientific community to advance hematopoietic cell transplantation (HSCT) and cellular therapy research worldwide. The CIBMTR was established in July 2004. The new organization joined together the existing research programs of the National Marrow Donor Program® (NMDP) and the International Bone Marrow Transplant Registry (IBMTR) at the Medical College of Wisconsin. Prospective and observational research is accomplished through scientific and statistical expertise, a large network of transplant centers and a clinical database of more than 430,000 transplant recipients. Support for the program is provided, in part, by grants and contracts from the National Institute of Health and Health Resources and Services Administration. Successful use of this funding has resulted in the completion of hundreds of studies that positively impact both clinical practice and transplant patients. Please view the 2013 Progress Report for more information.

The CIBMTR:

Collects and maintains outcomes data: CIBMTR collects outcomes data on every allogeneic transplantation performed in the U.S. (for the SCTOD, as required by U.S. law). U.S. transplant centers also voluntarily submit autologous transplantation data, and transplant centers worldwide voluntarily submit both autologous and allogeneic transplantation data. A complete listing of the research forms can be found on the CIBMTR data management page and a summary can be seen in Attachment 6.

Leads and conducts research studies: CIBMTR leads a worldwide collaboration of scientists and clinicians to advance understanding and outcomes of hematopoietic cell transplantation (HSCT). This research helps assess donor safety and helps identify the most promising transplant approaches and the patients most likely to benefit from this therapy. CIBMTR collaboratively addresses the most pressing clinical questions in transplantation. CIBMTR accomplishes this research through observational studies using its extensive database and prospective clinical trial through two organizations:

- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) – conducts multi-institutional phase II/III clinical trials with support of the National Heart Lung and Blood and the National Cancer Institutes.
- Resource for Clinical Investigation in Blood and Marrow Transplant (RCI BMT) – provides support for a wide array of clinical studies including multi-center trials, survey and quality of life assessments.

Provides access to outcomes data: Collected data can be accessed for patient care decisions, developing research studies, education, transplant center administrative needs, and CIBMTR research.

Provides access to research repository samples: The NMDP Research Sample Repository contains more than 22,000 related and unrelated paired transplant recipient/donor (or cord blood) samples linked with complete, validated clinical data collected by the CIBMTR. Samples can be used for local research studies or for CIBMTR research studies.

Provides statistical expertise to researchers: Both new and experienced investigators have access to biostatistical support to write study proposals and develop protocols.

Provide education, guidelines and training: CIBMTR provides trends, outcomes data and presentation graphics, develops post-transplant care guidelines and conducts meetings for education, science and training. The CIBMTR has published more than 900 peer-reviewed papers since 1972.

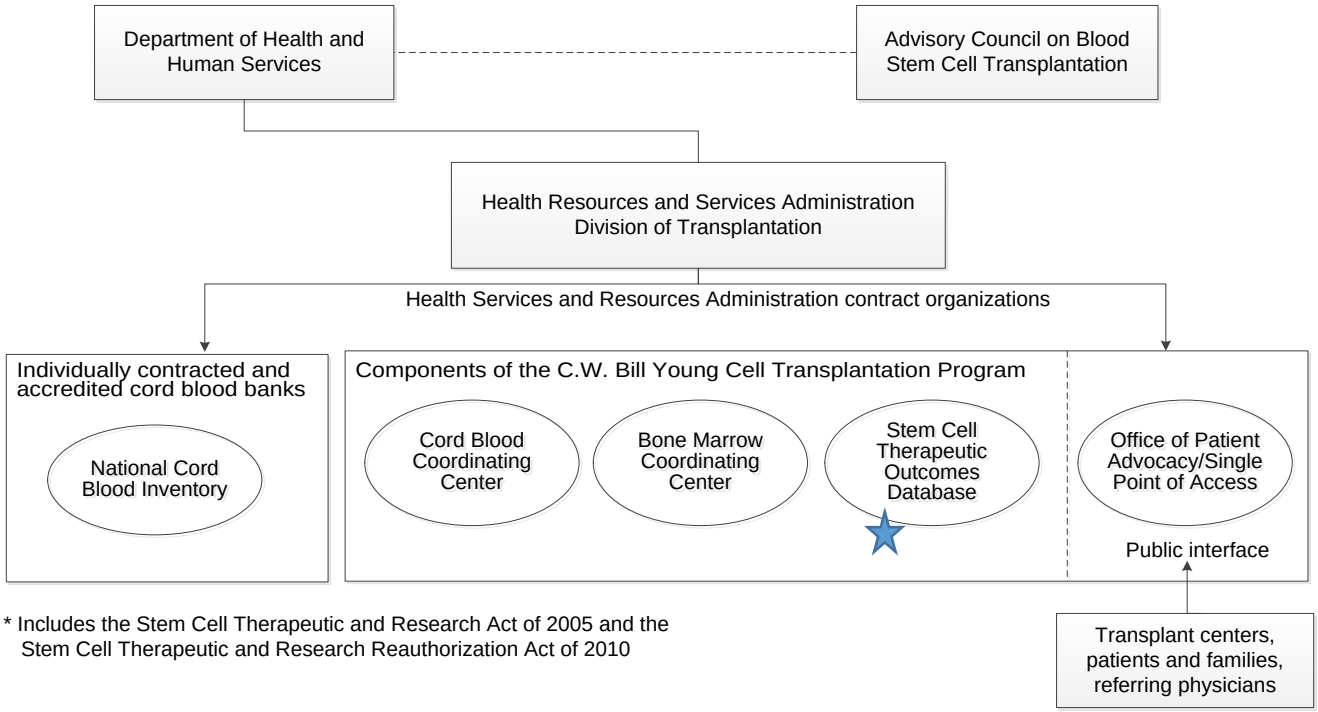
C.W. Bill Young Cell Transplantation Program & the Stem Cell Therapeutic Outcome Database

Since 2006, the CIBMTR has administered the Stem Cell Therapeutic Outcome Database (SCTOD) for the HRSA-sponsored C.W. Bill Young Cell Transplantation Program (the Program), which was established by the Stem Cell Therapeutic and Research Act of 2005 (Public Law 109-129). Continued support for the SCTOD is provided through the Stem Cell Therapeutic and Research Reauthorization Act of 2010 (Public Law #111-264) (**Figure 1**). http://bloodcell.transplant.hrsa.gov/about/

The Program has several goals:

- Collecting, analyzing, and reporting outcomes data for all allogeneic transplants and other therapeutic uses of blood stem cells;
- Publicizing information about HSCT available to patients, families, health care professionals, and the public;
- Defining better processes for identifying unrelated matched marrow donors, peripheral blood stem cell donors, and cord blood units through one electronic system;
- Increasing availability of unrelated adult volunteer donors and cord blood units;
- Expanding research to improve patient outcomes.

Figure 1: Overview of the Stem Cell Therapeutic Research Acts



* Includes the Stem Cell Therapeutic and Research Act of 2005 and the Stem Cell Therapeutic and Research Reauthorization Act of 2010

In September 2006, the Health Resources and Services Administration (HRSA) awarded a contract to CIBMTR to administer the SCTOD. SCTOD collects data on all allogeneic HSCTs performed in the United States with the purpose of increasing the safety, efficacy, and availability of HSCT. SCTOD data collection enables analysis of administrative program use, center-specific outcomes, donor registry, cord blood inventory size, and patient access to HSCT.

Under CIBMTR, all participating centers provide a standard dataset for all consecutive transplant recipients pre-transplant and post-transplant at 100-day, 6-month, and annual intervals. This dataset is an internationally agreed on set of information referred to as Transplant Essential Data (TED). TED-level data, with some additional details of donor and graft characteristics, encompass the obligatory data to be submitted to SCTOD for all U.S. allograft recipients per the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129). It is also the dataset required for transplant center accreditation by FACT.

Through use of TED forms and other data submission tools, researchers can use CIBMTR data to study a wide spectrum of treatment-related issues, including patient outcomes. Furthermore, CIBMTR provides broad database access to researchers, enabling robust data enterprise.

Researchers using CIBMTR data can identify the factors affecting transplant outcome, including patient-related factors like age and performance score; disease-related factors like stage and duration; and treatment-related factors like optimal pre-transplant therapy and conditioning regimens. There are two TED forms, one to collect pre-transplant and one to collect post-transplant clinical data. Key data points collected are listed below.

Pre-Transplant	Post-Transplant
• Disease Classification • Transplant History • Donor Type • Preparative Regimen • Comorbid Conditions • Graft-Versus-Host Disease Prophylaxis (allogeneic transplants only) • Post-Transplant Care Plan	• Outcomes » Absolute Neutrophil Count Recovery » Initial Platelet Recovery • Post-Transplant Therapy • First Relapse/Progression after Transplant and Use of Additional Treatment • Emergence of a New Malignancy (different from disease for which transplant was performed) • Presence and Classification of Acute or Chronic Graft-Versus-Host Disease • Survival Rates