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Decision Memo for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease) (CAG-00444R)



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Decision Summary

The Centers for Medicare & Medicaid Services (CMS) will modify our existing National Coverage Determinations Manual to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for three separate medical conditions:

- · Multiple Myeloma
- Myelofibrosis, and
- Sickle Cell Disease.

MULTIPLE MYELOMA

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with multiple myeloma (MM) using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for multiple myeloma will be covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma who are participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS staging, Durie-Salmon staging, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- · Quality of life (optional).

MYELOFIBROSIS

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with myelofibrosis (MF) using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for myelofibrosis will be covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

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Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with MF who receive allogeneic HSCT have improved outcomes as indicated by:

- · Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- · Quality of life (optional).

SICKLE CELL DISEASE

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with Sickle Cell Disease using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for sickle cell disease (SCD) will be covered by Medicare only for beneficiaries with severe, symptomatic sickle cell disease who participate in an approved prospective clinical study. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for sickle cell disease pursuant to Coverage with Evidence Development (CED) must address the following question:

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- · Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

All CMS-approved clinical studies and registries regarding allogeneic HSCT for the treatment of multiple myeloma, myelofibrosis, or sickle cell disease, must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
- b. The rationale for the study is well supported by available scientific and medical evidence.
- c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
- d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
- e. The study is sponsored by an organization or individual capable of completing it successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
- g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
- h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
- i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
- I. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

We are finalizing changes to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for these three separate medical conditions. See Appendix B for the manual language.

Back to Top

Decision Memo

TO: Administrative File: CAG-00444R

FROM: Tamara Syrek Jensen, JD Director, Coverage and Analysis Group

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SUBJECT: Final National Coverage Decision Memorandum for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease)

DATE: January 27, 2016

I. Decision

The Centers for Medicare & Medicaid Services (CMS) will modify our existing National Coverage Determinations Manual to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for three separate medical conditions:

- Multiple Myeloma
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A prospective clinical study seeking Medicare coverage of allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

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A prospective clinical study seeking Medicare coverage of allogeneic HSCT for sickle cell disease pursuant to Coverage with Evidence Development (CED) must address the following question:

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- Graft vs. host disease (acute and chronic);
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Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

We are finalizing changes to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for these three separate medical conditions. See Appendix B for the manual language.

II. Background

The scope of this National Coverage Analysis (NCA) is limited to allogeneic stem cell transplantation for beneficiaries with multiple myeloma, for beneficiaries with myelofibrosis, and for beneficiaries with sickle cell disease. This NCA will not reconsider the current NCD for any other indications.

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology:

ABMTR - Autologous Blood and Marrow Transplant Registry

ACCE Model - a model process named for the four criteria in evaluating a genetic test: Analytic validity, Clinical validity, Clinical utility, and associated Ethical, legal and social implications

AHRQ - Agency for Healthcare Research and Quality

AHSCT - Allogeneic Hematopoietic Stem Cell Transplantation

AlloSCT - Allogeneic Stem Cell Transplantation

AML - Acute Myelogenous Leukemia

ASBMT - American Society for Blood and Marrow Transplantation

ATG - Anti-thymocyte Globulin

AuSCT - Autologous Stem Cell Transplantation

BMT - Bone Marrow Transplantation

CALR - Calreticulin

CBT - Cord Blood Transplantation

CED - Coverage with Evidence Development

CFR - Code of Federal Regulations

CI - Confidence Interval

CIBMTR - Center for International Blood and Marrow Transplant Research

CMS - Centers for Medicare & Medicaid Services

CMS - Centers for Medicare DFS - Disease-free Survival

DIPSS - Dynamic International Prognostic Scoring System

EBMT - European (Society for) Blood and Marrow Transplantation

EFS - Event-free Survival

ELN - European LeukemiaNet

ESH - European School of Haematology

ET - Essential Thrombocythemia

ET-MF - Essential Thrombocythemia/Myelofibrosis

FDA - Food and Drug Administration

FISH - fluorescence in situ hybridization

GvHD/GVHD - Graft Versus Host Disease

h - Hour(s)

HCT/Ps - human cells, tissues, and cellular-and tissue based products

HLA - Human Leukocyte Antigen

HPC - Hematopoietic stem/progenitor cells

HR - Hazard Ratio

HRSA - Health Resources and Services Administration

HSCT - Hematopoietic Stem Cell Transplantation

IBMTR - International Bone Marrow Transplant Registry

la - Immunoalobulin

IMWG - International Myeloma Working Group

IPSS - International Prognostic Scoring System

ISS - International Staging System

JAK2 - Janus Kinase 2

LCD - Local Coverage Determination

MA - Myeloablative

MAC - Medicare Administrative Contractor

MDS - Myelodysplastic Syndrome

MF - Myelofibrosis

MM - Multiple Myeloma

MRA - Magnetic Resonance Angiography

MRI - Magnetic Resonance Imaging

NCA - National Coverage Analysis

NCD - National Coverage Determination

NHLBI - National Heart, Lung and Blood Institute

NIH - National Institutes of Health

NMDP - National Marrow Donor Program

NRM - Non-relapsing Mortality

OS - Overall Survival

PedsQL - Pediatric Quality of Life Inventory

PFS - Progression-free Survival

PHS - Public Health Service

PMF - Primary Myelofibrosis

PV - Polycythemia Vera

PV-MF - Polycythemia vera/Myelofibrosis

QoL - Quality of Life

RBC - Red Blood Cell

RIC - Reduced-intensity Conditioning

SCD - Sickle Cell Disease

SCOTD - Stem Cell Therapeutic Outcomes Database

SCT - Stem Cell Transplantation

TCD - Transcranial Doppler

TM - Thalassemia Major

TRM - Transplantation-related Mortality

URD - Unrelated Donor

US - United States

USPSTF - US Preventive Services Task Force

WHO - World Health Organization

STEM CELL TRANSPLANTATION (SCT)

Hematopoietic stem cells are multi-potent cells that give rise to all the blood cell types; these stem cells produce blood and immune cells. Hematopoietic stem cells can be sourced from peripheral blood, bone marrow and umbilical cord blood.

Stem cell transplantation (SCT) is a process that includes mobilization, harvesting, and transplant of stem cells and the administration of high dose chemotherapy and/or radiotherapy prior to the actual transplant. During stem cell transplantation, stem cells are harvested from either the patient (autologous) or a donor (allogeneic) and subsequently administered by intravenous infusion to the patient. For allogeneic transplants, the stem cell source may be a related or unrelated donor. In addition, the transplant can be HLA-identical (matched), unmatched or half-matched (also known as haploidentical). The degree of matching is important because if the HLA match is not close, the donor's immune cells, which are transplanted along with the donor's stem cells, will attack the patient's tissues; this is called graft versus host disease (GVHD).

Allogeneic stem cell transplants (alloSCT) may be used to restore function in recipients having an inherited (such as Sickle Cell Disease) or acquired (such as occurs after severely myelotoxic doses of chemotherapy and/or radiotherapy, which are used to treat various malignancies) deficiency or defect. Autologous stem cell transplants (AuSCT) are used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy and/or radiotherapy.

Until recently, the majority of patients who received a SCT were younger than 65 years and relatively free of concomitant morbidities such as cardiac disease. This is due to the high toxicity of the high intensity chemotherapy (referred to as myeloablative conditioning) administered prior to the transplantation and the inability of patients with concomitant morbidities to tolerate these pre-transplant chemotherapy-related toxicities. With the introduction of reduced-intensity conditioning (RIC) prior to transplantation, more patients with advanced age and/or concomitant morbidities are eligible for SCT.

The scope of this decision memorandum is limited to the use of alloSCT for MM, the use of alloSCT for MF, and the use of alloSCT for SCD. The use of alloSCT for acute myelogenous leukemia (AML), which MF can transform into, is not within the scope of this review.

MULTIPLE MYELOMA

Multiple myeloma (also called Kahler disease or plasma cell myeloma) is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction (Kyle & Rajkumar, 2004). Characteristics of the disease include lytic bone lesions, anemia, loss of kidney function, immunodeficiency, and myeloma-associated amyloid light-chain (AL) amyloid deposits in various tissues. In this malignancy, there is an overproduction of light and heavy chain monoclonal immunoglobulins. The specific immunoglobulin secreted by the malignant cell is the M-protein, named in reference to its monoclonal characteristics.

Epidemiology

Multiple myeloma accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers. In Western countries, the annual age adjusted incidence is 5.6 cases per 100,000 persons. The median age at diagnosis is approximately 66 years; 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older. The incidence rates are higher among males than females, and highest among African Americans. In patients presenting at an age under 60 years, 10-year survival is approximately 30%. Multiple myeloma is the ninth most common cause of cancer death among US females and the fourteenth most common cause of cancer death among US males, accounting for about 2% of cancer deaths for each gender.

A number of lifestyle, occupational as well as environmental risk factors have been explored to determine their association with MM. Lifestyle factors such as obesity, diet, tobacco and alcohol usage, reproductive as well as hormonal factors fail to reveal an association with MM. And when exploring occupational and environmental risk factors, most occupational cohort studies lack statistical power for rare outcomes such as MM. Many case-control studies suffer from small numbers of exposed subjects in specific occupation, job title or chemical exposure categories. And case-control studies may be hindered by bias due to differential recall of exposures between the cases and controls. Studies evaluating the association between asbestos exposure as well as other environmental risk factors and MM also do not support a causal link. In a meta-analysis of 18 cohort studies of chemical workers in the United States and western Europe, the authors found no excess of MM mortality (Greenberg et al., 2001).

When exploring family history and genetic influences, several studies have reported increased risks of developing MM in persons who have a family history of certain diseases; however, the role of specific malignant and nonmalignant conditions among relatives in the etiology of MM remains unknown. In terms of genetic variation a number of studies suggest that gene mutations, as well as particular genetic polymorphisms, may be associated with risk of MM. Results have been inconsistent, and significant findings have not been replicated convincingly (Alexander et al., 2007).

One observation noted that the risk of developing MM is approximately 3.7-fold higher for persons with a first-degree relative with the disease (Lynch & Sanger, 2001). Furthermore, clusters of two or more first-degree relatives, identical twins, and in four members spanning three generations in one family have been reported with an incidence of approximately three familial cases per 1000 patients with myeloma (Lynch et al., 2001, 2005, 2008; Camp, Werner and Cannon-Albright, 2008).

Pathogenesis

Multiple myeloma cells are the malignant counterparts of post-germinal center (GC) long-lived plasma cells, characterized by strong bone marrow dependence, somatic hypermutation (SHM) of immunoglobulin (Ig) genes, and isotype class switch resulting in the absence of IgM expression in all but 1 % of tumors (Kuehl & Bergsagel, 2002). However, MM cells differ from healthy plasma cells because they retain the potential for a low rate of proliferation.

Multiple myeloma is preceded by a pre-malignant plasma cell tumor called monoclonal gammopathy of undetermined significance (MGUS) which is derived from GC B cells. Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm that progresses to smoldering myeloma and, finally, to symptomatic myeloma. It is thought that genetic abnormalities that occur in tumor plasma cells play a major role in the pathogenesis of myeloma.

Based on chromosome content, MM is divided into two distinct genetic subtypes: Hyperdiploid myeloma which is characterized by multiple trisomies of chromosomes 3, 5, 7, 9 11, 15, 19 and 21, and lacks recurrent immunoglobulin gene translocations; and Non-hyperdiploid myeloma which is characterized by chromosome translocations t(4;14), t(14;16), t(14;20), t(6;14) and t(11;14). Both groups share the dysregulated expression of a cyclin D gene, either directly by juxtaposition to an immunoglobulin enhancer as a result of ectopic expression of a MAF family transcription factor, or indirectly by as yet unidentified mechanisms. Other genetic abnormalities associated with MM include rearrangements of MYC, activating mutations of NRAS, KRAS or BRAF, a promiscuous array of mutations that activate NFkB and deletions of 17p. Evidence seems to support the use of a risk-stratified approach in the treatment of patients with MM.

Clinical Presentation, Diagnosis and Staging

The diagnosis of MM is based on the presence of at least 10% clonal bone marrow plasma cells, and monoclonal protein in serum or urine. Multiple myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction. The CRAB criteria is often used to describe the extent of the disease, and symptoms and signs includes hyperCalcemia, Renal insufficiency, Anemia, and Bone disease (Durie et al., 2003, 2006; Kyle and Rajkumar, 2009).

Non-CRAB end-organ damage (e.g., hyperviscosity, recurrent bacterial infections, amyloidosis, peripheral neuropathy) are nonspecific and not diagnostic of MM. Most of the patient's symptoms are due to damage from excess light chains production, as well as the infiltration of plasma cells into target organs. Weight loss, fatigue and generalized weakness are also characteristics of the disease. Neurologic complications include cord compression, peripheral neuropathy and CNS involvement. And due to a combination of immune dysfunction and physical factors, patients with MM are also prone to infection.

The International Myeloma Working Group (IMWG), which emphasizes the importance of end organ damage, also has criteria which can be used in making the diagnosis. They suggest first a detailed medical history and physical examination. Diagnostic tools such as routine laboratory testing (complete blood count, chemical analysis, serum and urine protein electrophoresis with immunofixation, and quantification of monoclonal protein), and bone marrow examination (trephine biopsy plus aspirate for cytogenetic analysis or fluorescence in situ hybridization [FISH]) are required. Conventional radiography of the spine, skull, chest, pelvis, humeri, and femora can also be used to confirm clinical findings. Sometimes magnetic resonance imaging (MRI), as well as computed tomography (CT) and MRI are required to assess suspected cord compression if needed. Based on the occurrence of the disease in the population, the following risk stratifications had been noted by Rajkumar (2012):

- <u>High risk disease</u> Approximately 15 percent of people with multiple myeloma have high risk disease based on cytogenetic testing (patients with translocation t (14;16)), translocation t (14;20) and deletion chromosome 17p). This is the aggressive form of multiple myeloma and may shorten survival; patients at high risk disease are treated with more aggressive therapy.
- Intermediate risk disease Approximately 10 percent of people with multiple myeloma have intermediate risk disease based on cytogenetic testing (patients with translocation t (4;14)). With appropriate therapy, patients with this form of multiple myeloma can have outcomes similar to those of

standard risk multiple myeloma.

• Standard risk disease — All patients with multiple myeloma who lack high or intermediate risk genetic abnormalities are considered to have standard risk multiple myeloma, and with appropriate therapy have an estimated median survival of 8 to 10 years.

While survival has improved with the use of novel therapy, approximately 25% of patients have a median survival of 2 years or less (Biran, Jagannath, & Chari, 2013). Because the outcomes of patients with MM are highly variable, knowledge of tumor and host factors associated with prognosis are critical for understanding disease outcome, identifying risk groups, and optimizing patient treatment (Greipp et al., 2005). Previous staging systems have been used. For example, the Durie-Salmon Staging System, which is based on the risk factors on the amount of abnormal monoclonal immunoglobulin in the blood or urine, amount of calcium and hemoglobin in blood, and severity of bone damage based on x-rays (Durie & Salmon, 1975):

- Stage I All of the following:
 - Hemoglobin value > 10 g/dL
 - Serum calcium value normal or ≤ 12 mg/dL
 - Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only
 - Low M-component production rate (IgG value < 5 g/dL; IgA value < 3 g/dL)
 - Bence Jones protein < 4 g/24 hr
- Stage II Neither Stage I nor Stage III
- Stage III One or more of the following:
 - Hemoglobin value < 8.5 g/dL
 - Serum calcium value > 12 mg/dL
 - Advanced lytic bone lesions (scale 3)
 - High M-component production rate (IgG value > 7 g/dL; IgA value > 5 g/dL)
 - Bence Jones protein > 12 g/24 h
- Sub-classifications (either A or B)
 - A: Relatively normal renal function (serum creatinine value < 2.0 mg/dL)
 - B: Abnormal renal function (serum creatinine value = 2.0 mg/dL)

However, this Durie-Salmon system did not include factors which were felt to be most important in prognosis. Because of the inadequacies of the Durie-Salmon system, another staging system has been developed.

The International Staging System, which is the most recent, most reliantly used risk assessment system and identifies three risk groups on the basis of serum β2-microglobulin and albumin levels (Greipp et al., 2005):

- Stage I Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is 3.5 (g/dL) or greater
- Stage II Neither stage I or III, meaning that either: The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR the albumin is below 3.5 while the beta-2 microglobulin is less than 3.5
- Stage III Serum beta-2 microglobulin is 5.5 or greater.

Myeloma cell labeling as well as chromosomal changes detected by conventional cytogenetics and FISH (looking specifically for loss of a copy of chromosome 13 and translocation of material from chromosomes 4 and 14) can also be a part of a stratification system. These predictive models can have considerable influence on the choice of therapy which helps determine prognosis in patients with MM.

In general, studies have confirmed that patients with higher stage levels and patients with chromosomal abnormalities have worse outcomes than those with normal karyotypes or stage I disease.

Treatment

The main options for treatment of MM include non-chemotherapy drugs that target the cancer cells, standard chemotherapy drugs, corticosteroids, and hematopoietic stem cell transplant (HSCT). Drugs such as thalidomide, lenalidomide, bortezomib, carfilzomib and pomalidomide have had limited success in the treatment of MM, both in newly diagnosed patients and in patients with advanced disease who have failed chemotherapy or transplantation. These agents are usually used in combination with dexamethasone, with each other, or with standard chemotherapy agents. HSCT has also been used in the treatment of MM. When discussing HSCT use in patients with MM there are basically two varieties: Those using one's own stem cells (autologous) or those transplantations that use cells from a close relative or matched unrelated donor (allogeneic).

Most transplants performed in patients with MM are of the autologous in nature; although this is not curative, it has been shown to prolong life in selected patients. This form of transplantation can be done as initial therapy in newly diagnosed patients or at the time of relapse. In some selected patients more than one transplant (auto-auto) may be recommended to adequately control the disease.

Allogeneic HSCT has also been performed on patients with MM. There are four different types of allogeneic transplants (Rajkumar 2014):

- Myeloablative allogeneic HSCT which requires hematopoietic cells from an HLA-matched donor. These cells are given after the patient receives high dose chemotherapy and total body radiation. This form of transplant has two advantages over autologous HSCT: the graft does not contain tumor cells, and the transplant can produce a graft-versus-myeloma effect. But due to the high toxicity associated with this treatment (overall mortality can be as high as 50 percent due to fungal infections, interstitial pneumonitis, and graft-versus-host disease), less than 5 to 10 percent of patients with MM are candidates for this approach.
- Syngeneic HSCT this form of allogeneic transplant is performed on identical twins. Experience is limited due to the limited number of procedures performed and lack of studies.
- <u>T Cell Depleted Allogeneic HSCT</u> the advantages of this form of transplant is that it decreases the incidence of GVHD and it reduces transplant mortality. But due to the high mortality rate T cell depleted transplants are not recommended outside of a clinical trial setting.
- Nonmyeloablative Allogeneic HSCT this regimen uses less intensive chemotherapy or irradiation alone prior to the infusion of donor hematopoietic stem cells, and relies more on donor cellular immune effects and less on the cytotoxic effects of the regimen. Nonmyeloablative allogeneic HSCT and RIC HSCT are associated with lower rates of treatment-related toxicity and treatment-related mortality, but higher rates of relapse compared with rates previously seen with myeloablative allogeneic transplantation (Badros et al., 2001; Kroger et al., 2002; Crawley et al., 2007). Prospective trials investigating the use of nonmyeloablative HSCT have conflicting data regarding survival rates, but are consistent in their treatment-related mortality rates (11 to 18 percent at five years) and rates of extensive graft-versus-host disease (50 to 74 percent).

Randomized trials of allogeneic HSCT have not been feasible for patients with myeloma, though Autologous followed by nonmyeloablative allogeneic HSCT in newly diagnosed myeloma have been tried resulting in mixed results.

Approximately 25 percent of individuals who undergo allogeneic transplantation die from transplant-related complications, such as infection, lung inflammation, and graft-versus-host disease. Also, the efficacy of allogeneic HSCT compared with autologous HSCT has not been fully established.

MYELOFIBROSIS

Myleofibrosis is a stem cell-derived hematologic disorder. It is one of six types of chronic myeloproliferative neoplasm along with essential thrombocythemia (ET), polycythemia vera (PV), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, and chronic eosinophilic leukemia. In most of these myeloproliferative neoplasms, an abnormal proliferation of stem cells results in the overproduction of red blood cells (e.g., PV), white blood cells (e.g., chronic neutrophilic or eosinophilic leukemia) or platelets (e.g., ET). Alternatively, in MF the abnormal proliferation is associated with cytopenia (Tefferi, 2014). Primary MF is defined as MF having arisen *de novo*. Secondary MF is defined as having arisen from ET or PV (Cervantes, 2014).

The natural history of MF is highly variable (Alchalby & Kroger, 2014). Some patients may be initially asymptomatic. As the disease progresses, constitutional symptoms (e.g., fever, malaise, weight loss, night sweats) and cachexia occur along with abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly and extramedullary hematopoiesis, (Tefferi, 2014). These signs and symptoms typically occur and increase in a heterogeneous manner (Cervantes, 2014) and are frequently debilitating (Geyer & Mesa, 2014). MF may transform to AML, which has a median survival of 2.6 months and an overall survival at 12 months of 9% (Mesa et al., 2005).

In the US the annual incidence of MF is 0.5 - 1.5 cases per 100,000 individuals. MF mostly affects elderly individuals (Cervantes, 2014) with a median age at diagnosis of 65 years (Cervantes, 1997).

The pathogenesis of MF is unknown (Tefferi, 2011). Mutations in various genes (e.g., Janus kinase 2 [JAK2]; calreticulin [CALR]) have been found and can be useful for prognosis and potentially treatment but these mutations are not specific to MF (Tefferi, 2014) and may not be present in every patient (Cervantes, 2014).

The prognosis of MF was initially guided by the Lille score (a.k.a., the Dupriez score), which used hemoglobin and white blood cell counts to classify patients as "long-lived" (median survival of ten years) or "short-lived" (median survival of two years) (Dupriez, 1996). Patients were further grouped by risk, as shown in the table below:

Lille risk group	Number of risk factors	Median survival (years)
Low	None	7 - 8
Intermediate	1	2.2
High	2	1

In the past decade the International Prognostic Scoring System (IPSS), which has been progressively updated to first the dynamic IPSS (DIPSS) and now the DIPSSplus as the understanding of the natural history and especially the impact of cytogenetics on the pathogenesis of MF has increased (Alchalby & Kroger, 2014) has gained prominence. The DIPSSplus prognostic score is based on eight risk factors (need for red blood cell transfusion, hemoglobin level, platelet count, leukocyte count, circulating blasts in the blood, constitutional symptoms, unfavorable cytogenetic profile and age). There are four risk categories based on the DIPSSplus score as show in the following table (Gangat et al., 2011):

DIPSSplus risk category	Number of risk factors	Median survival (years)
Low	None	15.4
Intermediate-1	1	6.5
Intermediate-2	2 or 3	2.9
High	4 or more	1.3

Geyer and Mesa (2014) note that "MF treatment goals are based on assessment of both disease burden (symptoms, cytopenias, splenomegaly) and impact of disease on survival." The authors further state that observation, medical therapies and alloSCT are the three therapeutic options for patients with MF. Observation is generally recommended for asymptomatic patients with a DIPSSplus score of low or intermediate-1 (Tefferi, 2014). Tefferi (2014) suggests, however, that a higher risk genetic profile in this specific patient population may be a reason to begin therapy instead. Geyer and Mesa (2014), on the other hand, state that it "remains unclear whether patients who are considered low risk by DIPSS but harbor high-risk molecular features should be managed differently (i.e., earlier choice for allo-SCT)."

Conventional medical therapies, such as growth factors (e.g., erythropoietin, androgens, immunomodulatory drugs, interferon alfa, cytoreductive agents), blood transfusions, spleen irradiation and splenectomy, are generally recommended for patients with symptoms who have a DIPSSplus score of low or intermediate-1 (Tefferi, 2014). Of note, Alchalby and Kroger (2014) stated that "none of these approaches have been found to prolong survival." In his 2014 review, Tefferi presented a similar opinion and stated that current drug therapy for primary MF "is not curative and has not been show to prolong survival; although there is controversy regarding the value of JAK inhibitors, in this regard, these drugs have not been shown to display disease-modifying activity, including reversal of bone marrow fibrosis or induction of complete or partial remissions." The first FDA-approved JAK inhibitor is ruxolitinib; it is indicated for patients with intermediate- or high-risk MF (Alchalby & Kroger, 2014). The authors noted that ruxolitinib demonstrated an early and sustained reduction in splenomegaly, improvement of constitutional symptoms and a survival benefit during pre-market clinical trials. Tamari et al. (2015), however, stated that the post-market clinical experience "has not yielded as impressive results" due to the finding that about "50% of patients discontinue ruxolitinib

therapy at 3 years due to loss of clinical benefit or adverse side effects."

Investigational drug therapy and alloSCT are recommended for patients with a DIPSSplus score of intermediate-2 or high (Tefferi, 2014). AlloSCT is considered to be "potentially curative but dangerous" for the treatment of MF (Tefferi, 2014). Similarly, Geyer and Mesa (2014) stated that alloSCT "is the only curative option for MF patients and is typically reserved for patients whose life expectancy is < 5 years." The risks associated with alloSCT include graft failure, GVHD and transplantation-related drug treatment-associated toxicity (Geyer & Mesa 2014).

SICKLE CELL DISEASE

Sickle cell disease is a group of inherited red blood cell (RBC) disorders created by the presence of two abnormal hemoglobin genes. Hemoglobin, a protein in RBCs, carries oxygen throughout the body. The abnormal hemoglobin genes result in the formation of abnormal hemoglobin that causes the shape of the RBC to change from disc-like to crescent- or sickle-like. Sickle-shaped RBCs cannot carry oxygen, are less flexible than normal RBCs and can stick to blood vessel walls, which can slow or block blood flow (National Institutes of Health / National Heart, Lung and Blood Institute [NIH/NHLBI], 2015). The blockage of blood flow causes morbidity (pain and multi-organ dysfunction/failure). Multi-organ failure leads to premature death (Oringanje, Nemecek & Oniyangi, 2013).

In all forms of SCD, at least one of the two abnormal hemoglobin genes causes the body to make the abnormal hemoglobin, called hemoglobin S. For a person with two hemoglobin S genes, the resultant hemoglobin is called hemoglobin SS and the disease is called sickle cell anemia. This is the most common and often most severe kind of SCD. Two other common forms of SCD are hemoglobin SC disease and hemoglobin Sβ thalassemia (NIH/NHLBI, 2015). Hemoglobin Sβ thalassemia is also associated with a severe kind of SCD (NIH/NHLBI, 2014). When an abnormal hemoglobin gene is inherited from only one parent, a person will have sickle cell trait. People with sickle cell trait are generally healthy (NIH/NHLBI, 2015).

Sickle cell disease is a life-long illness that starts in infancy. Due to improved clinical management of the disease in children, currently more than 90% of children survive to adulthood (NIH/NHLBI, 2014). Compared to an average lifespan of 14 years for a person with SCD in 1973, currently the US life expectancy is 40 - 60 years; hence, today there is a greater prevalence of adults with SCD (NIH/NHLBI, 2015). In one recent study of adults with symptomatic SCD who were receiving conventional (i.e., non-alloSCT) therapies, the ten-year mortality rate was 45% (Steinberg et al., 2010).

In the US, approximately 100,000 people have SCD. Most people with SCD are of African ancestry or identify themselves as black. About one in every 365 black children is born with SCD (NIH/NHLBI, 2015). There are also many people of Middle Eastern, Hispanic, southern European, Central American, and Asian Indian descent with SCD (NIH/NHLBI, 2014).

The severity and clinical course of SCD varies widely from person to person and can change over time. Most of the signs and symptoms are related to complications of the disease that during a person's lifetime can damage the spleen, brain, eyes, lungs, liver, heart, kidneys, joints, bones or skin. Vaso-occlusive crisis is the most common acute complication of SCD. It consists of recurrent sudden episodes of intense pain, which usually occur without warning. The management of vaso-occlusive crises is central to the care of patients with SCD. Other major acute complications of SCD include life-threatening bacterial infections, acute chest syndrome, stroke (including clinical stroke as well as silent stroke and thinking problems associated with silent brain injury), splenic sequestration with resultant severe anemia in addition to the chronic milder anemia associated with the disease, acute renal failure and mental health issues such as depression and anxiety. Chronic complications of SCD include chronic pain, renal impairment, pulmonary hypertension and retinal problems (NIH/NHLBI, 2014).

Effective therapies exist to reduce symptoms, treat complications and prolong survival. Health maintenance measures to prevent complications such as immunizations and prophylactic use of penicillin (in children up to five years old and in any person who has had a splenectomy and/or past infection with pneumococcus) as well as regular medical care as needed contribute to improved well-being (NIH/NHLBI, 2015).

Conventional treatment of SCD consists mainly of hydroxyurea and RBC transfusions as well as any therapies necessary to treat the numerous complications of the disease. Hydroxyurea and the long-term administration of RBC transfusions "are the only currently proven disease-modifying treatments for people with SCD. Both therapies are used in primary and secondary stroke prevention. Although neither has been shown to prevent all SCD-related organ damage, these treatment modalities can improve the quality of life for individuals with SCD" (NIH/NHLBI, 2014).

Hydroxyurea has been shown to reduce or prevent several SCD complications (NIH/NHLBI, 2015). According to the NIH/NHLBI (2015), "studies of adults with hemoglobin SS or hemoglobin S β thalassemia showed that hydroxyurea reduced the number of episodes of pain crises and acute chest syndrome. It also improved anemia and decreased the need for transfusions and hospital admissions." NIH/NHLBI (2015) also noted "studies in children with severe hemoglobin SS or S β thalassemia showed that hydroxyurea reduced the number of vaso-occlusive crises and hospitalizations. A study of very young children (between the ages of nine and 18 months) with hemoglobin SS or hemoglobin S β thalassemia also showed that hydroxyurea decreased the number of episodes of pain and dactylitis." However, hydroxyurea can cause side effects such as leukocytopenia, thrombocytopenia and, rarely, worsening anemia that will prompt a temporary halt of administration of the medication and a resumption of administration at a lower dose (NIH/NHLBI, 2015).

Since the RBCs in a blood transfusion have normal hemoglobin, acute and chronic RBC transfusions are used to treat and prevent certain SCD complications by lessening vaso-occlusion and improving oxygen delivery to the person's tissues and organs. Common indications for acute RBC transfusions include severe anemia, acute stroke, acute chest crises and multi-organ failure. Regular administration of RBC transfusions is recommended for prevention of first stroke in children, for treatment of complications that do not improve with hydroxyurea or for people who experience too many side effects from hydroxyurea. Two significant complications of the routine administration of RBC transfusions include iron overload, which can severely impact heart and liver function and result in the need for chelation therapy, and alloimmunization, which can increase the risk of finding a matching unit of blood for future transfusions (NIH/NHLBI 2015).

These conventional treatments ameliorate the disease and its complications thereby temporarily lessening the impact of SCD on the person but, importantly, do not cure SCD. According to the NIH/NHLBI (2014), "there is hope for a cure using hematopoietic stem cell transplantation (HSCT). NIH further stated: "Additional research regarding patient and donor selection and the specific transplantation procedure is required before this potentially curative therapy will become more widely available." The goal of SCT is to eliminate the sickled RBCs (and the person's stem cells that contain the genetic code for the abnormal hemoglobin) and replace them with normal stem cells that have the genetic code for the production of normal hemoglobin (Oringanje et al., 2013). In addition, NIH/NHLBI (2015) notes, "unfortunately, most people with SCD are either too old for a transplant or don't have a relative who is a good enough genetic match for them to act as a donor. A well-matched donor is needed to have the best chance for a successful transplant."

Angelucci et al. (2014) stated that the indications for SCT for people with SCD are "less clearly defined because of the variability of the disease course." The authors note that historically "the indication for HSCT in SCD was mainly based on SCD-associated morbidity: the sicker the child, the stronger the indication. With the reduction in TRM in recent years, and with the increasing knowledge of the severity of complications in untreated patients, the

accepted indications for HSCT have become less restrictive." Walters et al. (1996) suggested a list of indications for alloSCT for people with SCD:

- "Stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
- Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
- Impaired neuropsychological function with abnormal cerebral MRI scan
- Stage I or II sickle lung disease
- Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
- Bilateral proliferative retinopathy with major visual impairment in at least one eye
- · Osteonecrosis of multiple joints
- Red-cell alloimmunization during long-term transfusion therapy"

King and Shenoy (2014) updated the Walters list of indications to account for the increased donor sources for stem cells:

Table 1. Indications for HSCT in SCD

Matched sibling donor (if available)	Matched Unrelated Donor transplant	Mismatched marrow donor, haploidentical donor, unrelated cord blood transplant
Consider early,* prior to or at onset of SCD symptoms, with the highest priority given to patients with HbSS and HbSβ0 thalassemia	Stroke	Recurrent stroke despite adequate chronic transfusion therapy; progressive CNS changes
Stroke	Elevated TCD velocity	Severe SCD symptoms and inability to tolerate supportive care resulting in symptom persistence/progression
Elevated TCD velocity	Recurrent acute chest syndrome despite supportive care	
Recurrent acute chest syndrome despite supportive care	Recurrent severe VOE despite supportive care	
Recurrent severe VOE despite supportive care	Red cell alloimmunization despite intervention + established indication for chronic transfusion therapy	
Red cell alloimmunization despite intervention + established indication for chronic transfusion therapy	Pulmonary hypertension	
Pulmonary hypertension	Recurrent priapism	
Recurrent priapism	Sickle nephropathy	
Sickle nephropathy	Bone and joint involvement	
Bone and joint involvement		
Sickle retinopathy		

For all genotypes, the morbidity of the disease is the driving factor in pursuing a HSCT. Preventative HSCT should be considered for children with higher-risk genotypes, HbSS, and HbSβ0. HSCT for adults with SCD is better tolerated with a low-intensity regimen, with the caveat of requiring prolonged immune suppression to maintain mixed-donor chimerism. AVN, avascular necrosis; TCD, transcranial Doppler; VOE, veno-occlusive episodes. *Especially in children with difficult access to adequate lifelong supportive medical care, we recommend reviewing statistics for OS, DFS, GR, and GVHD with families as they weigh these options.

(King & Shenoy, 2014)

NIH/NHLBI (2015) noted that currently "most SCD transplants are performed in children who have had complications such as strokes, acute chest crises, and recurring pain crises. These transplants usually use a matched donor. However, because only about 1 in 10 children with SCD has a matched donor without SCD in their families, the number of people with SCD who get transplants is low. HSCT is more risky in adults, and that is why most transplants are done in children." In addition, "HSCT is successful in about 85 percent of children when the donor is related and HLA matched. Even with this high success rate, HSCT still has risks. Complications can include severe infections, seizures, and other clinical problems. About 5 percent of people have died. Sometimes transplanted cells attack the recipient's organs (graft versus host disease). Medicines are given to prevent many of the complications, but they still can happen" (NIH/NHLBI, 2015).

III. History of Medicare Coverage

Section <u>110.8.1 of the Medicare National Coverage Determinations (NCD) Manual</u> currently lists various clinical indications and conditions for which SCT is nationally covered or non-covered to date.

MULTIPLE MYELOMA

NCD 110.8.1 subsection A.1.b states: "Effective for services performed on or after May 24, 1996, allogeneic stem cell transplantation is not covered as treatment for multiple myeloma."

NCD 110.8.1 subsection A.2.a.ii states: "Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function."

NCD 110.8.1 subsection A.2.b states, in pertinent part, that: Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma

MYELOFIBROSIS and SICKLE CELL DISEASE

CMS does not have a national policy that specifically addresses coverage of HSCT for MF or SCD. In the absence of a national coverage determination, contractors have the discretion to determine coverage under § 1862(a)(1)(A) for allogeneic HSCT for all other indications through the local coverage determination (LCD) process or by individual claim by claim adjudication.

A. Current Request

CMS received a formal request from the American Society for Blood and Marrow Transplantation (ASBMT) and the National Marrow Donor Program (NMDP) for reconsideration and expansion of the current NCD, specifically:

- for expansion or clarification of coverage of 'silent indications' (such as SCD and MF), and
- to reconsider its negative coverage status for MM

This NCA evaluates the available evidence to determine whether a national coverage determination is warranted for:

- allogeneic stem cell transplant in patients with SCD,
- allogeneic stem cell transplant in patients with MF, and
- allogeneic stem cell transplant in patients with MM.

The formal request letter can be viewed via the tracking sheet for this NCA on the CMS website at https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id280.pdf.

Autologous stem cell transplants for SCD, MF and MM will not be considered in this NCA.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act. CMS has determined that autologous and allogeneic stem cell transplantation fall within the benefit categories of inpatient hospital services under Part A and physicians' services under Part B. See §1812(a)(1) (inpatient hospital services); §1832 (outpatient hospital services incident to a physician's service); §1861(s)(2) (incident to physician's services); and §1861(b) (inpatient hospital services).

IV. Timeline of Recent Activities

Date	Action
April 30, 2015	CMS opens NCA. Initial 30-day public comment period begins.
May 30, 2015	First public comment period ends. CMS receives 215 comments.
October 29, 2015	CMS posts proposed decision. Second public comment period begins.
November 28, 2015	Second public comment period ends. CMS receives 237 comments.

V. Food and Drug Administration (FDA) Status

Hematopoietic stem/progenitor cells (HPC) for transplantation are regulated as human cells, tissues, and cellular-and tissue based products (HCT/Ps) by FDA. Title 21 CFR 1271.3(d) defines human cells, tissues, or cellular or tissue-based products (HCT/Ps) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of HCT/P include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."

The regulatory approach to HCT/Ps, including HPCs, distinguishes among autologous products, allogeneic products from first- or second-degree relatives, and allogeneic products from unrelated donors. Hematopoietic stem/progenitor cells derived from peripheral and cord blood are regulated solely under section 361 of the PHS Act and the regulations in 21 CFR Part 1271 if they meet all of the following criteria, as specified in 21 CFR 1271.10(a):

- Minimally manipulated;
- Intended for homologous use only as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- The manufacture of the HCT/P does not involve the combination with another article, (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HCT/P); and
- Either:
 - i. Do not have a systemic effect and are not dependent upon the metabolic activity of living cells for the primary function; or
 - ii. Have a systemic effect or are dependent upon the metabolic activity of the other cells for the primary function, and:
 - a. Are for autologous use;

b. Are for allogeneic use in a first or second-degree relative

HCT/Ps that do not meet all of the criteria in 21 CFR 1271.10(a) are regulated as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the PHS Act, and applicable regulations in title 21, chapter I, and require FDA premarket approval. Section 1271.3(a) defines the term autologous use as "the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." Section 1271.3(c) defines the term homologous use as "the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be redacted or, if the redaction renders the comment meaningless, will not be made available to the public. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final national coverage determination.

VII. Evidence

A. Introduction

The purpose of this NCA is to determine if the evidence is sufficient to conclude that beneficiaries with MM, MF, or SCD experience improved health outcomes with allogeneic HSCT compared to beneficiaries with MM, MF, or SCD whose management does not include allogeneic HSCT.

This section provides a summary of the evidence we considered during our review to date. Recent clinical studies, evidence-based clinical treatment guidelines, systematic reviews of the literature and clinical recommendations and consensus statements from professional societies were available.

MULTIPLE MYELOMA

When reviewing the medical literature on MM, overall survival (OS), event-free survival (EFS) progression-free survival and transplantation-related mortality (TRM) were the health outcomes of most importance to CMS. Some studies that evaluate patients with other forms of cancer might use outcomes such as disease-free survival, or time to progression, but these parameters all suffer from assessment bias, difficulty with precision measurement, as well as statistical issues.

Treatment options are limited for patients with MM. Currently, treatments will not cure the disease, but may prolong survival. Some studies have even confirmed that mortality and response rates are not significantly affected by the introduction of early treatment in the progression of myeloma, though treatment (both early and late) does results in improved quality of life (QoL). Allogeneic HSCT has been introduced as another option for patients with this condition. This complex procedure involves numerous steps which may span over many months, with the hope of extended longevity. Included in these steps are matters related to: donor matching (marrow versus peripheral blood source); the allogeneic transplant itself; non-chemotherapy drugs versus chemotherapeutic agents for induction purposes; standard myeloablative versus non-myeloablative versus reduced-intensity conditioning; and the specific types and doses of agents used for GVHD prophylaxis.

MYELOFIBROSIS

The evidence we examined has as its focus health outcomes, i.e., the periprocedural as well as long-term benefits and harms of a particular treatment. For MF, the primary clinical goals when using alloSCT are cure from disease while avoiding mortality and morbidity associated with transplantation.

With the use of alloSCT for patients with MF, overall survival (OS), preferably at one year or more, event-free survival (EFS) and transplantation-related mortality (TRM) were the health outcomes of most importance to CMS. Transplantation-related morbidity in the form of GVHD was also of importance. Study endpoints should be clearly defined *a priori* to both improve the quality of clinical research and so as to allow comparison between clinical studies. Independently-assessed, validated instruments to measure those endpoints are most heavily weighted.

We also looked for evidence concerning health-related quality of life (QoL) and function post-transplantation. Quality of life is important to Medicare beneficiaries and can weigh heavily in patients' decision-making. Therefore, valid and reliable measurement is important to inform patients. Quality of life measures can be disease specific or general. A common cancer specific measure used in patients with MF is the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire core 30 items (EORTC QLQ-C30), which is a validated, 15-domain survey for assessment of disease symptoms, overall QoL and treatment-related adverse effects (Harrison et al., 2013).

General QoL assessments include the SF-36 and the SF-12. There are advantages and disadvantages to each tool, and the end use can help with tool choice, i.e., disease specific to measure within the population, and general for a broad population comparison.

SICKLE CELL DISEASE

For SCD, the primary clinical goals when performing alloSCT are to cure the disease (which will avoid premature death due to the numerous, life-threatening complications of SCD that lead to multi-organ dysfunction and failure) while avoiding mortality and morbidity associated with transplantation (Panepinto et al., 2007). With the use of alloSCT for patients with SCD, overall survival (OS), preferably at one year or more, event-free survival (EFS) and transplantation-related morbidity (TRM) were the health outcomes of most importance to CMS. Transplantation-related morbidity in the form of GVHD was also of importance. Study endpoints should be clearly defined a priori to both improve the quality of clinical research and so as to allow comparison

between clinical studies. Independently-assessed, validated instruments to measure those endpoints are most heavily weighted.

We also looked for evidence concerning health-related quality of life (QoL) and function post-transplantation. Quality of life is important to Medicare beneficiaries and can weigh heavily in patients' decision-making. Therefore, valid and reliable measurement is important to inform patients. Quality of life measures can be disease specific or general. A similar tool for patients with SCD is the SCD module of the PedsQL Generic Core Scale. The generic PedsQL is a validated, 23-item tool for children that assesses QoL based on physical, social, psychological, and school functioning status. The SCD module is specific for children with SCD (Arnold et al., 2015). Additional tools are the CHRIs-General measurement and its SCT-specific module (Kelly et al., 2012) and the EQ-5D (Arnold et al., 2015).

General QoL assessments include the SF-36 and the SF-12. There are advantages and disadvantages to each tool, and the end use can help with tool choice, i.e., disease specific to measure within the population, and general for a broad population comparison.

B. Discussion of Evidence

1. Evidence Question(s)

Multiple Myeloma - Is the evidence sufficient to determine that alloSCT beneficiaries improves health outcomes for Medicare beneficiaries with MM?

Myelofibrosis - Is the evidence sufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with MF?

Sickle Cell Disease - Is the evidence sufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with SCD?

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on any of these topics.

3. Internal Technology Assessment

<u>Literature Search Methods</u> - The reviewed evidence for MM, MF, and for SCD was gathered from peer-reviewed, published, full-text literature articles submitted by the requester or a public commenter, or from peer-reviewed, published, full-text articles found during a literature search of PubMed and from citations of peer-reviewed, published, full-text literature articles.

MULTIPLE MYELOMA

On September 8, 2015 CMS searched PubMed using the following search terms: "multiple myeloma," "stem cell transplantation and last 10 years," "human," "English," "clinical trial," "comparative study," "observational study," "systemic review," "randomized controlled trial," "controlled clinical trial," "practice guideline," and "meta-analysis."

A review of the literature failed to reveal any randomized controlled trials comparing allogeneic HSCT to autologous HSCT, or any other form of therapy. A number of prospective studies have been performed based on a "genetic randomization," in which patients were assigned to treatment with or without allogeneic HSCT based on the presences or absence of an HLA-matched sibling donor. The results of these donor versus no donor trials have been mixed. However, they all demonstrated lower relapse rates and higher rates of non-relapse mortality among the allogeneic recipients, and the majority of these studies failed to reveal a survival benefit. In addition, a number of case series studies have been published which describe allogeneic HSCT as the initial or salvage therapy for multiple myeloma (Kumar, Loughran, Alsina, Durie, & Djulbegovic, 2003). Though most of these studies resulted in a high mortality rate, information from a South West Oncology Group (SWOG) assessment that studied both autologous as well as allogeneic patients receiving chemoradiotherapy revealed that some patients receiving allogeneic transplants had long term survival (Barlogia et al., 2006).

During the second public comment period, one public commenter mentioned an article from the medical literature that met the criteria presented above (Shah et.al., 2015), which was incorporated into the evidence summary below.

Evidence Summary

Meta-Analyses / Systematic Reviews for Multiple Myeloma

Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced intensity allogeneic transplantation in the upfront management of multiple myeloma: meta-analysis of trials with biologic assignment. Bone Marrow Transplantation (2013) 48, 562-567.

Armeson and associates performed a systematic review of the literature as well as a meta-analysis of all known prospective trials comparing autologous with autologous (tandem) plus RIC in newly diagnosed multiple myeloma patients to determine if approaches including RIC allogeneic transplantation resulted in improved progression free survival or overall survival (Armeson, Hill, & Costa, 2013). Though their initial search revealed 1183 reports, after excluding studies because they were either case reports, review articles, correlative studies, retrospective in nature, duplicative publications or because there were no comparisons with autologous transplantations, only six clinical trials and one meeting abstract remained. A total of 1192 participants were in the tandem autologous group, while 630 were in the allogeneic group. The analysis revealed that though allogeneic patients had a higher likelihood of treatment-related mortality and complete response than tandem autologous patients, there was no difference in overall survival (HR = 0.0.74, 95% CI = 0.53-1.04). Limitations of the study noted by the authors include heterogeneity amongst the studies, as well as differing definitions of high risk multiple myeloma. The authors concluded that RIC allogeneic HSCT was not superior to tandem autologous HSCT in patients with newly diagnosed multiple myeloma.

Kharfan-Dabaja M, Hamadani M, Reljic T, et al. Comparative efficacy of tandem autologous versus autologous followed by allogeneic hematopoietic cell transplantation in patients with newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. J Hematol Oncol. 2013; 6:2.

Kharfan-Dabaja and associates reviewed the analysis performed by Armeson et al. (2013), and felt the systematic review did not attempt to evaluate the quality of the studies (Kharfan-Dabaja et al., 2013). For that reason they performed a second systematic review and meta-analysis comparing auto-auto HSCT with auto-allo HSCT in patients with newly diagnosed multiple myeloma. In their study after performing a systematic search they identified 152

publications, of which five studies (enrolling 1538 patients) where included in their final analysis. To help assure quality, all studies eligible for inclusion utilized biologic randomization, which reported data on prognostic risk factors.

Results of the study revealed that response rates (defined as achieving at least a very good partial response) did not differ among the treatment arms [risk ratio (RR) (95% CI) = 0.97 (0.87-1.09), p = 0.66]; but complete remission was higher in the auto-allo HSCT arm [RR = 1.65 (1.25-2.19), p = 0.0005]. Also event-free survival did not differ between auto-allo HSCT group versus auto-auto HSCT group using per-protocol analysis [hazard ratio (HR) = 0.78 (0.58-1.05)), p = 0.11] or using intention-to-treat analysis [HR = 0.83 (0.60-1.15), p = 0.26]. Overall survival (OS) did not differ among these treatment arms whether analyzed on per-protocol [HR = 0.88 (0.33-2.35), p = 0.79], or by intention-to-treat [HR = 0.80 (0.48-1.32), p = 0.39] analysis. Non-relapse mortality (NRM) was significantly worse with auto-allo HSCT [RR (95%CI) = 3.55 (2.17-5.80), p < 0.00001]. The authors concluded, just as the Armeson study demonstrated, that despite higher complete remission rates, there was no improvement in overall survival with auto-allo HSCT compared to auto-auto HSCT. Also, this approach did result in higher non-relapse mortality in patients with newly diagnosed multiple myeloma. The authors noted that due to the lack of evidence, an auto-allo HSCT approach for patients with newly diagnosed myeloma should not be offered outside the setting of a clinical trial.

Shah N, Callander N, Ganguly S, et al. Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2015 Jul; 21(7):1155-66. doi: 10.1016/j.bbmt.2015.03.002. PMID: 25769794

During the second comment period we received an article that was not previously reviewed. This article addresses stem cell transplant guidelines for multiple myeloma (Shahet et. al., 2015). The authors note that the role allo-HCT in MM remains controversial and poorly defined. In their assessment of the topic they note a number of randomized trials that have utilized biological assignment of patients to prospectively compare tandem auto-HCT-allo-HCT versus tandem auto-HCT in the transplantation setting. The studies varied in terms of research design, eligibility, pretransplantation induction therapy, use of total body irradiation in the conditioning regimen, use of anti-hymoglobulin, as well as graft-versus-host disease (GVHD) prophylaxis. The studies had mixed results: Two trials with the longest duration of follow up revealed superior progression free survival and overall survival among patients assigned to auto-HCT-allo-HCT, but the remaining studies, including the largest of the trials performed found no difference in progression free survival and overall survival and overall survival between the two approaches.

The authors also noted that a meta-analyses of the published allo-HCT versus auto-HCT studies confirmed that although complete response rates are higher for allo-HCT, so are the rates of treatment-related mortality. "Thus, a consistent progression free survival or overall survival benefit for allo-HCT cannot be demonstrated."

MYELOFIBROSIS

On June 10, 2015 CMS searched PubMed using the following search terms: "myelofibrosis," "stem cell transplantation AND last 10 years," "human," "English," "clinical trial," "comparative study," "observational study," "systemic review," "randomized controlled trial," "controlled clinical trial," "practice guideline," and "meta-analysis."

For the purposes of this NCA, we reviewed clinical studies that focused on the use of alloSCT in patients with MF and were published in full-text in peer-reviewed English language journals. Abstracts were excluded because they do not provide sufficient information about the study to support further review. Studies with less than 100 patients were excluded because studies limited by such small numbers are of insufficient evidentiary weight for the analytic questions we must address in this review. Reviews, case reports of adverse events and commentaries were excluded because they either did not present the results of a data analysis (reviews), were limited by small numbers of patients and therefore were of insufficient evidentiary weight (case reports of adverse events), or were subjective (commentaries).

The literature search produced 227 citations, of which eight met the criteria presented above (Kerbauy et al., 2007; Patriarca et al., 2008; Kroger et al., 2009; Ballen et al., 2012; Robin et al., 2011; Gupta et al., 2014; Lussana et al., 2014; Rondelli et al., 2014).

The requestor submitted numerous citations of which five met the criteria presented above, and are the same as five of the eight found during the literature search (Kroger et al., 2009; Ballen et al., 2012; Gupta et al., 2014; Lussana et al., 2014; Rondelli et al., 2014).

Of the citations submitted by public commenters that met the criteria presented above, none contained new, relevant evidence.

During the second public comment period, one public commenter mentioned an article from the medical literature that met the criteria presented above (Kroger et.al., 2015), which was incorporated into the evidence summary below.

Evidence Summary

Retrospective Clinical Studies for Myelofibrosis

Kerbauy DMB, Gooley TA, Sale GE, et al. Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia. Biology of Blood and Marrow Transplantation 2007;13(3):355-365.

The authors reported the outcome of an uncontrolled retrospective analysis performed on data collected from 104 patients (101 were evaluable) with MF who received alloSCT at the Fred Hutchinson Cancer Research Center in Seattle, Washington. The date range for transplantation was not provided. Outcomes measured were survival and nonrelapse mortality.

The age range was 18 - 70 years with a median of 49 years. There were 57 males and 47 females. The diagnosis was primary MF for 62 patients; ET with MF for 18 patients and PV with MF for 12 patients. An intermediate or high Dupriez score was found for 60 patients (58%) and a low score for 44 patients.

Fifty-nine patients (57%) received a related donor transplant (52 of these were from a HLA-identical sibling); 45 patients (43%) received an unrelated donor transplant (36 of these were from an HLA-identical source); the source of the stem cells was peripheral blood for 61 patients (59%) and the remaining stem cells were from bone marrow. The conditioning regimens administered varied over time however all but 15 patients received busulfan in some combination with another chemotherapeutic drug and/or total body irradiation. Nine patients (9%) received reduced-intensity conditioning due to older age (range, 41 - 70 years; median, 60 years) or comorbidities.

Range of follow-up was 1.3 - 15.2 years (median, 5.3 years). Nonrelapse mortality was 34% at 5 years (95% confidence interval (CI), 28% - 48%). The estimated probability of survival was 61% (95% CI, 43% - 65%) at seven years. In the univariate regression model for overall mortality, patients with a diagnosis of ET with MF or PV with MF had a significantly lower hazard of mortality compared to patients with a diagnosis of primary MF (p = 0.03)

however this was not seen in the multivariate regression model. The multivariate regression model also did not show statistical significance for Dupriez score, unrelated vs. related donor or stem cell source. Sixty-five (64%) of 99 evaluable patients developed acute GVHD (grade II in 44, grade III in 19, and grade IV in two). The incidence of acute GVHD was 58% for patients who received HLA-identical sibling transplants and 73% for patients who received either unrelated (both HLA-identical and nonidentical) or mismatched family member transplants. Eighty-five patients (84%) developed chronic GVHD and was extensive, requiring therapy, in 59%. No statistically significant difference was seen between HLA-identical sibling and unrelated donor or mismatched family member transplants.

The authors concluded that "although questions remain in terms of the timing of HSCT and optimization of conditioning regimens, HSCT clearly has curative potential for patients with myelofibrosis and promotes long-term survival in remission."

Patriarca F, Bacigalupo A, Sperotto A, et al. Allogeneic hematopoietic stem cell transplantation in myelofibrosis: the 20-year experience of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Haematologica 2008;93(10):1514-1522. doi: 10.3324/haematol.12828. Epub 2008 Aug 25.

Patriarca et al. (2008) reported the outcome of an uncontrolled retrospective analysis performed on GITMO registry data collected from 100 patients with MF who received alloSCT at 26 centers in Italy between 1986 and 2006. Outcomes measured were overall survival, transplant-related mortality (TRM) and relapse-free survival.

The age range was 21 - 68 years with a median of 49 years. There were 65 males. The diagnosis was primary MF for 73 (82% of evaluable patients) patients; the remaining patients had a diagnosis of ET with MF or PV with MF. An intermediate or high Dupriez score was found for 90% of patients.

The types of conditioning drugs varied from patient to patient. The majority of donors were HLA matched siblings (78%) but the source of stem cells (peripheral blood cells vs. bone marrow) and type of conditioning regimen (MA vs. RIC) were evenly split.

Median follow-up was 13 months (range, 1 - 234 months). Transplant-related mortality at one year was 35% and at three years was 43%. The estimated overall survival was 42% at three years and 31% at five years. The three-year relapse-free survival was 35%. During multivariate regression modeling, a statistically significant increase in the hazard ratio for transplant-related mortality was seen with an unrelated or mismatched donor source (HR, 2.49; 95% CI, 1.19 - 5.23; p = 0.016); a statistically significant decrease in the hazard ratio for transplant-related mortality was seen with a post-1995 time-period of alloSCT vs. pre-1995 (for time-period 1996 - 2000: HR, 0.37; 95% CI, 0.14 - 0.96; p = 0.041; for time-period after 2001: HR, 0.24; 95% CI, 0.10 - 0.58; p = 0.001). By day 100 after alloSCT, 40 patients (41%) developed acute GVHD grades II to IV (95% CI, 0.9 - 1.3). Thirty-seven patients (43%) developed chronic GVHD (limited in 26 and extensive in 11 patients) at two years after alloSCT (95% CI, 0.4 - 0.8). Age, Dupriez score, source of stem cell and conditioning regimen did not influence the incidence of acute or chronic GVHD.

The authors noted some limitations to their study. These include "the heterogeneity of the patients' clinical features," the retrospective nature of the study design, the multicenter nature of the registry (especially where the majority of centers contributed only one or two patients to the registry), and the 20-year period of the registry (where "policies and strategies for transplantation in myelofibrosis have changed"). The authors concluded that "despite these limitations, our results confirm that allogeneic HSCT may be an attractive treatment approach for patients with high-risk myelofibrosis. The outcome of such patients has improved significantly since 1996 due to the reduction of TRM."

Ballen KK, Woolfrey AE, Zhu X, et al. Allogeneic hematopoietic cell transplantation for advanced polycythemia vera and essential thrombocythemia. Biology Blood and Marrow Transplantation 2012;18(9):1446-1454. doi: 10.1016/j.bbmt.2012.03.009. Epub 2012 Mar 24.

Ballen et al. (2012) performed an uncontrolled, retrospective analysis of data from the registry maintained by the Center for International Blood and Marrow Transplant Research (CIBMTR), which is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR) and the National Marrow Donor Program (NMDP). Registry data included in the analysis were from patients with primary MF who were transplanted in 29 countries between 1989 and 2002 with an HLA-matched sibling donor, an unrelated donor, or an alternative related donor. Patients with secondary MF or AML were excluded. The goal was to identify prognostic indicators. The primary outcomes included overall survival, disease-free survival, and treatment-related mortality.

The analysis was conducted on a sample size of 289 patients. Patient characteristics were presented by donor transplant group. The table below provides some key patient characteristics:

Patient characteristic HLA-matched sibling donor		Alternative related donor	Unrelated donor	
Sample size	162	26	101	
Age 46 years or older, n (%)	82 (5)	14 (54)	68 (67)	
Male, n (%)	101 (62)	18 (69)	60 (59)	

Thirty-two percent of patients had a low Lille score, 36% had an intermediate Lille score and 31% had a high Lille score; what percent of each Lille score was found for each donor transplant group was not reported by the authors. The majority of patients received a transplant of bone marrow-sourced stem cells and myeloablative conditioning without total body irradiation. A variety of myeloablative regimens was used.

Results per donor transplant group are presented in the table below:

Result	HLA-matched sibling donor	Alternative related donor	Unrelated donor
Median (range) follow-up in months	41 (3 - 144)	46 (12 - 118)	48 (4 - 124)
Treatment-related mortality, % (95% CI) 1-year 5-year	27 (20 - 34) 35 (27 - 43)	24 (9 - 44) 38 (17 - 62)	43 (33 - 53) 50 (39 - 61)*
Overall survival, % (95% CI) 1-year	54 (46 - 62)	60 (39 - 79)	41 (31 - 51)

5-year	37 (26 - 46)	40 (19 - 63)	30 (20 - 40)
Disease-free survival, % (95% CI) 1-year 5-year	48 (40 - 56) 33 (25 - 42)	64 (43 - 82) 22 (1 - 59)	37 (27 - 47) 27 (18 - 37)

*p = 0.02, Unrelated donor vs. HLA-matched sibling donor

Multivariate analysis did not indicate a difference in disease-free survival based on Lille score in the HLA-matched and unrelated donor groups (multivariate analysis did not include data from the alternative related donor group due to small sample size). Forty-three percent of patients who received a matched sibling transplant, 40% of patients with an unrelated donor (URD) transplant and 24% of patients with other related donors developed grade II - IV acute GVHD. Forty percent of patients with a matched sibling transplant, 32% of patients with a URD, and 23% of patients with other related donors developed chronic GVHD. There was no effect of GVHD on relapse or survival.

The authors noted the "analysis was hampered by its retrospective nature and included patients treated in many transplant centers with a variety of conditioning regimens. The majority of patients received MA conditioning regimens, and, as expected, had a median age lower than the median age reported for myelofibrosis patients at diagnosis. Diagnosis was not confirmed by central pathology review." In addition, the authors stated that due to "missing data, Cervantes and Dupriez scores could not be used in a multivariate analysis. Multivariate analysis was not performed for the alternative donors, because of the small sample numbers."

The authors concluded that "allogeneic HSCT for myelofibrosis is being performed in many centers worldwide, with long-term survival rates of 30% to 40%, depending on donor source."

Robin M, Tabrizi R, Mohty M, et al. Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). British Journal of Haematology 2011;152(3):331-339. doi: 10.1111/j.1365-2141.2010.08417.x. Epub 2010 Dec 7.

Robin et al. (2011) performed an uncontrolled, retrospective analysis of data from the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) registry, which included patients with MF who were transplanted between 1997 and 2008 in 27 centers. The analysis was conducted on a sample size of 147 patients (101 received RIC; 46 received myeloablative conditioning) with primary (53%) or secondary (47%) MF. The report did not present specific inclusion/exclusion criteria. The goal was to determine potential risk factors for nonrelapse mortality, overall survival, and progression-free survival.

For the RIC group, the age range was 28 - 68 years with a median of 56 years. There were 70 males. An intermediate or high Lille score was found for 60% of patients; 23% had AML. For the myeloablative group, the age range was 20 - 56 years with a median of 47 years. There were 31 males. An intermediate or high Lille score was found for 61% of patients; ten percent had AML.

Treatment varied from patient to patient and from group to group. The majority (90%) of patients in the RIC group received peripheral blood stem cells while the majority (63%) in the myeloablative group received bone marrow-sourced stem cells. A small majority in each group received a HLA-identical sibling transplant. The RIC regimen for 87% of patients consisted of fludarabine plus some combination of busulfan, melphalan, or low dose total body irradiation. The myeloablative regimen for 94% of patients was cyclophosphamide plus busulfan or total body irradiation.

Median follow-up was 35 months (range, 4 - 90 months). Overall survival at four years was 39% (95% CI, 31 - 50). Progression-free survival at four years was 32% (95% CI, 24 - 43). The cumulative incidence of relapse at four years was 29% (95% CI, 21 - 37). The NRM at four years was 39% (95% CI, 30 - 48). The overall survival at four years was 58%, 46%, and 26% for patients with low, intermediate, or high risk Lille scores including AML, respectively. Sixty-three patients (43%) developed grades II - IV acute GVHD at 100 days after transplantation (95% CI, 35 - 51). Fifty-three patients developed chronic GVHD (limited in 20, extensive in 29 and unknown extent in five patients) for a four-year cumulative incidence of chronic GVHD of 39% (95% CI, 30 - 47).

The authors noted that the conditioning regimen (i.e., RIC vs. MA conditioning) did not have an impact on nonrelapse mortality or survival. However, they continue to state that "no definitive conclusion can be drawn because of the retrospective aspect of the study. Conditioning regimen choice was at the treating physician's discretion in each centre. Patients conditioned by RIC were older and more frequently grafted from a non-HLA identical sibling donor." The authors concluded that "the potential cure of myelofibrosis by HSCT is no longer debated but the management of the patient before transplantation and the optimal timing of the transplantation remains unclear."

Gupta V, Malone AK, Hari PN, et al. Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: a cohort analysis from the center for international blood and marrow transplant research. Biology of Blood and Marrow Transplantation 2014;20(1):89-97. doi: 10.1016/j.bbmt.2013.10.018. Epub 2013 Oct 23.

Gupta et al. (2014) performed an uncontrolled, retrospective analysis of data from the CIBMTR registry. Registry data included in the analysis were from patients with primary MF who were transplanted between 1997 and 2010 and received RIC. Patients with secondary MF or AML were excluded. The goal was to determine outcomes when using RIC as well as to identify patient-, disease- and transplantation-related factors on outcome. The primary outcome was overall survival; progression-free survival and nonrelapse mortality were also examined.

The analysis was conducted on a sample size of 233 patients from 83 centers. The age range was 19 - 79 years with a median of 55 years; 64 patients (27%) were older than 60 years. There were 151 males (65%). Twelve percent of patients had a low DIPSS score, 49% had an intermediate-1 score, 37% had an intermediate-2 score, and one percent had a high score. Peripheral blood stem cells were administered to 88% of patients. Thirty-four percent of patients received a matched sibling donor transplant, 45% received a well-matched unrelated donor, 17% received a partially matched unrelated donor, and four percent received a mismatched unrelated donor. Various RIC treatment regimens were used.

Median follow-up was 50 months (range, 3 - 134 months). Overall survival at five years was 47% (95% CI, 40% to 53%). Adjusted overall survival at five years was 56% (95% CI, 44% to 67%) for matched sibling donor, 48% (95% CI, 37% to 58%) for well-matched unrelated donor and 34% (95% CI, 21% to 47%) for partially matched/mismatched unrelated donor (P = 0.002). No statistically significant relationship was found between overall survival and DIPSS score or between overall survival and type of RIC regimen.

Nonrelapse mortality at five years was 24% (95% CI, 18% to 31%). In a multivariate analysis, donor type was associated with higher nonrelapse mortality (p < 0.0001). The main causes of nonrelapse mortality were GVHD, infections, and organ failure, and the rates of all these complications were higher in

partially matched/mismatched unrelated donors. There was no statistically significant relationship between nonrelapse mortality and DIPSS score.

Progression-free survival at five years was 27% (95% CI, 21% to 34%), was significantly impacted by donor type (p = 0.03) and was significantly inferior for partially matched/mismatched unrelated donor (RR, 1.75; 1.14 - 2.68; p = 0.01). DIPSS score had no impact on progression-free survival.

The cumulative incidence of grade II - IV acute GVHD at 100 days after transplantation was 37% (95% CI, 30% to 43%). The cumulative incidence of grade III - IV acute GVHD at 100 days after transplantation was 19% (95% CI, 15% to 25%). The cumulative incidence of chronic GVHD at five years was 51% (95% CI, 44% to 58%). Patients who developed acute GVHD but not chronic GVHD had significantly higher NRM and lower relapse/progression compared with those who did not develop acute GVHD or chronic GVHD. No differences in PFS or survival were shown.

The authors noted the study results found donor type but not age to have an independent prognostic impact. The small sample size for the analysis was noted as a limitation. The authors concluded that alloSCT with RIC is a "potentially curative option for some patients with MF. Donor type is the most important factor predicting survival after RIC HSCT for MF. Future prospective trials are needed to determine the preferred RIC regimen."

Lussana F, Rambaldi A, Finazzi MC, et al. Allogeneic hematopoietic stem cell transplantation in patients with polycythemia vera or essential thrombocythemia transformed to myelofibrosis or acute myeloid leukemia: a report from the MPN Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 2014;99(5):916-921. doi: 10.3324/haematol.2013.094284. Epub 2014 Jan 3.

Lussana et al. (2014) performed an uncontrolled, retrospective analysis of data from 250 consecutive patients with secondary MF or AML who underwent alloSCT between 1994 and 2010 at 89 European centers from 20 different countries and whose data was entered into the European Society for Blood and Marrow Transplantation (EBMT) registry. The goal was to determine nonrelapse mortality and overall survival as well as examine relative contributions of different risk factors on outcomes.

Unless noted, patient characteristics and outcomes were not reported separately for patients with secondary MF. The age range was 22 - 75 years with a median of 56 years; 136 patients (54%) were 55 years old or older. There were 137 males. Ninety-two percent of patients received stem cells from peripheral blood. HLA related matched donor transplants were used for 115 patients; mismatched donor transplants for two patients, unrelated matched donor for 124 patients and mismatched donor transplants for nine patients.

Of the 250 patients, 193 had secondary MF (77%). The Lille score was available for 75 patients with secondary MF. Thirty (16%) patients had a low score; 37 (19%) had an intermediate score; eight (four percent) had a high score; for 118 (61%) patients the score was unknown. One hundred and seventy (68%) patients with secondary MF were given RIC. Specific regimens for RIC were not reported by the authors.

Median follow-up was 13 months (range, 0.03 - 123 months). Overall survival at three years for patients with secondary MF was 62% (variance such as 95% CI not reported). Compared to patients younger than 55 years, overall survival at three years for patients 55 years and older was statistically significantly lower (47% vs. 65%; p = 0.015).

Nonrelapse mortality at three years for patients with secondary MF was 27% (variance not reported). Compared to patients younger than 55 years, nonrelapse mortality at three years for patients 55 years and older was statistically significantly higher (35% vs. 20%; p = 0.032). Nonrelapse mortality at three years was also statistically significantly high for patients who received an unrelated donor transplant compared to a related donor transplant (34% vs. 18%; p = 0.034). The authors noted that age impacted survival primarily because patients older than 55 years had higher nonrelapse mortality.

Twenty-seven percent of patients developed grade II - IV acute GVHD. Sixty percent of patients developed chronic GVHD (the extensive form occurred in 37% of patients and the limited form in 23%) however data about chronic GVHD were unknown for 67 (27%) of the patients.

The authors noted some limitations including the retrospective nature of their analysis, which "collected data from many different European centers performing transplants over a long period of time with marked heterogeneity in terms of the patients' age, co-morbidities, pre-transplant transfusion dependency, use of conditioning regimens and GVHD prophylaxis. Moreover, although to our knowledge it is the largest analysis published, it still does not allow an in-depth evaluation of the different risk factors that may characterize these patients, such as previous cytoreductive treatments or cytogenetics at transplantation. Similarly, it was not possible to get an accurate estimate of progression-free survival. The lack of this information in the database probably reflects the difficulties in assessing response in these diseases. Finally, the follow-up of the patients reported in the registry was relatively short, although we consider that this follow-up was probably sufficient to enable a correct evaluation of the main clinical outcomes. However, even if definitive conclusions cannot be drawn due to these limitations, the clinical implications of our findings are potentially very important: indeed, the potential curative effect of allogeneic HSCT is more consistently supported, with a similar 3-year survival rate compared to that of high-risk patients with MF who did not undergo allogeneic HSCT, with the advantage that transplanted patients may be definitely cured. These EBMT data are consistent with those recently reported by other cooperative study groups, indicating that overall survival following allogeneic HSCT may reach approximately 50%."

The authors concluded that "this large retrospective study confirms that allogeneic HSCT is potentially curative for end-stage PV/ET patients progressing to MF or AML. Innovative treatment approaches with new molecular targeted therapies may increase the number of patients eligible for transplantation and reduce the risk of relapse and non-relapse mortality, but they need to be assessed in prospective clinical trials."

Kröger N, Giorgino T, Scott BL, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. Blood 2015 May 21;125(21):3347-50; quiz 3364. doi:10.1182/blood-2014-10-608315. Epub 2015 Mar 17.

Kroger et al. (2015) reported the outcome of a retrospective analysis performed on data collected from two independent international multicenter databases: 188 patients with primary MF who received alloSCT in Europe or the US (transplant cohort) and 255 patients in Europe who received only conventional (but non-JAK inhibitor) treatment. Patients had to be 65 years of age or younger (nontransplant cohort). The authors noted that "within the transplant cohort, there were no significant differences in outcome between reduced-intensity and myeloablative conditioning, or between HLA-matched unrelated and HLA-matched sibling donor transplants (data not shown); thus, data were combined for analysis." Outcome measured was survival using an "ad hoc statistical analysis."

The median (range) for age was 50 (20 - 65) years for the transplant cohort and 55 (18 - 65) for the nontransplant cohort. Male/female ratio was 108/80 in the transplant cohort and 154/101 in the nontransplant cohort. For the transplant cohort, 128 patients (68%) had an intermediate-2 or high DIPSS score, 38 patients (20%) had an intermediate-1 score and 22 patients (12%) had a low score at time of transplantation. For the nontransplant cohort, 55 patients (22%) had an intermediate-2 or high DIPSS score, 75 patients (29%) had an intermediate-1 score and 125 patients (49%) had a low score at the time of diagnosis.

In the transplant cohort, 86 patients received a matched related donor transplant and 102 patients received a matched unrelated or mismatched related donor transplant. Roughly half of the patients in the transplant cohort received reduced-intensity conditioning and the other half received myeloablative conditioning. Specific information about the administered conditioning regimens was not reported.

For patients with low risk MF, "the relative risk of death after allogeneic SCT vs those treated with nontransplant modalities was 5.6 (95% CI, 1.7-19; P 5.0051); for intermediate-1 risk it was 1.6 (95% CI, 0.79-3.2; P 5.19), for intermediate-2 risk, 0.55 (95% CI, 0.36-0.83; P 5.005), and for high risk, 0.37 (95% CI, 0.21-0.66; P 5.0007)."

The authors noted a couple of limitations to their study due to the inability to address the possibility of selection bias and the possible correlations between time of transplant and patient characteristics.

The authors concluded that "this study indicates that non-ruxolitinib-treated PMF patients 65 years of age or younger at diagnosis with int-2 or high-risk disease are likely to benefit from allogeneic SCT, whereas for patients with low-risk disease, nontransplant approaches may be appropriate. Individual counseling is indicated for int-1 risk patients."

Prospective Clinical Studies for Myelofibrosis

Kröger N, Holler E, Kobbe G, Bornhäuser M, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood 2009;114(26):5264-5270. doi: 10.1182/blood-2009-07-234880. Epub 2009 Oct 7.

Kroger et al. (2009) conducted a multicenter, prospective, uncontrolled, Phase Two clinical trial from 2002 to 2007 in Germany and the Netherlands to study the efficacy of RIC in 103 patients with primary or secondary MF. Patients had to have either an intermediate-risk or high-risk Lille score or a low-risk Lille score with constitutional symptoms, or a high-risk Cervantes score (the presence of two or three risk factors and aggressive disease) and an age between 18 and 70 years. Patients should also have had an HLA-compatible related or unrelated donor. The outcomes of interest were nonrelapse mortality at 1 year, overall and disease-free survival, and incidence of relapse.

The age range was 32 - 68 years with a median of 55 years. There were 62 males. The diagnosis was primary MF for 63 (61%) patients; the remaining patients had a diagnosis of ET with MF or PV with MF. An intermediate or high Lille score was found for 86 of the 103 patients (83%); a high Cervantes score was found in 73 of 103 patients (71%) but the authors did not report how many patients overlapped between the two scores.

Each patient received RIC with busulfan, fludarabine, and antilymphocyte-globulin. The majority of donors were HLA matched (80%); matched and unrelated was 70%. Peripheral blood stem cells were administered in 96% of the transplantations.

For the survival outcome, median follow-up was 33 months (range, 12 - 76 months). The five-year estimated disease-free survival was 51% (95% ci, 38% - 64%) and the five-year overall survival was 67% (95% CI, 55% - 79%). In the multivariate analysis, mismatched HLA donor (HR = 2.39; 95% CI, 1.22 - 4.69; p = 0.01) and a high-risk Lille score (HR = 5.37; 95% CI, 1.58 - 18.24; p = 0.007) were risk factors for disease-free survival. Age greater than 55 years (HR = 2.70; 95% CI, 1.21 - 6.03; p = 0.02) and mismatched HLA donor (HR = 2.70; 95% CI, 1.21 - 6.03; p = 0.006) were significant risk factors for overall survival. Nonrelapse mortality at one year was 16% (95% CI, 9% - 23%). The cumulative incidence of relapse at five years was 29% (95% CI, 16% - 42%). In the multivariate analysis, a high-risk Lille score was a significant factor for higher incidence of relapse (HR = 5.23; 95% CI, 1.14 - 24.01; p = 0.003). Twenty-seven percent of transplanted patients developed grade II - IV acute GVHD; 11% developed grade III - IV acute GVHD. Forty-nine percent of patients developed chronic GVHD (limited disease in 24% and extensive disease in 24%).

The authors noted that an "important risk factor for outcome was age. Patients younger than 55 years had an estimated 5-year overall survival of 82%, whereas transplantation of patients older than 55 years of age resulted in an estimated 5-year survival of 48% This is the results of a nonsignificant higher relapse and higher NRM for elderly patients." Another important risk factor highlighted by Kroger et al. (2009) was "the stage of the disease determined by the Lille score. Independently, the stage of the disease influenced mostly the incidence of relapse, which was lowest for low-risk (14%) and highest for high-risk disease (34%), resulting in lower disease-free survival for patients with intermediate- and high-risk disease. Therefore, the timing of stem cell transplantation seems to be crucial and should be performed before the disease has developed to a very advanced stage. Whether a more intensified conditioning regimen might lower the risk of relapse in Lille high-risk patients should be investigated in a further trial."

The authors concluded that "this large prospective multicenter trial shows that a reduced-intensity conditioning regimen followed by allogeneic stem cell transplantation from related or unrelated histo-compatible donors is a reasonable and potential curative treatment option, even for elderly patients with PM or post-PV/ET myelofibrosis.

Rondelli D, Goldberg JD, Isola L, et al. MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. Blood 2014;124(7):1183-1191. doi: 10.1182/blood-2014-04-572545. Epub 2014 Jun 24.

Rondelli et al. (2014) conducted a multicenter, prospective, uncontrolled, Phase Two clinical trial from 2007 to 2011 in 11 centers in the US, Europe and Canada to study the efficacy of RIC in 66 patients with primary or secondary MF. Patients had to be 18 to 65 years old, have no significant comorbidities, have either an intermediate or high Lille score, or a low Lille score with a platelet count < 100 x 10⁹/L, and have a sibling or unrelated stem cell donor available. The goal of the trial was to examine the efficacy of the fludarabine/melphalan-based RIC regimen in two parallel arms based on type of donor although the authors stated that the trial "was designed to estimate progression-free survival and overall survival." Of note, in the reporting of the results the authors appear to refer to the progression-free survival as the event-free survival (EFS).

The sibling donor group had 32 patients; the unrelated donor group had 34 patients. Patient characteristics are presented in the table below:

Patient characteristic	Sibling donor	Unrelated donor
Median (range) age, years	55 (40 - 65)	56 (30 - 65)
PMF, n (%)	14 (44)	25 (74)
PV-MF, n (%)	3 (9)	5 (15)

ET-MF, n (%)	15 (47)	4 (12)
Lille score 0 1 2	3 (9) 20 (63) 9 (28)	0 23 (68) 11 (32)
Male, n (%)	19 (59)	19 (56)
Peripheral blood stem cell source	26 (81)	31 (91)
Full matched HLA donor	30 (94)	25 (74)

Median follow-up was 25 months (range, 10 - 30 months). Seventy-five percent in the sibling group and 32% in the unrelated group were alive. Nonrelapse mortality was 22% in the sibling group and 59% in the unrelated group. Results of statistical significance testing for these outcomes were not reported. However, the authors noted that the "median OS for the sibling group has not been reached, whereas for the unrelated group it was 6 months (95% confidence interval [CI]: 3,25). A significantly higher risk of death was observed for patients receiving a transplant from an unrelated as compared with a sibling donor (hazard ratio 3.9; 95% CI: 1.8, 8.9) (P < 0.001). Median EFS has not been reached in the sibling group and was 6 months (95% CI: 2, 25) in the unrelated group." Statistical analysis did not find an association between overall survival and age of patient.

In addition, the authors reported that "survival curves based on diagnosis (primary or secondary MF), degree of donor HLA match, presence of JAK2V617F, and age >/= 57 years showed no statistical difference within the sibling or unrelated groups" (i.e., these variables did not predict survival). Moreover, "when patients in each group were stratified based on the age-adjusted DIPSS, patients with low/int-1 and int-2/high risk in the sibling cohort had comparable survival, whereas patients in the unrelated cohort at int-2/high risk had lower survival rates than those at low/int-1 risk (2-year survival: 42% vs 17%, P = .1). Survival was examined in each of the two transplant groups in relation to diagnosis, age, gender, Lille score and DIPSS score at the time of transplant, donor HLA compatibility, and presence of Jak2V617F mutation. The results, shown in Table 3, demonstrate that none of these factors predicted survival individually in either group of patients."

Thirty-nine percent of patients developed grade II - IV acute GVHD (38% in the sibling group; 41% in the unrelated group). Of the 43 evaluable patients, 36% in the sibling group developed chronic GVHD (extensive in 25%) and 38% in the unrelated group developed chronic GVHD (extensive in 20%).

The authors concluded that "regimens including melphalan or busulfan are both very effective in transplants from sibling donors. However, a busulfan-based regimen seems preferable in case of transplant from an unrelated donor." In addition, the authors "also suggest that an initial search for matched donors should be performed for all the MF patients at ≥ int-1 risk. In patients at int-2 or high risk, allogeneic hematopoietic stem cell transplantation (AHSCT) should be offered immediately. In patients at int-1, especially if they have only a matched unrelated donor, AHSCT should be offered as soon as the disease shows any sign of overall progression, such as worsening of anemia or symptoms or increase in spleen size, even before they meet the criteria for the int-2 risk category." Finally, the authors stated that "large prospective studies testing new strategies to reduce NRM in high-risk AHSCT, such as from no sibling or HLA-mismatched donors or in patients with more advanced disease, are warranted."

Quality-of-Life Studies for Myelofibrosis

None found that meet the criteria for review as stated above.

SICKLE CELL DISEASE

On July 23, 2015 CMS searched PubMed using the following search terms: "sickle cell disease," "stem cell transplantation AND last 10 years," "human," "English," "clinical trial," "comparative study," "observational study," "systemic review," "controlled clinical trial" and "meta-analysis."

For the purposes of this NCA, we reviewed clinical studies focused on the use of alloSCT in patients with SCD and published in full-text in peer-reviewed English language journals. Abstracts were excluded because they do not provide sufficient information about the study to support further review. Studies with less than 50 patients were excluded because studies limited by such small numbers are of insufficient evidentiary weight for the analytic questions we must address in this review. Reviews, case reports of adverse events and commentaries were excluded because they either did not present the results of a data analysis (reviews), were limited by small numbers of patients and therefore were of insufficient evidentiary weight (case reports of adverse events), or were subjective (commentaries).

The literature search produced 22 citations, of which two met the criteria presented above (Bernaudin et al., 2007; Panepinto et al., 2007).

The requestor submitted numerous citations of which two met the criteria presented above and are the same two found during the literature search.

Of the citations submitted by public commenters that met the criteria presented above, one contained new, relevant evidence (Dedeken et al., 2014).

One citation was found during a review of an evidence-based guideline (Locatelli 2013).

Evidence Summary

Retrospective Clinical Studies for Sickle Cell Disease

Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood 2007;110:2749 - 2756. Epub 2007 Jul 2.

The authors analyzed data from 87 consecutive patients from 14 centers in France with severe SCD who received alloSCT with HLA-identical sibling donor stem cells from bone marrow, cord blood, or peripheral blood during a 16-year timespan (1988 - 2004). Indications for alloSCT included history of stroke, neurovascular abnormalities demonstrated by transcranial Doppler (TCD), arteriography and/or magnetic resonance angiography (MRA)/magnetic

resonance imaging (MRI), severe anemia, recurrent (more than three per year) vaso-occlusive crises and/or acute chest syndromes, or failure of hydroxyurea therapy. A myeloablative conditioning regimen was used (busulfan and cyclophosphamide). In 1992, ATG was added to the regimen due to high rates of transplant rejection. There was no control group for the analysis.

Forty patients (47%) were female. At the time of alloSCT, the median age was 8.8 years (range, 2.2 - 22 years); ten patients were older than 15 years. The ethnicity of the patients was not reported. Eighty-five patients received bone marrow stem cells and 14% received cord blood stem cells.

Engraftment was successful in all but one patient (n = 86). There were six transplantation-related deaths. The estimated five-year TRM rate was 6.9%. Overall EFS at five years was 86.1%. Median follow-up of suvivors was six years (range, 1.6 - 17.5 years). At the time the results were published, 81 patients were alive with a mean age of 16.2 years (range, 6.1 - 28 years). Seventy-nine patients did not experience vaso-occlusive crises or acute chest syndrome episodes, and they had not been given transfusions since engraftment. Seventeen of 86 assessable patients (20%) developed grade II or higher acute GVHD. The incidence of acute GVHD was significantly higher in patients older than 15 years (p = 0.003) and in patients transplanted with HLA-mismatched stem cells (p = 0.007). A mild form of chronic GVHD occurred in nine of 83 (11%) assessable patients and an extensive form occurred in two of 83 (0.4%) patients.

The authors concluded that these "results indicate that HLA-identical sibling HSCT after myeloablative conditioning with ATG should be considered as a standard of care for SCD children who are at high risk for stroke." In addition, the authors noted that "considering the hope to cure 95% of SCD children with genoidentical HSCT, this therapeutic approach should be discussed early with families, especially as soon as a long-term transfusion program becomes necessary."

Panepinto JA, Walters MC, Carreras J, et al. Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research. British Journal of Haematology 2007;137:479 - 485. Epub 2007 Apr 24.

The authors reported the results of an uncontrolled retrospective analysis of the CIBMTR observational data from 67 patients from 30 centers worldwide who had SCD and received alloSCT with HLA-matched sibling donor stem cells from bone marrow, cord blood, or peripheral blood during a 13-year timespan (1989 - 2002). The most frequent indications for alloSCT were stroke (24 patients) and vaso-occlusive crises (25 patients). Other indications included acute chest syndrome (six patients) and chronic RBC transfusion/iron overload (five patients). A myeloablative conditioning regimen was used (busulfan and cyclophosphamide) in 94% of patients.

At the time of alloSCT, the median age was ten years (range, 2 - 27 years); three patients were older than 21 years. Sixty-three percent were male. The ethnicity of the patients was not reported. Eighty-one percent received bone marrow stem cells and 13% received peripheral blood stem cells.

Median follow-up of survivors was 61 months (range, 3 - 178 months). There were three deaths and all occurred three months or more after transplantation. The five-year probability of overall survival was 97% (95% CI, 91 - 100; n = 67). Fifty-five patients were free of sickle cell symptoms at a median of five years after alloSCT. Probability of five-year disease-free survival was 85% (95% CI, 74 - 92; n = 65). Eight of 67 (12%) developed grade II or higher acute GVHD; two of these eight had grade III or IV. The overall probability of acute GVHD at day 100 after transplantation was ten percent. Thirteen of 67 patients had chronic GVHD; three of these 13 had limited chronic GVHD and nine had extensive chronic GVHD (the severity was not reported for the remaining patient with chronic GVHD). The five-year probability of chronic GVHD was 22%.

The authors concluded that their "report confirms and extends earlier reports that HSCT from HLA-matched related donors offers a very high survival rate, with few transplant-related complications and the elimination of sickle-related complications in the majority of patients who undergo this therapy."

Locatelli F, Kabbara N, Ruggeri A, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood 2013;122:1072 - 1078. doi: 10.1182/blood-2013-03-489112. Epub 2013 May 21.

Locatelli et al. (2013) performed a retrospective analysis of data from the EUROCORD registry (n = 411) in Europe combined with the Sibling Donor Cord Blood Program registry (n = 74) in California (total n = 485). Of the 485 patients, 160 had SCD; the remaining patients had TM. There was no control group. AlloSCT was performed between 1994 and 2005 at a total of 28 centers. All patients were children who received HLA-identical family stem cells. The goal of the analysis was to determine whether patients with SCD (or TM) have different probabilities of benefiting from HLA-identical sibling cord blood transplantation or HLA-identical sibling bone marrow transplantation.

Thirty patients with SCD received cord blood (cord blood group) and 130 received bone marrow (bone marrow group). The number of males and females was essentially equal for each group. Median age at transplantation was eight years (range, 0.7 - 24) for the bone marrow group and six years (range, 2 - 20) for the cord blood group. The ethnicity of the patients was not reported. The majority of patients in each group received myeloablative conditioning.

The median time of follow-up for surviving patients was 70 months (range, 12 - 165) for the bone marrow group and 70 months (range, 12 - 151) for the cord blood group. The ethnicity of the patients was not reported. The six-year disease-free survival for patients with SCD was 92% in the bone marrow group and 90% in the cord blood group. The incidence of acute and chronic GVHD was not reported separately based on disease (i.e., SCD vs. TM).

The authors concluded that patients with SCD "have excellent outcomes" after both HLA-identical sibling cord blood transplantation and bone marrow transplantation. They also noted that "future studies on the occurrence and severity of late effects after either CBT or BMT from an HLA-identical sibling are desirable for a comprehensive and meaningful comparative evaluation of these two transplant options."

Dedeken L, Lê PQ, Azzi N, et al. Haematopoietic stem cell transplantation for severe sickle cell disease in childhood: a single centre experience of 50 patients. British Journal of Haematology 2014;165:402 - 408. doi: 10.1111/bjh.12737. Epub 2014 Jan 16.

Dedeken et al. (2014) performed a retrospective analysis of data from 50 consecutive children with severe SCD in Belgium who received alloSCT between 1988 and 2013. Myeloablative conditioning was administered to all patients. The type of medications given for GvHD prophylaxis was consistent but the use of ATG, hydroxyurea, or seizure prophylaxis varied over the timespan. Geno-identical transplantation was performed with bone marrow in 39 (78%) patients, with cord blood in three patients, with bone marrow and cord blood in seven patients and with peripheral blood stem cells in one patient. There was no control group.

There were 27 males and 23 females. Median age at transplantation was 8.3 years (range, 1.7 - 15.3). The median time of follow-up was 7.7 years (range, 0.4 - 21.3). The ethnicity of the patients was not reported. The patient population was divided into three groups based on pre-transplantation management and conditioning regimen (which varied over the 25-year timespan due to improving disease knowledge with resultant improvement of clinical management): Group One = myeloablative conditioning without ATG or HU (n = 6); Group Two = myeloablative conditioning plus ATG but no HU (n = 36). The patient characteristics and analysis results were reported by group. Median

patient age did not differ significantly between the three groups but median follow-up time was statistically-significantly shorter for Group Three compared to the other groups.

For the entire population, eight-year OS was 94.1% (95% CI, 0.86 - 1.0) and event-free survival was 85.6% (95% CI, 0.75 - 0.98). The eight-year event-free survival by group was 50% (95% CI, 0.23 - 1.0) for Group One; 66.7% (95% CI, 0.38 - 1.0) for Group Two; 97.4% (95% CI, 0.92 - 1.0; p = 0.001 vs. Group One and p = 0.006 vs. group 2) for Group Three. Eleven of 50 patients (22%) developed acute GVHD (grade I or II: six patients; grade III or IV: five patients). Ten of 50 (20%) patients developed chronic GVHD (none had an extensive form).

The authors concluded that event-free survival in this study cohort "has improved with time" and postulated that the administration of HU before alloSCT "might have played a role in this improvement."

Prospective Clinical Studies for Sickle Cell Disease

None found that meet the criteria for review as stated above.

Quality-of-Life Studies for Sickle Cell Disease

None found that meet the criteria for review as stated above.

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened on any of these issues.

5. Evidence-Based Guidelines

The pertinent evidence-based guidelines are summarized below:

MULTIPLE MYELOMA

National Comprehensive Cancer Network (NCCN)

The NCCN mentions in their guidelines that allogeneic stem cell transplants should only take place as part of a clinical trial. This was based on the results of a study by Barlogia and associates that revealed that autologous and myeloablative allogeneic patients who received conventional chemotherapy had similar survival rates (Barlogia et al., 2006). NCCN considers myeloablative allogeneic HSCT an option in the setting of a clinical trial (category 2A).

International Myeloma Working Group (IMWG)

The IMWG also mentions in their Consensus Statement regarding the Current Status of Allogeneic Stem Cell Transplantation for Multiple Myeloma that allogeneic transplants should only be performed in the context of clinical trials. This was based on a phase III tandem auto vs. auto/mini allogeneic study that was presented at an annual American Society of Hematology meeting which demonstrated no difference between two arms of the study in terms of progression-free or overall survival at three years. The authors noted that potential benefits of graft-versus-myeloma to reduce disease progression or relapse were offset by increased treatment related mortality.

UK Myeloma Forum (UKMF) Executive Committee and British Committee for Standards in Haematology (BCSH)

The UKMF and BCSH updated their guidelines in 2014 addressing the diagnosis and management of multiple myeloma. In the document they state, "AlloSCT should be carried out in EBMT accredited centres where data are collected prospectively as part of international transplant registries and, where possible, should be carried out in the context of a clinical trial" (Grade A1).

European Perspective on Multiple Myeloma Treatment Strategies in 2014

In the document, the authors note, "There is consensus that, in general, auto-allo-SCT should not be used outside clinical trials" (levels of evidence: 1a; grade of recommendation: A).

European Myeloma Network

The European Myeloma Network notes that the role of alloSCT remains controversial due to the TRM (10-20%) and GvHD rates even with non-myeloablative regimens. Therefore, alloSCT is considered investigational and actively pursued in clinical trials by several entities such as:

- DSMM- Deutsche Studiengruppe Multiples Myelom (Germany),
- HOVON Hemato-Oncologie voor Volwassenen Nederland (Netherlands),
- GIMEMA Gruppo Italiano Malattie EMatologiche dell'Adulto (Italy),
- PETHEMA Para el Tratamiento de la Leucemia y el Limforma (Spain)
- EBMT European Society for Blood and Marrow Transplantation, and
- CIBMTR Center for International Blood and Marrow Transplant Research

MYELOFIBROSIS

The British Committee for Standards in Haematology

Reilly et al. (2012) published a guideline for the management of primary and secondary MF. Levels and grades of evidence were assigned using the British Committee for Standards in Haematology's Procedure for Guidelines. The GRADE system was used to determine the strength and quality of evidence. The General Haematology and Haemato-oncology Task Forces of the British Committee for Standards in Haematology, a panel of UK hematologists, and the British Society of Haematology Committee were involved with creating the guideline.

With regards to prognosis, the guideline recommended that "therapeutic decisions in PMF, especially regarding the use of allo-SCT, should be based on the patient prognosis as determined by the DIPSS Plus as this is validated for any timepoint of the disease and is more discriminating in median survival prediction than the IPSS score." In addition, the guideline recommended that while "the IPSS, DIPSS and DIPSS Plus have not been validated for post-PV MF and post-ET MF, it is suggested that they still be used in this setting (Evidence level 2, Grade B)." Evidence level two is considered to have weak strength of evidence "where the magnitude of benefit or not is less certain" and "recommendations require judicious application to individual patients. Regard as 'suggest'." Grade B corresponds to moderate quality of evidence where "further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence interval or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient)."

For allo-SCT, the authors noted that it "should be stressed, however, that there are no randomized controlled trial (RCTs) comparing allo-HSCT to any alternative/supportive therapy; nor are there any RCTs comparing myeloablative (MA) versus reduced intensity conditioning (RIC) allo-HSCT. We are reliant, therefore, on non-comparative reported series as the principal evidence base (Table V). Attempts to evaluate these are further complicated by the substantial heterogeneity of the patient populations with respect to age, prognostic groups, co-morbidities, stem cell source, donor source, conditioning protocols (MA and RIC), GvHD prophylaxis, pre-transplant red cell and platelet transfusion dependency and iron loading. Patients with differing prognostic scores at the time of transplant are often included in the same series, making the outcomes difficult to evaluate against a median predicted survival in the absence of a transplant. Additionally, some of the larger published case series include transplants carried out up to 20 years ago. In the interim there have been substantial changes in transplant practice, from the introduction of high resolution molecular typing for volunteer unrelated donors, the introduction of RIC regimens and improvements in supportive care, all of which have potentially resulted in better transplant outcomes and thus making the results of earlier reports difficult to interpret."

The following alloSCT-specific treatment recommendations were presented by the authors:

"Definition: A transplant-eligible patient is defined as one deemed fit enough to undergo the procedure with manageable co-morbidities and having an HLA-matched sibling or unrelated donor available.

- Transplant-eligible patients < 45 years of age, with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic abnormalities, should be considered for MA allo-HSCT (Evidence level 2, Grade C).
- Transplant-eligible patients with an IPSS risk of Intermediate 2 or High, especially with transfusion dependence and/or adverse cytogenetic
 abnormalities, together with an HSCT co-morbidity index 3, or who are aged over 45 years, should be considered for RIC allo-HSCT (Evidence level 2,
 Grade C).
- Patients should be transplanted before they have received more than 20 units of red cells (Evidence level 2, Grade C).
- Use of oral busulfan should be accompanied by targeted dosing according to plasma levels. Alternatively, intravenous busulfan can be used, guided by plasma levels where possible (Evidence level 2, Grade C).
- There is no convincing evidence for pre-transplant splenectomy and some evidence of harm both from surgical morbidity and mortality and a possible increased risk of relapse post-transplant Evidence level 2, Grade C).
- JAK2 V617F mutated patients monitored by quantitative polymerase chain reaction (Q-PCR) post-transplant who do not achieve or who relapse from
 molecular CR are candidates for donor lymphocyte infusions in the absence of GvHD (Evidence level 2, Grade B). The role of Q-PCR for other mutations
 post-bone marrow transplantation remains unclear.
- There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favourable results have been achieved following BUCY and FLUBU and anti-lymphocyte globulin. Every effort should be made to enroll patients in prospective clinical studies and data should be reported to National and International Registries (Evidence level 2, Grade C)."

Grade C corresponds to a low quality of evidence where "further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Current evidence from observational studies, case series or just opinion."

EBMT-ESH Handbook on Haematopoietic Stem Cell Transplantation

The European Society for Blood and Marrow Transplantation (EBMT) and the European School of Haematology (ESH) periodically conduct a health technology assessment of stem cell transplantation, which is presented publically as the EBMT-ESH Handbook on Haematopoietic Stem Cell Transplantation (the EBMT-ESH Handbook). In 2012 the two organizations published a revised edition of the EBMT-ESH Handbook.

The EBMT-ESH Handbook noted the following:

- "Allogeneic stem cell transplantation is the only curative treatment for primary and secondary myelofibrosis.
- Since this is a disease of the elderly, relatively few patients are candidates for transplant although encouraging results using reduced-intensity conditioning regimens have been recently reported, and offer the possibility of extending the age for consideration of intensive therapy.
- At present it is not clear that reduced-intensity procedures offer any benefit over myeloablative conditioning in younger patients. The issue of splenectomy before transplant remains controversial.
- The identification of the JAK2V617F mutation in the pathophysiology of many cases of myelofibrosis allows accurate monitoring of disease response and the possibility of early intervention with donor lymphocyte infusions for residual or recurrent disease."

For adult patients with primary or secondary MF with a Lille intermediate or high prognostic score, the EBMT-ESH Handbook recommendations are based on donor type. AlloSCT is considered to be the "standard of care" for HLA-identical sibling donors and matched, unrelated donors. The use of mismatched donors is considered to be "developmental; should be carried out only at accredited and experienced centres on IRB approved protocols." The use of autologous SCT is considered to be "generally not recommended."

SICKLE CELL DISEASE

The Cochrane Collaboration

In 2013 The Cochrane Collaboration published the results of a systematic review of the literature (the Cochrane Central Register of Controlled Trials; MEDLINE; unpublished work found by searching the abstract books of five major US, British and European conferences; ClinicalTrials.gov) regarding the use of SCT for people with SCD (Oringanje et al., 2013). The date of the most recent search was September, 2012. The objective was to examine the cure rate and risks of SCT for children and adults with SCD. Inclusion criteria used were randomized controlled and quasi-randomized clinical trials that compared any method of SCT with either each other or with any of the preventive or supportive interventions (e.g., periodic blood transfusion or

hydroxyurea) in people with SCD regardless of the type of SCD, gender and setting. No definition of quasi-randomized clinical trial was reported in the article. The primary outcome was event-free survival. Secondary outcomes included overall mortality, mortality at one-year, transplant-related mortality and morbidity, incidence of acute and chronic GVHD, QoL, and the incidence of various complications of SCD.

The authors reported that the search found 10 trials initially but none of these trials met the inclusion criteria because none of them were randomized or quasi-randomized controlled. Given the lack of findings, the authors did not report any conclusions. They did note, however, that while "some studies have reported high event-free survival rate, this research evidence is currently limited to observational and other less robust studies. Clinicians should therefore inform people with SCD about the uncertainty surrounding this clinical procedure if it is to be used." The authors stated the "the need for a well-designed prospective randomized controlled trial of HSCT in people with SCD in order to make necessary recommendations regarding its use."

"While ideally, trials comparing HSCT to supportive care could be carried out, the high variability in the clinical course of SCD and characteristics of patient population hinders its feasibility and may be considered unethical. Thus, trials may compare the different types of HSCT with one another with subgroup analyses by sickle status, severity of disease, setting and age groups carried out to provide guidance on the optimal HSCT for each individual with SCD. Outcomes to be included in these trials should address the needs and concerns of patients, care-givers and health providers, in order to assess the risks and benefits of the procedure. Similar outcomes should be measured in trials to allow comparability of results and future synthesis of data in a meta-analysis. Long-term follow up of participants is also necessary."

National Institutes of Health (NIH) Evidence Report: Evidence-based Management of Sickle Cell Disease

While this report focused on SCD, the authors did address the current status of SCT as a treatment for SCD (NIH/NHLBI, 2014). An expert panel was convened in 2009 to perform an evidence-based review of SCD and write clinical guidelines. The most recent literature search of numerous databases including MEDLINE, Embase, and Cochrane was conducted in July, 2014. Evidence-based recommendations from numerous other entities including USPSTF and WHO were also included. The focus was on randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm or when rare complications were expected to be reported. The GRADE framework was used. There was a public comment period; over 1300 public comments were submitted and reviewed.

The authors stated that "there is hope for a cure using hematopoietic stem cell transplantation (HSCT). However, at present, the procedure is infrequently performed and very expensive. Additional research regarding patient and donor selection and the specific transplantation procedure is required before this potentially curative therapy will become more widely available." In addition, "unfortunately, most people with SCD are either too old for a transplant or don't have a relative who is a good enough genetic match for them to act as a donor. A well-matched donor is needed to have the best chance for a successful transplant."

In conclusion, the authors noted that the "process of developing guidelines for the management of persons with SCD has been challenging, as high quality evidence is limited in virtually every area related to SCD management. The systematic review of the literature identified a very small number of RCTs in individuals with SCD (for example, only three evaluating hydroxyurea, one of the most promising treatments), clearly demonstrating the extensive knowledge gaps in SCD and care of individuals with SCD."

"Cure is always the most desirable outcome for any chronic disease. Therefore, research that increases the evidence for and availability of a cure for SCD is a high priority. Hematopoietic stem cell transplantation (HSCT, formerly called bone marrow transplantation) is a treatment option for an increasing but still small number of people with SCD. The procedure involves "conditioning" therapy, utilizing myelosuppressive and/or immune-modifying drugs, followed by infusion of histocompatible stem cells (derived from bone marrow, peripheral blood, or umbilical cord blood). Substantial risks are involved with the procedure, and it is not yet feasible in the majority of people with SCD. Although clinical trials have provided promising results, and cure appears to be possible in a large proportion of patients receiving HSCT, additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HSCT can become a widely used therapy."

6. Professional Society Recommendations / Consensus Statements / Other Expert Opinions

MULTIPLE MYELOMA

During our review of the medical literature and the internet, other than the formal NCD reconsideration request from ASMBT, CMS did not find/receive any professional society position statements, consensus statements, or other expert opinions for the decision.

American Society for Blood and Marrow Transplantation (ASBMT)

In Majhail et al. (2015), the ASBMT presented a table of indications for autologous and allogeneic hematopoietic cell transplantation and a list of citations from the medical literature. The results of an analysis of these citations were not presented. For sensitive relapse as well as refractory multiple myeloma patients, alloSCT is considered the standard of care and clinical evidence is available. They also note that in initial response patients with multiple myeloma alloSCT is a promising treatment option.

MYELOFIBROSIS

During our review of the medical literature and the internet, other than the formal NCD reconsideration request from ASMBT, one professional society position statement/consensus statement was found that exclusively focused on MF or the use of alloSCT for the treatment of MF (European LeukemiaNet). During the second public comment period, one public commenter mentioned an article that was published since our search of the medical literature was performed (ASBMT).

European LeukemiaNet (ELN)

In 2011 the ELN reviewed the critical concepts of myeloproliferative neoplasms and published its findings as well as clinical management recommendations (Barbui et al., 2011). For primary MF (secondary MF was not addressed in the document), the authors noted that the "main goals of therapy in PMF are prolongation of survival, and, if possible, also cure, which is currently only achieved by allogeneic stem-cell transplantation (alloSCT). If prolongation of survival or cure is not possible, symptom-orientated palliation and quality of life are the main goals." Specifically with regards to alloSCT, Barbui et al. (2011) stated that it "is currently the only treatment approach in myelofibrosis that is potentially curative, but it is complicated by relatively high treatment-related mortality and morbidity. The estimated 1-year treatment-related mortality associated with conventional-intensity conditioning alloSCT is approximately 30%, and overall survival is 50%; with reduced-intensity conditioning alloSCT, 5-year median survival is estimated at 45% with a similar incidence of treatment-related and relapse-related death rates. By comparison, in a recent study of transplantation-eligible patients with PMF (high- or intermediate-risk patients, age < 60 year) who did not undergo transplantation, the 1- and 3-year survival rates ranged from 71% to 95% and 55% to 77%,

respectively." The authors concluded that it "is reasonable to justify the risk of alloSCT-related complications in otherwise transplantation-eligible patients whose median survival is expected to be less than 5 years. This would include IPSS high-risk (median survival, approximately 27 months) or intermediate2—risk (median survival, approximately 48 months) patients, as well as patients with either RBC transfusion need (median survival, approximately 20 months) or unfavorable cytogenetic abnormalities (median survival, approximately 40 months). Other additional adverse factors of outcome from alloSCT, including RBC transfusion load, presence of marked splenomegaly, use of a non-HLA-identical sibling donor, increased alloSCT-specific comorbidity index, advanced age, advanced stage of disease, and unrelated donor who is not fully HLA matched, must be considered."

American Society for Blood and Marrow Transplantation (ASBMT)

In Majhail et al. (2015), the ASBMT presented a table of indications for autologous and allogeneic hematopoietic cell transplantation and a list of citations from the medical literature. The results of an analysis of these citations were not presented. For patients with primary (all risk categories) and secondary MF, ASBMT categorized alloSCT as "C," which represents "Standard of Care, Clinical Evidence Available."

SICKLE CELL DISEASE

During our review of the medical literature and the internet, other than the formal NCD reconsideration request from ASMBT, one professional society position statement/consensus statement was found that focused on SCD or the use of SCT for the treatment of SCD (European Blood and Marrow Transplantation). During the second public comment period, one public commenter mentioned an article that was published since our search of the medical literature was performed (ASBMT).

European Blood and Marrow Transplantation (EBMT)

Angelucci et al. (2014) reported the findings of a literature review by and the resultant clinical management recommendations of the EBMT Inborn Error and EBMT Pediatric Working Parties. The EBMT noted in 2011, when a consensus committee was convened, that only a few hundred transplants had been performed for SCD and there was a "lack of consensus about the indications and time point for HSCT in SCD." The authors also noted that "the decision to perform HSCT and the details of transplant management remain principally dependent on data derived from predominantly retrospective investigations and on the clinical expertise of the different transplant centers." The consensus committee was comprised of experts from 18 institutions in eight countries. Sources of literature included PubMed, abstracts from recent international hematology and stem cell transplant meetings, EBMT educational meetings and unpublished data from European SCT centers. Evidence was assessed using the GRADE system.

The authors found that "survival has improved significantly in the last two decades and 94% of children with SCD now survive until the age of 18 years thanks to better surveillance, pneumococcus vaccination, penicillin prophylaxis, and treatment with hydroxyurea. However, mortality is still significant once patients reach adulthood."

"SCD-associated morbidity and mortality in young adults is largely due to as yet unpreventable complications such as priapism, avascular necrosis, chronic pulmonary impairment, hypertension, stroke and recurrent venoocclusive crises."

The consensus committee recommendation that "young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age." Additional recommendations included:

- Unmanipulated bone marrow or unrelated cord blood (whenever available) from matched sibling donors are the recommended stem cell source.
- SCT from unrelated bone marrow or cord blood donors should only be considered in the presence of at least one of the indications suggested by Walters 1996 and should be performed only in the context of controlled trials in experienced centers.
- The gold standard for conditioning in patients with SCD is busulfan, cyclophosphamide and ATG (i.e., myeloablative conditioning).
- RIC regimen should be explored in and confirmed by prospective trials.
- Post-transplantation evaluation and care should be undertaken in cooperation with hematologists experienced in SCD.

The committee concluded that SCT "currently remains the only available curative treatment for hemoglobinopathies. In contrast with some recommendations, our group strongly suggests early transplantation for TM and SCD if a suitable donor is available and if the patient can be treated in an experienced transplantation center. The development of improved supportive care, including transfusion services, chelation therapy and prevention of infectious complications, does not modify this position. However, much more uncertainty applies to the complex challenge of where to place the curative, but potentially lethal, HSCT treatment as an alternative to a medical, noncurative therapy in adults and patients with advanced disease. Transplantation outcomes today are much improved compared with the 1980s and 1990s, with more than 90% of patients surviving transplantation and more than 80% of them being disease-free after having been treated in a number of different centers worldwide, including centers outside industrialized countries. If in the future gene therapy could provide a cure, it needs to demonstrate at least equivalent results in terms of cost/benefit ratio with HSCT, which is today a widely applied, standard practice for the cure of hemoglobinopathies."

American Society for Blood and Marrow Transplantation (ASBMT)

In Majhail et al. (2015), the ASBMT presented a table of indications for autologous and allogeneic hematopoietic cell transplantation and a list of citations from the medical literature. The results of an analysis of these citations were not presented. For patients with SCD (pediatric or adult), ASBMT categorized alloSCT as "C," which represents "Standard of Care, Clinical Evidence Available."

7. Public Comment

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?
NCAId=280&ExpandComments=n&bc=gAAAABAAAgAAAA%3d%3d&.

Initial Comment Period - April 30, 2015 to May 30, 2015

During the initial 30-day public comment period, we received a total of 215 comments, 22 (10%) of which were redacted due to personal health information content. The majority of comments were submitted by beneficiaries or relatives and friends of beneficiaries (60%). We also received comments from physicians (30%), and pediatricians (5%), and other health professionals (5%). Many of these commenters represented a number of health care facilities

including general hospitals (5%), children's hospitals (3%), university-based medical centers (14%), cancer centers (6%), transplant centers (5%), and blood disorder centers (2%). We also received comments from research foundations (4%) such as the Mayo Clinic and the Pediatric Blood Marrow Transplant Consortium, and other professional organizations (3%) including the American Society for Blood and Marrow Transplantation (ASBMT), the American Society for Apheresis (ASFA), the American Society of Hematology (ASH), and the National Marrow Donor Program/Be The Match (NMDP).

All except two of the total comments were in favor of expanding Medicare coverage of HSCT for myelofibrosis and sickle cell disease. In addition, we had comments asking CMS to add multiple myeloma to our NCA. We reviewed the comments in their entirety, including reviewing all referenced literature submitted in part as comments from professional organizations. The commenters were in support of expanding coverage as well as consistent in the substantive issues they represented throughout the comments. In general, they referred to the clinical and financial benefits of HSCT and reflected like concerns related to the currently limited national coverage of HSCT.

Second Comment Period - October 29, 2015 to November 28, 2015

During the second 30-day public comment period, we received a total of 237 comments, 8 (4%) of which were not posted on the web due to personal health information content. Of the remaining 229 public comments, the majority of comments were submitted by patients or relatives and friends of patients (70%). We also received comments from physicians (10%), and other health professionals (3%). Many of these commenters represented a number of health care facilities including general hospitals (4%), children's hospitals (3%), university-based medical centers (10%), cancer centers (4%), transplant centers (8%), and blood disorder centers (2%). We also received comments from research foundations (4%) such as the Cleveland Clinic and the Pediatric Blood Marrow Transplant Consortium, and other professional organizations (4%) including the American Society for Blood and Marrow Transplantation (ASBMT), the American Society for Apheresis (ASFA), the American Society of Hematology (ASH), and the National Marrow Donor Program/Be the Match (NMDP).

Comment: In favor of expanding coverage of HSCT for Medicare beneficiaries with multiple myeloma, myelofibrosis, and sickle cell disease.

Response: CMS appreciates the supportive comments. All of the comments were in favor of our efforts to expand Medicare coverage of HSCT for multiple myeloma, myelofibrosis, and/or sickle cell disease. Specifically, 20% of the comments mentioned all three diseases, while 47% mentioned myelofibrosis only, 7% mentioned sickle cell disease only, and 2% mentioned multiple myeloma only. Less than 2% of the comments supported the proposed coverage decision as was written with the CED requirements of a randomized controlled trial.

Comment: Many commenters suggested expanding coverage for HSCT to other diseases such as all myeloproliferative neoplasms, essential thrombocytopenia, polycythemia vera, as well as breast cancer.

Response: This NCA only addressed the use of HSCT in patients with MM, MF, and SCD. The other suggested diseases are beyond the scope of this NCA and will not be addressed here.

Comment: Many commenters wanted unrestricted coverage without the CED requirement for all patients with these three diseases. They felt that requiring a trial under CED would limit patient access to the treatment.

Response: CMS recognizes the importance of access to therapies. Since there is insufficient evidence from clinical studies that definitely demonstrates that the use of allogeneic stem cell transplants in patients with multiple myeloma, sickle cell disease or myelofibrosis results in a clinically meaningful benefit, CED will provide access while collecting data to ensure that benefits outweigh harms. We have also modified the decision language to be consistent with the CED language in the NCD on allogeneic stem cell transplantation for myelodysplastic syndrome (CAG-00415N).

With respect to the commenters that suggested unrestricted Medicare coverage for all patients, the currently available medical evidence would not support this approach. As for any type of treatment, stem cell transplantation has potential risks as well as potential benefits. There is considerable risk of treatment-related morbidity and mortality with alloSCT. This reality has been acknowledged repeatedly in the published literature by numerous parties in the professional community. The patient restrictions included in our final decision for CED are supported by the medical guidelines and evidence currently available as well as by most of the physician commenters that acknowledged the need for carefully screening patients before stem cell transplantation.

Comment: Many commenters expressed concerns about the proposed CED requirement of a concurrent non-transplanted control arm. They felt that requiring concurrent non-transplanted controls would hinder the ability to enroll patients into a trial.

Response: CMS recognizes that trials with a concurrent non-transplanted control arm may be challenging to accomplish. We have therefore removed the requirement for a "concurrent control arm." However, we believe the required clinical study must include a comparison arm so that conclusions may be made about the benefit of stem cell transplant. Researchers are welcome to propose alternative study designs, such as pre-post designs, and designs that include retrospective controls.

Comment: Some commenters suggested using national clinical registries or databases such as that maintained by the CIBMTR as an alternative to concurrent non-transplanted controlled trials for the CED.

Response: CMS currently has an NCD that specifies CED of stem cell transplantation for myelodysplastic syndrome, and data is being collected by the CIBMTR registry. However, it contains only patients who have received a stem cell transplant and there are no non-transplanted control patients in that registry. CMS believes that a research study that uses data collected by a registry or database can enhance its persuasiveness if it has the following attributes:

- It is a prospectively collected clinical research data base for stem cell transplants that acquires, at minimum, the following standardized data elements:
 - patient health history, such as, (use elements included in stem cell registries)
 - patient health characteristics, such as comorbidities,
 - status of the disease, functional status (using validated methods),
- There is longitudinal follow up. Registry patients would have to be followed for prespecified and well defined outcomes measured using standardized methods including:
 - Overall survival;
 - Quality of life:
 - Disease-related mortality;
 - · Graft vs. host disease (acute and chronic); and
 - Other transplant-related adverse events;

However, using data only from a registry cannot be used for comparative research. A comparator group, as discussed above, should be ascertained.

Comment: Two commenters suggested we follow the FDA's approval process for orphan products to treat rare diseases.

Response: CMS recognizes the FDA has an expedited process to evaluate orphan treatment options for orphan or rare diseases. However, our general NCA process does not take into account whether or not a product or service is for an orphan rare disease. In our final decision we have provided added flexibility for potential CED studies by removing the requirement for a concurrent control arm. However, we believe the required clinical study must include a comparison arm so that conclusions may be made about the benefit of stem cell transplant. Researchers are welcome to propose alternative study designs, such as pre-post designs, and designs that include retrospective controls.

Comment: One commenter suggested revising the proposed CED research questions to include quality of life, performance status, and subsequent hospitalizations as outcome measures.

Response: CMS appreciates this suggestion. Quality of life (QoL) is an important outcome. A number of registries that collect data on transplants patients also uses this outcome. CMS will include QoL as an optional outcome measure in the CED questions. These CED questions incorporate performance status; and subsequent hospitalizations could be ascertained by researchers from Medicare claims.

Comment: Two commenters suggested we include gene expression profiling as one of the metrics required to qualify a patient as high risk for multiple myeloma.

Response: CMS appreciates this suggestion. When considering the use of genetic biomarkers for diagnostic purposes, CMS uses the ACCE model process as a standard. Not only must analytic validity and clinical validity be demonstrated, but also clinical utility. The use of such tests is beyond the scope of this NCD, but could be possibly addressed in a future NCD.

Comment: Another commenter requested we reconsider our current non-coverage decision of tandem HSCT for multiple myeloma.

Response: This NCA is only considering new allogeneic HSCT for MM, MF, and SCD. Tandem HSCT is beyond the scope of this NCA.

Comment: Some commenters submitted references for consideration.

Response: CMS appreciates the submitted references. Most of them were already considered during the initial analysis. Two new references are added to our final analysis (Majhail NS et al., 2015; and Kröger N et al., 2015).

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Social Security Act.

In addition to § 1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

- (a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
- (1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]

Section 1142 of the Act describes the authority of the Agency for Healthcare Research and Quality (AHRQ) to conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage diseases, disorders, and other health conditions. That section includes a requirement that the Secretary assure that AHRQ research priorities under Section 1142 appropriately reflect the needs and priorities of the Medicare program.

CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. In making coverage decisions involving CED, CMS decides after a formal review of the medical literature to cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary. (See <u>Guidance for the Public, Industry, and CMS Staff Coverage with Evidence Development Document, November 20, 2014</u>).

CMS expects that results of all CED approved studies under 1862(a)(1)(E) will be analyzed and published in peer reviewed clinical journals. CMS has used and will continue to use the results of published CED studies to inform new or revised coverage decisions.

This section of the decision memorandum provides an analysis of the evidence we considered during our review.

MULTIPLE MYELOMA

This section provides an analysis of the evidence we considered during our review to answer to the following question:

Is the evidence sufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with multiple myeloma?

Another question that Medicare is interested in answering is whether or not the evidence is generalizable to the Medicare population.

Meta-Analyses / Systematic Reviews for Multiple Myeloma

Specific criteria, including search terms, were used in accessing studies to assess multiple myeloma and the use of allogeneic HSCT. Based on that

schema the medical literature failed to reveal any randomized clinical trials evaluating the sole use of allogeneic HSCT compared to other forms of transplant or treatment. Though there were a number of case studies found, this particular research design (case studies) does not carry the same evidentiary weight compared to other more credible research designs. The literature did reveal two meta-analyses using prospective studies (Armeson et al., 2013; Kharfan-Dabaja et al., 2013). They evaluated auto-auto HSCT compared to auto-allo HSCT. The later meta-analysis was performed due to concerns related to the quality of the studies chosen in the first meta-analysis study. One limitation noted in both meta-analyses was the small number of studies included in each meta-analysis. Other limitations noted in both studies were heterogeneity amongst studies (no attempt was made to adjust for this), as well as inclusion/exclusion bias. Both studies came to the same conclusion - no improvement in overall survival with auto-allo HSCT.

During the second comment period we received an article that was not previously reviewed. This article addresses stem cell transplant guidelines for multiple myeloma (Shah et al., 2015). The authors note that the role allo-HCT in MM remains controversial and poorly defined, and that although complete response rates are higher for allo-HCT, so are the rates of treatment-related mortality. They conclude that a consistent progression free survival or overall survival benefit for allo-HCT cannot be demonstrated. The authors also point out that the parameters chosen, including research design, eligibility, pretransplantation induction therapy, use of total body irradiation in the conditioning regimen, use of anti-thymoglobulin, and graft-versus-host disease (GVHD) prophylaxis were highly variable between studies.

Discussion for Multiple Myeloma

Multiple myeloma is a cancerous condition that predominantly affects the elderly population. Treatment options are limited. Though allogeneic HSCT has been used to treat this condition, evidence is lacking that it results in disease cure. Studies have failed to reveal that patients undergoing this treatment have increased survival compared to patients who have not undergone this form of treatment.

A review of the medical literature failed to reveal any randomized clinical trials, though prospective as well as case series studies have been performed. A number of meta-analysis based on prospective studies have failed to show any benefit from the use of allogeneic HSCT for this population. A number of guidelines have addressed the use of this treatment in patients with MM. One common feature of the medical guidelines is the suggestion that allogeneic HSCT should take place in a clinical trial setting. Based on this limited evidence, we are not able to find that allogeneic HSCT is reasonable and necessary to treat multiple myeloma under section 1862(a)(1)(A) of the Social Security Act.

The public comments suggest that a number of large national commercial insurers reimburse coverage of allogeneic HSCT for MM, but it must be noted that their decision to cover this procedure is based on their respective policies, population cohorts, and business models, rather than on the legal requirements set forth in title XVIII of the Social Security Act.

There are a number of evidence gaps and questions that exist when discussing the use of allogeneic HSCT for MM in the Medicare population, for example:

- What patient characteristics are prognostic of good outcomes?
- Does treatment vary depending on the risk level based on ISS, Durie-Salmon or IMWG classifications?
- Could allogeneic HSCT in combination with other treatment options provide the best outcomes?

Some of these gaps could be addressed through the use of a longitudinal prospective controlled study. Additionally, there currently exist national registries that collect data on transplant procedures, including patients receiving allogeneic HSCT for MM.

CMS notes that the opportunity to decrease morbidity and mortality for Medicare beneficiaries as well as to address knowledge gaps is enhanced by the Stem Cell Therapeutic Outcomes Database (SCTOD) registry administered through contract by the Health Resources and Services Administration (HRSA), which provides a mechanism for collection of evidence. As integrated national registries, such as HRSA's SCTOD registry, continue to evolve and advance, we expect that stakeholders using data in this registry will work to facilitate a greater understanding of health outcomes of allogeneic HSCT in patients with multiple myeloma by linking to administrative databases and other national efforts and assessing improvements in health outcomes over time.

Due to the evidence gaps, additional research should be conducted that might narrow or close these gaps, resulting in a definitive answer to the questions that we have posed. We believe Medicare could support this endeavor with CED if there are systematic patient safeguards, including assurances that the technology is only provided to clinically appropriate patients. As noted in the background section, MM is an illness that commonly affects the elderly. Studies have revealed that the median age of onset of disease is 66 years of age. Since this illness does occur within the Medicare population, it is important to find therapeutic options that are effective in this population. However, based on our assessment of the medical literature, this technology has not demonstrated that it is beneficial. Thus, CMS will cover items and services necessary for research under § 1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with multiple myeloma (MM) using the Coverage with Evidence Development (CED) paradigm.

Disparities for Multiple Myeloma

There are a limited number of studies evaluating the use of allogeneic HSCT for MM in the Medicare population. Though age, race, and gender were common parameters used in the assessment of allogeneic HSCT in patients with MM, there was little additional information provided about other demographic features in this population, including socioeconomic status, ethnicity, religion, sexual orientation, special needs population, education status, comorbidities, etc. Because of these evidence gaps Medicare believes that trial designers should consider them when proposing future clinical study protocols.

Summary for Multiple Myeloma

Based on the above discussion, CMS found that the evidence is not adequate to conclude that alloSCT improves health outcomes for Medicare beneficiaries with MM. We believe that in the absence of overwhelming risk the chance for cure/benefit in this patient population with a disease that can cause significant morbidity and mortality is an important consideration for patients. We believe that CMS should support evidence development for therapies that are likely to show benefit for the Medicare population, but where the available evidence does not support coverage outside the context of a clinical study, which may be the case for therapies, new technologies, or for existing technologies for which the evidence is insufficient.

Coverage in the context of ongoing clinical research protocols or with additional data collection can expedite earlier beneficiary access to treatments or technology while ensuring that systematic patient safeguards, including assurance that the treatment or technology is provided to clinically appropriate patients, are in place to reduce the risks inherent to new technologies, or to new applications of existing treatments or older technologies.

Therefore, we will require that any Medicare approved clinical study under CED control for selection bias and potential confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS staging, Durie-Salmon staging, comorbid conditions,

type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

MYELOFIBROSIS

Our review sought an answer to the following question:

Is the evidence sufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with MF?

We found eight clinical studies that met our criteria. Of these eight, six were uncontrolled, retrospective analyses (Kerbauy et al., 2007; Patriarca et al., 2008; Robin et al., 2011; Ballen et al., 2012; Gupta et al., 2014; Lussana et al., 2014). Two clinical studies had a prospective but still uncontrolled design (Kroger et al., 2009; Rondelli et al., 2014). After the second public comment period, another retrospective analysis that met our criteria was added (Kroger et al., 2015).

Retrospective Clinical Studies for Myelofibrosis

Kerbauy et al. (2007) retrospectively analyzed data from 104 patients with primary or secondary MF who underwent alloSCT in Seattle, Washington (timespan not reported). The authors used a decent sample size and duration of follow-up (median, 5.3 years) but the median age of the patients (49 years) was younger than the typical Medicare beneficiary. Also, there was variation in the prognostic score; approximately half of the patients had an intermediate or high Dupriez score while the remaining patients had a low Dupriez score. There was variation in the components of the alloSCT regimens as well. Roughly half of the patients received a related donor transplant and the other half received an unrelated donor transplant. Similarly, approximately half of patients received peripheral blood stem cells while the remaining patients received stem cells from the bone marrow. Variation was also seen with the specific drugs used in the conditioning protocol. The authors found a nonrelapse mortality rate at five years of 34%. The estimated probability of survival at seven years was 61%. Sixty-four percent of patients developed grade II - IV acute GVHD and 84% developed chronic GVHD (59% extensive).

Patriarca et al. (2008) performed a retrospective analysis of data from the Italian GITMO registry for the time span of 1986 to 2006. The majority (82%) of patients had primary MF. This analysis also had a decent sample size but suffered from the same limitations found with a retrospective study design as described for Kerbauy 2007. The authors noted the limitations to their study. These limitations included "the heterogeneity of the patients' clinical features," the retrospective nature of the study design, the multicenter nature of the registry (especially where the majority of centers contributed only one or two patients to the registry and the 20-year period of the registry (where "policies and strategies for transplantation in myelofibrosis have changed"). Transplant-related mortality at one year was 35% and at three years was 43%. The estimated overall survival was 42% at three years and 31% at five years. The three-year relapse-free survival was 35%. During multivariate regression analysis, a statistically-significant increase in the hazard ratio for transplant-related mortality was seen with donor source (i.e., the hazard ratio increased with unrelated or mismatched donors); a statistically-significant decrease in the hazard ratio for transplant-related mortality was seen over the timespan of alloSCT (i.e., the hazard ratio decreased over the timespan from pre-2001 to post-2001). By day 100 after alloSCT, 41% developed grade II to IV acute GVHD and 43% developed chronic GVHD at two years.

Robin et al. (2008) performed a retrospective analysis of data on 147 patients from 27 centers in the French SFGM-TC registry. The timespan was 1997 and 2008. The median age was 56 years for the 101 patients who received RIC; 60% had an intermediate or high Lille score and 23% had AML. The median age was 47 years for patients who received myeloablative conditioning; 61% had an intermediate or high Lille score and 10% had AML. Once again, the treatment regimen varied significantly from patient to patient and from group to group. Median follow-up was 35 months. The nonrelapse mortality at four years was 39%. The overall survival at four years was 58%, 46% and 26% for patients with low, intermediate, or high risk Lille scores including AML, respectively. Progression-free survival at four years was 32%. Forty-three percent of patients developed grades II - IV acute GVHD at 100 days and the four-year cumulative incidence of chronic GVHD was 39%.

Ballen et al. (2012) performed a retrospective analysis of CIBMTR registry data on 289 patients with primary MF who were transplanted in 29 countries between 1989 and 2002. The number of patients 46 years or older comprised roughly one-half of the total sample size studied. Lille scores were evenly distributed across the low, intermediate, and high categories. Most patients received a transplant of bone marrow-sourced stem cells and myeloablative conditioning but a variety of myeloablative regimens was used. Outcomes were reported by donor transplant group. Treatment-related mortality at one-year was 27% for HLA-matched sibling donor transplants and 43% for unrelated donor transplants. Treatment-related mortality at five-years was 35% for HLA-matched sibling donor transplants and 50% for unrelated donor transplants. Overall survival at five-years was 37% for HLA-matched sibling donor transplants and 30% for unrelated donor transplants. Disease-free survival at one-year was 48% for HLA-matched sibling donor transplants. Disease-free survival at one-year was 48% for HLA-matched sibling donor transplants. Disease-free survival at five-years was 37% for unrelated donor transplants and 27% for unrelated donor transplants. Disease-free survival at one-year was 48% for HLA-matched sibling donor transplants and 27% for unrelated donor transplants.

Multivariate analysis did not indicate a difference in disease-free survival based on Lille score in the HLA-matched and unrelated donor groups. The authors acknowledged the limitations of using a retrospective study design by stating that the "analysis was hampered by its retrospective nature and included patients treated in many transplant centers with a variety of conditioning regimens. The majority of patients received MA conditioning regimens, and, as expected, had a median age lower than the median age reported for myelofibrosis patients at diagnosis." In addition, the authors stated that due to "missing data, Cervantes and Dupriez scores could not be used in a multivariate analysis." Forty-three percent of patients who received a matched sibling transplant, 40% of patients with a URD transplant and 24% of patients with other related donors developed grade II - IV acute GVHD. Forty percent of patients with a matched sibling transplant, 32% of patients with a URD and 23% of patients with other related donors developed chronic GVHD. There was no effect of GVHD on relapse or survival.

Similar to Ballen et al. (2012), Gupta et al. (2014) reported the results of a retrospective analysis of CIBMTR registry data on 233 patients with primary MF in 83 centers. Unlike in Ballen et al. (2012), all of these patients received RIC prior to alloSCT (although various RIC treatment regimens were used) and the timespan was more contemporary (from 1997 to 2010—and nearly identical to the timespan examined by Robin et al. (2011)). The median age was 55 years; 64 patients (27%) were older than 60 years. The use of the DIPSS score also reflects the later timespan for this analysis. Twelve percent of patients had a low DIPSS score, 49% had an intermediate-1 score, 37% had an intermediate-2 score and one percent had a high score. While peripheral blood stem cells were administered to the majority (88%) of patients, the variety of possible stem cell donor types is highlighted by this study: 34% of patients received a matched sibling donor transplant, 45% received a well-matched unrelated donor, 17% received a partially matched unrelated donor and four percent received a mismatched unrelated donor. Median follow-up was 50 months. Nonrelapse mortality at five years was 24%. In a multivariate analysis, donor type was statistically-significantly associated with higher nonrelapse mortality but there was no statistically-significant relationship between nonrelapse mortality and DIPSS score. Overall survival at five years was 47%. Adjusted overall survival at five years was 56% for matched sibling donor, 48% for well-matched unrelated donor and 34% for partially matched/mismatched unrelated donor compared to matched sibling donor, the results for well-matched unrelated donor and for partially matched/mismatched unrelated donor were statistically significant. No statistically donor, the results for well-matched unrelated donor and for partially matched/mismatched unrelated donor. Compared to matched sibling donor, the results for well-matched unrelated donor and for partially matched/mismatched unrelated donor. Progressi

37%. The cumulative incidence of chronic GVHD at five years was 51%.

Lussana et al. (2014) performed a retrospective analysis of EBMT registry data from 250 consecutive patients with secondary MF (77%) or AML who underwent alloSCT between 1994 and 2010 at 89 centers in 20 European countries. Patient characteristics and outcomes generally were not reported separately for patients with secondary MF. The median age was 56 years; 136 patients (54%) were 55 years old or older. The Lille score was not available for 61% of patients. Median follow-up was only 13 months. Nonrelapse mortality at three years was 27%. Compared to patients younger than 55 years, nonrelapse mortality at three years for patients 55 years and older was statistically-significantly higher (35% vs. 20%). Nonrelapse mortality at three years was also statistically-significantly higher for patients who received an unrelated donor transplant compared to a related donor transplant (34% vs. 18%). Overall survival at three years was 62%. Compared to patients younger than 55 years, overall survival at three years for patients 55 years and older was statistically-significantly lower (47% vs. 65%). Twenty-seven percent of patients developed grade II - IV acute GVHD and 60% developed chronic GVHD.

Kroger et al. (2015) performed a retrospective analysis of registry data from two different international databases. Survival was determined for 188 patients with primary MF who received alloSCT in Europe or the US and 255 patients in Europe who received only conventional (but non-JAK inhibitor) treatment. All patients were 65 years of age or younger. Of note, 68% of the patients who received alloSCT had a DIPSS score of intermediate-2 or high, as expected, while only 22% of patients in the conventional treatment group had such a DIPSS score. As noted by the authors, this study also could not address the possibility of selection bias and the possible correlations between time of transplant and patient characteristics. Compared to the conventionally-treated group, the relative risk of death after alloSCT was statistically significantly higher in the low risk primary MF group and statistically significantly lower in the intermediate-2 and high risk primary MF groups.

Prospective Clinical Studies for Myelofibrosis

Kroger et al. (2009) conducted a multicenter, prospective, uncontrolled, Phase II clinical trial from 2002 to 2007 in Germany and the Netherlands. One hundred and three patients with primary or secondary MF, an intermediate-risk or high-risk Lille score or a low-risk Lille score with constitutional symptoms, or a high-risk Cervantes score (the presence of two or three risk factors and aggressive disease) and an age between 18 and 70 years were given RIC and alloSCT using either an HLA-compatible related or unrelated donor. The median age was 55 years. Sixty-one percent of patients had primary MF. Eighty-three percent had an intermediate or high Lille score; 71% had a high Cervantes score but the authors did not report how many patients overlapped between the two scores. The majority of donors were HLA matched (80%). Peripheral blood stem cells were administered in 96% of the transplantations. Nonrelapse mortality at one year was 16%. The five-year overall survival was 67%. In the multivariate analysis, age greater than 55 years and mismatched HLA donor were statistically-significant risk factors for overall survival. The five-year estimated disease-free survival was 51%. In the multivariate analysis, mismatched HLA donor and high-risk Lille score were statistically-significant risk factors for disease-free survival. Twenty-seven percent of transplanted patients developed grade II - IV acute GVHD and 49% developed chronic GVHD.

Rondelli et al. (2014) conducted a multicenter, prospective, uncontrolled, Phase Two clinical trial from 2007 to 2011 in 11 centers in the US, Europe and Canada. Thirty-two patients with primary MF and 34 patients with secondary MF, 18 to 65 years old, an intermediate or high Lille score or a low Lille score with a platelet count < 100 x 10⁹/L but without significant comorbidities were given RIC and alloSCT using either a sibling (sibling group) or unrelated (unrelated group) stem cell donor. The sample size was small especially since the data were analyzed and the results were reported by donor group. The median age was 55 years in the sibling group and 56 years in the unrelated group. The majority of patients (90 - 91%) in the sibling and unrelated groups had a Lille score of one or two. A full-matched HLA donor was transplanted in 94% of the sibling group and in 74% of the unrelated group. Median time of follow-up was 25 months. Seventy-five percent in the sibling group and 32% in the unrelated group were alive. Nonrelapse mortality was 22% in the sibling group and 59% in the unrelated group. A statistically-significantly higher risk of death was observed for patients receiving a transplant from an unrelated donor as compared with a sibling donor. The median overall survival for patients in the sibling group had not been reached while median overall survival for the unrelated donor group (unrelated group) was six months. Similarly, median event-free survival had yet to be achieved in the sibling group and was six months in the unrelated group. Statistical analysis did not find an association between overall survival and the age of patient. Thirty-nine percent of patients developed grade II - IV acute GVHD (38% in the sibling group; 41% in the unrelated group). Thirty-six percent in the sibling group developed chronic GVHD.

Discussion for Myelofibrosis

The retrospective analyses examined data from a wide variety of sources (CIBMTR, French registry, Italian registry) that included patient populations that likely varied clinically due to the long timespans investigated (e.g., 16 years in the Lussana 2014 study), the selection of patients for alloSCT based on a continuously-evolving prognostic scoring system over that time span, the mix of patients with primary MF or secondary MF or AML, and the varying treatment regimens (e.g., conditioning drugs and regimens; stem cell sources; HLA-matched vs. unmatched). A retrospective study design is subject to limitations. Such limitations include variation in treatment protocols (conditioning regimens and stem cell sources) from center to center as well as from patient to patient within a center. In the absence of statistical adjustments, the long timespan of data collection typically analyzed in these studies) can significantly impact the quality of the analysis due to naturally changing alloSCT treatment protocols over time as well as the continual updates over time of the prognostic scores used to define the patient population and select patients for alloSCT. Separate statistical analyses based on subsets of treatment protocols and patient population should be performed. This requires an *a priori* statistical plan, a sufficiently large sample size and access to the actual data generated during a study in order to generate results with confidence. In the absence of a sufficiently large sample size to account for the variation in treatment protocols and patient population, it is difficult to reach confident conclusions about the outcomes of alloSCT. A prospectively-designed study generally can avoid these design issues but can have other critical limitations such as the lack of control group (Kroger et al., 2009) or a small sample size and the lack of a relevant control group (Rondelli et al., 2014).

Overall, for mortality (i.e., treatment-related mortality or nonrelapse mortality) the retrospective analyses reported a range of results including 35% at one year (Patriarca et al., 2008), 27% (Lussana et al., 2014) to 43% (Patriarca et al., 2008) at three years and 24% (Gupta et al., 2014) to 34% (Kerbauy et al., 2007) at five years. In their prospective study, Kroger at al. reported a nonrelapse mortality of 16% at one year.

For overall survival, the results ranged from 42% (Patriarca et al., 2008) to 62% (Lussana et al., 2014) at three years and from 31% (Patriarca et al., 2008) to 47% (Gupta et al., 2014) at five years. The five-year oval survival reported by Kroger et al. (2009) was 67%. The progression-free survival was reported to be 35% at three years (Patriarca et al., 2008) and 27% at five years (Gupta et al., 2014). No evidence regarding QoL was reported.

As judged by the reported median age for these studies, the majority of patients were less than 65 years old. Results of analyses of data from patients older than 65 years generally were not reported separately. This is despite the fact that the median age of patients at diagnosis of MF is 67 years (Ballen et al., 2012) and a number of studies reviewed for this NCA reported outcomes of alloSCT in patients who were given RIC, which is a conditioning regimen typically used in patients who have comorbidities (such as patients 65 years of age or older like Medicare beneficiaries) that until recently have been a contraindication for transplantation. However, one multivariate analysis showed higher nonrelapse mortality and lower overall survival at three years for patients 55 years and older under certain circumstances (Lussana et al., 2014). The prospective study conducted by Kroger et al. (2009) also showed an age greater than 55 years to be a risk factor for overall survival. Overall, the generalizability of the results of these studies to Medicare beneficiaries is low.

Given the limitations of the evidence as noted above, CMS finds the evidence in the published literature to be incomplete, and is not adequate to demonstrate that alloSCT is reasonable and necessary to treat MF under § 1862(a)(1)(A). CMS acknowledges that a number of professional organizations have published recommendations for the clinical management of patients with MF. In its evidence-based guideline for primary and secondary MF, the British Committee for Standards in Haematology noted the lack of randomized controlled trials as well as the limitations of retrospective analyses. Despite the weak strength and moderate quality of evidence available, the Committee's recommendations included RIC-based alloSCT for a patient who is older than 45 years and has an IPSS risk of Intermediate-2 or High provided the patient is otherwise eligible for transplantation and has an HLA-matched sibling or unrelated donor available.

After performing a health technology assessment, EBMT-ESH recently noted that relatively few elderly patients "are candidates for transplant although encouraging results using reduced-intensity conditioning regimens have been recently reported, and offer the possibility of extending the age for consideration of intensive therapy." For adult patients with primary or secondary MF and a Lille intermediate or high prognostic score the EBMT-ESH recommended alloSCT as the "standard of care" for HLA-identical sibling donors and matched, unrelated donors. The use of mismatched donors is considered to be "developmental; should be carried out only at accredited and experienced centres on IRB approved protocols." The use of autologous SCT is considered to be "generally not recommended."

The ELN published clinical management recommendations. The organization recommended that it "is reasonable to justify the risk of alloSCT-related complications in otherwise transplantation-eligible patients whose median survival is expected to be less than 5 years. This would include IPSS high-risk (median survival, approximately 27 months) or intermediate-2—risk (median survival, approximately 48 months) patients, as well as patients with either RBC transfusion need (median survival, approximately 20 months) or unfavorable cytogenetic abnormalities (median survival, approximately 40 months). Other additional adverse factors of outcome from alloSCT, including RBC transfusion load, presence of marked splenomegaly, use of a non-HLA-identical sibling donor, increased alloSCT-specific comorbidity index, advanced age, advanced stage of disease, and unrelated donor who is not fully HLA matched, must be considered."

CMS acknowledges the limited treatment options for patients with MF who have high risk disease or highly symptomatic disease despite maximal conventional therapy. While there is the risk of morbidity and mortality for patients with MF, especially within the higher risk scoring categories and with the transformation to AML, there is also risk of treatment-related morbidity and mortality with alloSCT. A primary concern for CMS is the potential for MR to transform in to AML. Myelofibrosis progresses to AML in approximately 20% of patients (Tefferi et al., 2014) and has a one-year mortality of 9% with a median survival of 2.6 months (Mesa et al., 2005). Of note, Medicare currently covers alloSCT for AML but in the best interests of the beneficiary it is preferable to avoid the morbidity and substantially increased risk of mortality associated with the transformation to AML.

The clinical management of patients with MF is an actively evolving area, especially for prognostic scoring (which will permit better patient selection alloSCT) and for conditioning regimens such as RIC. Given the still-evolving nature of managing patients with MF and in the interest of best serving Medicare beneficiaries, CED is the most appropriate path for Medicare coverage at this time because it will permit the treatment of beneficiaries with MF (i.e., minimize morbidity) while providing systematic patient safeguards that may help to avoid transformation to AML (i.e., minimize substantial increased risk of death). The NCD requestors acknowledge that "more data in the Medicare population is needed."

CMS notes that the opportunity to decrease morbidity and mortality for Medicare beneficiaries as well as to address knowledge gaps is enhanced by the existing Stem Cell Therapeutic Outcomes Database (SCTOD) registry administered through contract by the Health Resources and Services Administration (HRSA), which provides a mechanism for collection of evidence. As integrated national registries, such as HRSA's SCTOD registry, continue to evolve and advance, we expect that stakeholders using data in this registry will work to facilitate a greater understanding of outcomes of allogeneic HSCT in patients with MF by linking to administrative databases and other national efforts and assessing improvements in health outcomes over time

Medicare Patient Population

Tefferi (2014) stated that observation is "generally recommended for asymptomatic patients with a DIPSSplus score of low or intermediate-1" but he also noted "that a higher risk genetic profile in this specific patient population may be a reason to begin therapy instead." On the other hand, Geyer and Mesa (2014) stated that it "remains unclear whether patients who are considered low risk by DIPSS but harbor high-risk molecular features should be managed differently (i.e., earlier choice for allo-SCT)." The British Committee for Standards in Haematology, EBMT-ESH and ELN also slanted their recommendations toward the higher risk profiles (i.e., Intermediate-2 and High) albeit they were referring to an older prognostic scoring system. It is noted that these three organizations also acknowledge the possibility that additional patient (e.g., age) and clinical factors (e.g., transfusion dependence or unfavorable cytogenetic abnormalities) may impact the decision to transplant a patient with a lower prognostic score.

Despite the lack of strong evidence to indicate health outcomes for patients with MF who receive alloSCT, CMS found a general consensus in the professional community for selecting patients for alloSCT based on prognostic score risk profile. Hence, the target Medicare patient population for treatment of MF with alloSCT is limited to Medicare beneficiaries who are considered to be at DIPSS Plus score Intermediate-2 or High risk as determined by the patient's clinical team.

Disparities for Myelofibrosis

Myelofibrosis mostly affects elderly individuals (Cervantes 2014) with a median age at diagnosis of 65 years (Cervantes et al., 1997). According to Lal (2014), primary MF "appears to be more common in white people than individuals of other races. In addition, an increased prevalence rate of the disorder has been noted in Ashkenazi Jews. A slight male preponderance appears to exist for primary myelofibrosis."

Summary for Myelofibrosis

Based on the above discussion, CMS found that the evidence is insufficient to demonstrate that alloSCT improves health outcomes for Medicare beneficiaries with MF. However, we believe that because the evidence suggests a potential chance for cure/benefit in this patient population with a disease that can cause significant morbidity and mortality, it is important to support additional research of this service for Medicare patients using the CED paradigm.

Coverage in the context of ongoing clinical research protocols or with additional data collection can expedite earlier beneficiary access to innovative treatments or technology while ensuring that systematic patient safeguards, including assurance that the treatment or technology is provided to clinically appropriate patients, are in place to reduce the risks inherent to new technologies, or to new applications of existing treatments or older technologies.

For coverage of allogeneic HSCT for myelofibrosis under CED, a clinical study will control for selection bias and potential confounding by age, duration of diagnosis, disease classification (primary or secondary MF), DIPSS plus score, comorbid conditions, type of preparative/conditioning regimen, graft vs.

host disease (GVHD) prophylaxis, donor type and cell source.

SICKLE CELL DISEASE

Our review sought an answer to the following question:

Is the evidence sufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with SCD?

We found four clinical studies that met our criteria (Bernaudin et al., 2007; Panepinto et al., 2007; Locatelli et al., 2013; Dedeken et al., 2014). All of these studies were retrospective, uncontrolled analyses.

Retrospective Clinical Studies for Sickle Cell Disease

CMS found four retrospective clinical studies of reasonable sample size that focused on measuring health outcomes of relevance to Medicare beneficiaries.

Bernaudin et al. (2007) analyzed data from 87 children in France who received an alloSCT in 14 centers during a 16 year timespan (1988 to 2004); the last of which was performed 11 years ago. There was variability in the patient population and treatment regimens due to the long timespan and the constantly evolving state of the practice of transplantation medicine. The lack of a control group for this retrospective analysis was another limitation of the study design. A reasonably long median duration of follow-up of six years with a range of 1.6 - 17.5 years was available. The estimated five-year TRM rate was 6.9%. Overall EFS at five years was 86.1%. At the time the results were published, 81 patients between the ages of six and 28 years were alive. Seventy-nine of these patients had not experienced vaso-occlusive crises or acute chest syndrome episodes and had not received blood transfusions. Twenty percent of patients developed grade II or higher acute GVHD while 2.4% suffered from extensive chronic GVHD.

As with Bernaudin et al. (2007), Panepinto et al. (2007) performed an uncontrolled retrospective analysis of data from an observational database from the CIBMTR. These data were from 67 patients (all children except for three patients were older than 21 years) who received alloSCT during a 13 year timespan (1989 to 2002) in 30 centers worldwide; the last of which was performed 13 years ago. Each center was free to determine patient selection and treatment regimens (although myeloablative conditioning was consistently used and the majority of patients received alloSCT with HLA-matched sibling donor stem cells from bone marrow) hence there was great potential for variability in the treatment regimens and therefore in the data, which may have impacted the results. There were three deaths early after transplantation. The median follow-up of survivors was a useful 61 months. The five-year probability of overall survival was 97%. Fifty-five patients were free of sickle cell symptoms at a median of five years after alloSCT. The probability of five-year disease-free survival was 85%. Two patients developed grade III or IV acute GVHD. The overall probability of acute GVHD at day 100 after transplantation was ten percent. Three patients developed extensive chronic GVHD. The five-year probability of chronic GVHD was 22%.

The uncontrolled retrospective analysis performed by Locatelli et al. (2013) included data from 160 children with SCD from the EUROCORD registry in Europe and the Sibling Donor Cord Blood Program registry in California (for a total of 28 centers). This dataset was a bit more contemporary (1994 - 2005) but still had a long time span (11 years). All patients received HLA-identical family stem cells from either cord blood or bone marrow. The six-year disease-free survival was 92% in the bone marrow group and 90% in the cord blood group.

Dedeken et al. (2014) performed a retrospective analysis of data from children with SCD. However, the timespan was considerably longer than in the previous analyses (25 years), and the total sample size was considerably smaller than in the previous analyses (50) especially since the authors divided the cohort into three groups for analysis due to the clinically-significant changes in the medical management of patients during the 25 year timespan. The resultant sample size for each of the first two groups, which represent alloSCTs that were performed prior to 1991 (group one) and from 1991 to 1995 (group two), was only six. In addition, while each child received myeloablative conditioning and the type of medications given for GVHD prophylaxis was consistent over the timespan, other critical aspects of medical management such as stem cell source and use of seizure prophylaxis varied substantially given the small sample sizes. The lack of a control group was another limitation of the study design that decreased confidence in the results of the analysis. That said, the authors reported an eight-year event-free survival for group three (the group that received the most current medical management and had the largest sample size) of 97.4%. The incidence of acute GVHD was 22% (five patients had grade III or IV). The incidence of chronic GVHD was 20% (none had an extensive form).

Prospective Clinical Studies for Sickle Cell Disease

CMS did not find any prospective clinical studies of reasonable sample size that focused on measuring health outcomes of relevance to Medicare beneficiaries.

Discussion for Sickle Cell Disease

CMS did not find any prospective studies that met our criteria. Hence, this review relied on evidence from the retrospective analysis of observational data. We found four retrospective analyses that met our criteria and subsequently were included in the evidence summary. Of note, these four were selected only after decreasing our criterion for minimum sample size from 100 to 50. We did this upon noticing that most published reports of clinical studies of alloSCT for patients with SCD had a sample size less than 100 and, typically, substantially smaller than 50. We were unable to find a meta-analysis in the published literature.

We believe the most important health outcomes focus on the benefits and risks of the procedure. Accordingly, Medicare was most interested in the transplantation-related benefits such as event-free survival as well as transplantation-related mortality and the transplantation-related morbidity associated with acute and chronic GVHD. All four studies we found reported a high, relatively long-term event- or disease-free survival of 85% to 97%. Panepinto et al. (2007) also reported overall survival at five-years, which was an impressive 97%. Only Bernaudin et al. (2007) reported transplantation-related mortality (6.9% at five years). These findings compare favorably to a ten-year mortality rate of 45% for patients with SCD who are treated with conventional therapies (Steinberg et al., 2010). The four studies reported a ten to 20% rate of acute GVHD and up to a 22% rate of chronic GVHD.

The Medicare population is comprised of beneficiaries who are 65 years and older and beneficiaries who are disabled. According to the 2013 Statistical Supplement of the Medicare and Medicaid Research Review, in 2012 (the latest year that data were available) 50,811,259 people were enrolled in the Medicare program for hospital insurance and/or supplementary medical insurance. Of this total, 83% were 65 years of age or older with or without ESRD and the remaining 17% (8,606,842 people) were disabled with or without ESRD. Within the disabled beneficiary population (with or without ESRD), 2360 people were under 19 years old, 777,191 people were 19 - 34 years old, 3,746,386 people were 35 - 54 years old and 4,080,905 people were 55 - 64 years old. Males comprised 52% (4,482,069 people) of the disabled population with or without ESRD. The racial profile of the disabled population with or without ESRD was: 6,136,379 (71%) White; 1,699,841 (20%) Black; 113,941 (one percent) Asian; 391,966 (five percent) Hispanic; 72,075 (one percent)

North American Native; 139,361 (two percent) Other; and 53,279 (one percent) Unknown.

The evidence we found focused solely on children and a small number of young adults. No evidence was found in people 65 years of age or older, which is not unexpected since patients with SCD rarely live to this age range. The ethnicity of these patients was not provided. The gender of these patients was generally evenly divided. Hence, most of the evidence reviewed has limited generalizability to the majority of the Medicare population but is generalizable to the disabled Medicare population based on age and gender.

CMS notes that the Cochrane Collaboration reached the same general opinion of the evidence. After recently performing a systematic review of the literature, Oringanje et al. (2013) noted the complete lack of randomized or quasi-randomized controlled studies. The authors therefore decided not to state any conclusions. They continued by acknowledging the reports of high event-free survival rates but noted that "this research evidence is currently limited to observational and other less robust studies. Clinicians should therefore inform people with SCD about the uncertainty surrounding this clinical procedure if it is to be used." Finally, the authors stated the need for well-designed prospective RCTs but acknowledged that RCTs for this patient "may be considered unethical. Thus, trials may compare different types of HSCT with one another with subgroup analyses by sickle status, severity of disease, setting and age groups carried out to provide guidance on the optimal HSCT for each individual with SCD."

EBMT published clinical management recommendations regarding alloSCT for patients with SCD after a review of the literature (Angelucci et al., 2014) that also noted the low strength of evidence. At the initiation of their effort in 2011, the EBMT acknowledged the small number of alloSCT that had been performed in patients with SCD, the "lack of consensus about the indications and time point for HSCT in SCD," the predominance of retrospective studies in the published literature and the reliance on the clinical expertise of the different transplant centers. The authors stated that "much more uncertainty applies to the complex challenge of where to place the curative, but potentially lethal, HSCT treatment as an alternative to medical, noncurative therapy in adults and patients with advanced disease." EBMT also recognized that SCD-related morbidity and mortality in young adults was primarily due to unpreventable complications of the disease such as stroke and recurrent vaso-occlusive crisis. After remarking that alloSCT outcomes have improved "compared with the 1980s and 1990s, with more than 90% of patients surviving transplantation and more than 80% of them being disease-free," the authors recommended that "young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age" provided that "the patient can be treated in an experienced transplantation center."

CMS acknowledges the recent, extensive evidence-based report from the NIH/NHLBI (2014), which focused on the management of patients with SCD. The report was based on the findings of a literature search that was last performed in July 2014 as well as on the input from over 1300 public comments. The authors noted the challenge of developing the guideline because "high quality evidence is limited in virtually every area related to SCD management." NIH/NHLBI stated that while "the procedure is infrequently performed," it "is a treatment option for an increasing but still small number of people with SCD." In addition, "substantial risks are involved with the procedure, and it is not yet feasible in the majority of people with SCD. Although clinical trials have provided promising results, and cure appears to be possible in a large proportion of patients receiving HSCT, additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HSCT can become a widely used therapy."

The strength of the evidence for the use of alloSCT in patients with SCD is low. The strength of evidence was significantly, negatively impacted by the lack of prospective studies that met our criteria for review, which resulted in a reliance on retrospective studies. Retrospective studies are well-recognized to suffer from a number of significant limitations that decrease the strength of the evidence including a lack of randomization and lack of controls. The smaller sample size for analysis further decreased the strength of evidence. An additional limitation that decreased the strength of evidence was the substantial variation in the treatment regimens used for transplantation secondary to the long timespans used in the retrospective analyses. We found that the evidence is not sufficient to support coverage of alloSCT in patients with SCD under § 1862(a)(1)(A) of the Social Security Act.

CMS acknowledges the promise of ongoing and future studies regarding the use of alloSCT for patients with SCD. The clinical management, with conventional therapies as well as SCT, of patients with SCD is an active area of research. For example, the Bone Marrow Transplantation in Young Adults with Severe Sickle Cell Disease (STRIDE) Phase II trial is currently recruiting to determine the safety and feasibility of a bone marrow transplant in young adults with severe SCD using RIC (ClinicalTrials.gov, NCT01565616). There are numerous variables to consider in the treatment of SCD and there are many factors to consider when performing alloSCT. Hence, there are still many unanswered questions including such fundamental matters as patient selection for alloSCT, best conditioning regimens (e.g., RIC vs. myeloablative; donor source of stem cells) and the role of and timing of non-SCT therapies.

CMS is keenly aware of the need for successful therapies for patients with SCD, especially children and young adults, who have a disease that can be highly symptomatic and incapacitating despite maximal conventional therapy and can lead to premature death. While there is the risk of morbidity and premature mortality for patients with SCD, there is considerable risk of treatment-related morbidity and mortality with alloSCT. This reality has been acknowledged repeatedly in the published literature by numerous parties in the professional community. However, given the limitations of the evidence as noted above, CMS finds the currently available evidence in the published literature to be weak.

There are numerous knowledge gaps regarding the clinical management of patients with SCD. The NIH/NHLBI (2014) report addresses this reality. The NCD requestors acknowledge that "more data in the Medicare population is needed." Given the gaps in knowledge in and the still-evolving nature of managing patients with SCD and in the interest of best serving Medicare beneficiaries, coverage under the CED paradigm will offer the chance of a cure for a disease that causes premature death.

CMS notes that the opportunity to decrease morbidity and mortality for Medicare beneficiaries as well as to address knowledge gaps is enhanced by the existing Stem Cell Therapeutic Outcomes Database (SCTOD) registry administered through contract by the Health Resources and Services Administration (HRSA), which provides a mechanism for collection of evidence. As integrated national registries, such as HRSA's SCTOD registry, continue to evolve and advance, we expect that stakeholders using data in this registry will work to facilitate a greater understanding of health outcomes of allogeneic HSCT in patients with sickle cell disease by linking to administrative databases and other national efforts and assessing improvements in health outcomes over time.

Medicare Patient Population

One critical knowledge gap concerns the selection of patients for alloSCT. The published clinical literature shows a difference of opinion regarding the most appropriate patients with SCD for alloSCT. In 1996, Walters et al. provided a list of indications for alloSCT for people with SCD including neurological events such as stroke lasting longer than 24 hours, pulmonary complications such as acute chest syndrome with recurrent hospitalizations, recurrent vaso-occlusive pain (more than two episodes per year over several years), renal complications such as sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value), bilateral proliferative retinopathy with major visual impairment in at least one eye, osteonecrosis of multiple joints and/or RBC alloimmunization due to long-term transfusion therapy. These indications clearly represent patients who have severe, symptomatic SCD and are at increased risk for premature death.

Meanwhile, in 2011, Hsieh et al. noted the dilemma that "there has always been difficulty in determining which patients with SCD warrant the potential risks of this technique. Early efforts to develop criteria to distinguish the more severe patients proved difficult in a disorder with chronic, yet mostly manageable complications, punctuated by rarer, more severe, even life-threating complications. There remains a temptation to intervene early when patient status would improve the odds against complications from the conditioning regimen. Alternatively, intervening later when chronic, irreversible disease complications clearly establish the severity of the patient's phenotype limits its application because the conditioning regimen is less likely to be well tolerated."

In their review of the status of alloSCT for patients with SCD and TM, King and Shenoy (2014) noted indications for alloSCT that aligned closely with the Walters, 1996 indications and updated to account for the newer donor sources of stems cells available today. Also in 2014, Elmariah et al. noted that "SCD patients are now living long enough that many patients, families, and physicians might not wish to incur further risk in order to obtain a chance at cure. Thus, in order to give patients and physicians the opportunity to make informed decisions, more detailed data are needed to identify truly favorable and unfavorable phenotypic traits and thus help better identify individualized treatment options for patients with this disease." The authors examined factors associated with survival in adults with SCD and found that "elevated white blood count, lower estimated glomerular filtration rate, proteinuria, frequency of pain crisis, pulmonary hypertension, cerebrovascular event, seizures, stroke, sVCAM-1 and short-acting narcotics use were significantly associated with decreased survival."

On the other hand and also in 2014, Angelucci et al. (writing for the EBMT) suggested a more liberal application of alloSCT for SCD by recommending that alloSCT be performed as early as possible if a suitable donor is available and if the patient is treated in an experienced transplantation center, while acknowledging the uncertainty and complex challenges associated with performing alloSCT.

Given the lack of a clear consensus regarding which patients should be selected for alloSCT, CMS believes the target Medicare patient population for treatment of SCD with alloSCT should be limited to Medicare beneficiaries with severe, symptomatic SCD who meet the criteria originally outlined by Walters, 1996 and updated by King and Shenoy, 2014.

Disparities for Sickle Cell Disease

Sickle cell disease was most commonly considered a disease of childhood with an average lifespan of 14 years however today in the US the life expectancy is 40 - 60 years (NIH/NHLBI, 2015). Most people with SCD are of African ancestry or identify themselves as black (NIH/NHLBI, 2015). There are also many people of Middle Eastern, Hispanic, southern European, Central American and Asian Indian descent with SCD (NIH/NHLBI, 2014).

Summary for Sickle Cell Disease

Based on the above discussion, CMS found that the evidence is insufficient to determine that alloSCT improves health outcomes for Medicare beneficiaries with SCD. However, we believe that because the evidence suggests a potential chance for cure/benefit in this patient population with a disease that can cause significant morbidity and mortality is an important to support additional research on this service for Medicare patients using the CED paradigm.

Coverage in the context of ongoing clinical research protocols or with additional data collection can expedite earlier beneficiary access to innovative treatments or technology. Further, coverage in this context ensures that systematic patient safeguards, including assurance that the treatment or technology is provided to clinically appropriate patients, are in place to reduce the risks inherent to new technologies, or to new applications of existing treatments or older technologies.

Overall Summary

CMS has reviewed all the comments submitted during the initial as well as the second comment period, and would like to thank those who contributed for their input. There were a few new articles submitted, but the evidence in these articles did not completely fulfill the overall need for additional supportive data to show improvements in health outcomes. One addressed the use of allogeneic HSCT in patients with multiple myeloma. A second article looked at its impact on patients with myelofibrosis. In both studies the authors noted that the use of allogeneic HSCT afforded no advantage over conventional treatment. They also noted limitations of the studies. During the last comment period we also received a guideline created by the ASBMT/NMDP that addresses patients with multiple myeloma, myelofibrosis, and sickle cell disease. The information provided a list of indications and citations; but the authors did not provide an analysis of the citations to support the indications.

These three new sources of information, though interesting, do not provide sufficient evidence to demonstrate that allogeneic HSCT improves health outcomes in Medicare beneficiaries with multiple myeloma, myelofibrosis or sickle cell disease. During this comment period we also received information about our proposed research design. A number of responders, for ethical or practical reasons, felt that using concurrent controls was not appropriate. We have listened to your concerns and have modified the research design. With appropriate statistical methods, a prospective clinical study should be sufficient to demonstrate benefits of allogeneic HSCT in the target population. The studies can use a variety of data sources such as registries, administrative data derived from claims, or a study design using alternative control groups. The additional evidence, professional society statements and public comments did provide support to remove the requirement for concurrent non-transplanted controls. We have modified the decision language to be consistent with the CED language in our other NCD on allogeneic stem cell transplantation for myelodysplastic syndrome (CAG-00415N) and between multiple myeloma, myelofibrosis and sickle cell disease. We also modified the outcomes of the CED study to be the same for all three conditions for adverse events and added quality of life (optional). Graft versus host disease is an important transplant related adverse event to mention specifically and myeloma specific survival will be considered in overall survival to make data collection easier and to reduce burden and confusion of participating registry entities that may choose to study stem cell transplantation for all three conditions. Quality of life is important but we recognize that some eligible ongoing studies may not have included this outcome in their current operational protocols.

Based on the totality of the information reviewed, CMS will cover allogeneic HSCT in patients with multiple myeloma, myelofibrosis and sickle cell disease under the CED paradigm.

IX. Conclusion

The Centers for Medicare & Medicaid Services (CMS) will modify our existing National Coverage Determinations Manual to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for three separate medical conditions:

- Multiple Myeloma
- Myelofibrosis, and
- Sickle Cell Disease.

MULTIPLE MYELOMA

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with multiple myeloma (MM) using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for multiple myeloma will be covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma who are participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS staging, Durie-Salmon staging, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

MYELOFIBROSIS

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with myelofibrosis (MF) using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for myelofibrosis will be covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. All Medicare approved studies must use appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for myelofibrosis pursuant to Coverage with Evidence Development (CED) must address the following question:

Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with MF who receive allogeneic HSCT have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- · Overall survival; and
- Quality of life (optional).

SICKLE CELL DISEASE

CMS will cover items and services necessary for research under §1862(a)(1)(E) for allogeneic HSCT for certain Medicare beneficiaries with Sickle Cell Disease using the Coverage with Evidence Development (CED) paradigm. We are finalizing the following decision:

Allogeneic HSCT for sickle cell disease (SCD) will be covered by Medicare only for beneficiaries with severe, symptomatic sickle cell disease who participate in an approved prospective clinical study. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage of allogeneic HSCT for sickle cell disease pursuant to Coverage with Evidence Development (CED) must address the following question:

Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with SCD who receive allogeneic HSCT have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

All CMS-approved clinical studies and registries regarding allogeneic HSCT for the treatment of multiple myeloma, myelofibrosis, or sickle cell disease, must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
- b. The rationale for the study is well supported by available scientific and medical evidence.
- c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
- d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
- e. The study is sponsored by an organization or individual capable of completing it successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.

- g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
- h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
- i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
- I. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

We are finalizing changes to expand national coverage for allogeneic hematopoietic stem cell transplantation (HSCT) for these three separate medical conditions. See Appendix B for the manual language.

APPENDIX A

General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to that group patients were assigned (intervention or control). This is important
 especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived
 outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is to the extent that differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of that have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials Non-randomized controlled trials Prospective cohort studies Retrospective case control studies Cross-sectional studies Surveillance studies (e. g., using registries or surveys) Consecutive case series Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in that confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to that the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

<u>APPENDIX B</u>

Medicare National Coverage Determinations Manual

Draft

This information is representative of Medicare's national coverage determination (NCD) for implementation purposes only. The information is subject to formal revisions and formatting changes prior to the release of the final NCD contractor instructions and publication in the Medicare National Coverage Determinations Manual.

Table of Contents

(Rev.)

110.23 - Stem Cell Transplantation (Formerly 110.8.1) (Various Effective Dates Below) (Rev.)

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by

which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

B. Nationally Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary.
- b) Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
- c) Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patients in the United States by the Center for International Blood and Marrow Transplant Research. The elements in this dataset, comprised of two mandatory forms plus one additional form, encompass the information we require for a study under CED.

A prospective clinical study seeking Medicare payment for treating a beneficiary with allogeneic HSCT for MDS pursuant to CED must meet one or more aspects of the following questions:

- 1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes as indicated by:
 - Relapse-free mortality,
 - o progression free survival,
 - o relapse, and
 - overall survival?
- 2. Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do International Prognostic Scoring System (IPSS) scores, patient age, cytopenias, and comorbidities predict the following outcomes:
 - Relapse-free mortality,
 - o progression free survival,
 - o relapse, and
 - o overall survival?
- 3. Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:
 - Relapse-free mortality,
 - o progression free survival,
 - relapse, and
 - o overall survival?

In addition, the clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
- g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the ClinicalTrials.gov Web site by the principal sponsor/investigator prior to the enrollment of the first study subject.
- k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than 3 years after the end of data collection.
- I. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, the Agency for Health Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The clinical research study should also have the following features:

- It should be a prospective, longitudinal study with clinical information from the period before HSCT and short- and long-term follow-up information.
- Outcomes should be measured and compared among pre-specified subgroups within the cohort.
- The study should be powered to make inferences in subgroup analyses.
- Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

Patient selection:

- Patient Age at diagnosis of MDS and at transplantation
- Date of onset of MDS
- Disease classification (specific MDS subtype at diagnosis prior to preparative/conditioning regimen using World Health Organization (WHO) classifications). Include presence/absence of refractory cytopenias
- Comorbid conditions
- IPSS score (and WHO-adapted Prognostic Scoring System (WPSS) score, if applicable) at diagnosis and prior to transplantation
- Score immediately prior to transplantation and one year post-transplantation
- Disease assessment at diagnosis at start of preparative regimen and last assessment prior to preparative regimen Subtype of MDS (refractory anemia with or without blasts, degree of blasts, etc.)
- Type of preparative/conditioning regimen administered (myeloabalative, non-myeloablative, reduced-intensity conditioning)
- Donor type
- Cell Source

Facilities must submit the required transplant essential data to the Stem Cell Therapeutics Outcomes Database.

d) Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma, and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

Compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:

- · Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population as listed in section g.

e)Effective for claims with dates of service on or after, allogeneic HSCT for myelofibrosis (MF) is covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for myelofibrosis pursuant to Coverage with Evidence Development (CED) must address the following question:

Compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with MF who receive allogeneic HSCT transplantation have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population as listed in section g.

f)Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study. There must be appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for sickle cell disease pursuant to Coverage with Evidence Development (CED) must address the following question:

Compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with SCD who receive allogeneic HSCT have improved outcomes as indicated by:

- · Graft vs. host disease (acute and chronic),
- Other transplant-related adverse events;
- Overall survival; and
- Quality of life (optional).

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population

listed in section a:

g)All CMS-approved clinical studies and registries in sections d, e and f must adhere to the below listed standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
- b. The rationale for the study is well supported by available scientific and medical evidence.
- c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
- d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
- e. The study is sponsored by an organization or individual capable of completing it successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
- g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
- h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
- i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
- I. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

II. Autologous Stem Cell Transplantation (AuSCT)

- a) Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:
- 1. Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- 2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- 3. Recurrent or refractory neuroblastoma; or,
- 4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.
- b) Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial
 response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration,
 sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function.
- c) Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.

C. Nationally Non-Covered Indications

I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Effective for claims with dates of service on or after May 24, 1996, through January 27, 2016, allogeneic HSCT is not covered as treatment for multiple myeloma.

II. Autologous Stem Cell Transplantation (AuSCT)

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- a. Acute leukemia not in remission;
- b. Chronic granulocytic leukemia;
- c. Solid tumors (other than neuroblastoma);
- d. Up to October 1, 2000, multiple myeloma;
- e. Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- f. Effective October 1, 2000, non primary AL amyloidosis; and,
- g. Effective October 1, 2000, through March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.

D. Other

All other indications for stem cell transplantation not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2016)

APPENDIX C Application Instructions for CED Study Proposal

Background on Coverage with Evidence Development (CED): CED allows coverage of certain items or services where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. Medicare coverage may be extended to patients enrolled in a clinical research study. In this case, the research is conducted under section 1862(a)(1)(E) of the Social Security Act, which authorizes Medicare coverage for certain studies supported by AHRQ.CED allows us to provide coverage for an item or service because it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.

CED projects provide the necessary new evidence to influence clinical practice and help Medicare beneficiaries and providers make more informed diagnostic and therapeutic decisions. CMS may use the evidence in a National Coverage Determination (NCD) reconsideration to determine if a change in Medicare coverage is appropriate under section 1862(a)(1)(A).

Instructions for Submitting CED Study Proposals:

Please complete the "Required Information" and "NCD/CED Coverage Requirements" sections listed below and submit to CMS for review (see email and mailing addresses below). Electronic submissions are preferable.

After preliminary review of the application (and any attached documentation) CMS will electronically notify the principal investigator (or the designated contact person) that we have received the application with all required information. Alternatively, we will request further information about an application with incomplete items.

The information provided in the sections on the following pages pertains to clinical research studies which intend to qualify for CED as specified in the NCD on Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease), CAG-00444R, issued in final form on January 27, 2016, by CMS, and available at http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=280.

If the information provided fulfills these NCD requirements as judged by CMS, then allogeneic hematopoietic stem cell transplantation (HSCT) for multiple myeloma, myelofibrosis, or sickle cell disease, as required by the study may be reimbursable for study participants who are Medicare beneficiaries, pursuant to §1862(a)(1)(E) of the Social Security Act. If CMS approves the study, we will provide billing instructions for Medicare reimbursement of allogeneic HSCT for multiple myeloma, myelofibrosis, or sickle cell disease under CED.

Generally, within 90 days of receipt of a completed application, we will send the results of CMS' review of the application. There are three possible outcomes of the review process: accept, revise, and reject. If we request a revision, the applicant should submit the revision within 30 days of notification. CMS will review the revised application and notify the applicant of our final decision generally within 30 days of receipt of the revised application.

REQUIRED INFORMATION

- 1. Date of submission
- 2. Descriptive title
- 3. Contact information:
 - Name and title of principal investigator (PI)
 - Name and title of contact person if other than the PI
 - PI's (or contact person's) mailing address, telephone number, fax, and email address
 - Institutional or organizational affiliation
 - Study sponsor(s)

NCD/CED COVERAGE REQUIREMENTS

CMS will review and evaluate the protocol to ensure that the proposed study protocol meets the following requirements.

1. Study population: qualifications for study

The protocol should describe the criteria for Medicare beneficiaries to be included and excluded from the study.

2. Evaluation of outcomes

The protocol should define each outcome to be studied and explain method(s) and timing(s) of outcome assessment(s). The description should include expected length of follow up for participants. The study sample size and duration should allow for reliable estimate(s) of all outcome endpoints.

At minimum, the outcomes to be studied for the chosen indication must include the following for the study to be eligible for coverage:

- a. <u>Multiple Myeloma</u> Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:
 - Graft vs. host disease (acute and chronic);
 - Other transplant-related adverse events;
 - Overall survival: and
 - Quality of life (optional).
- b. Myelofibrosis (MF) Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with MF who receive allogeneic HSCT transplantation have improved outcomes as indicated by:
 - Graft vs. host disease (acute and chronic);
 - Other transplant-related adverse events;
 - Overall survival; and
 - Quality of life (optional).
- c. <u>Sickle Cell Disease (SCD)</u> Prospectively, compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with SCD who receive allogeneic HSCT have improved outcomes as indicated by:
 - Graft vs. host disease (acute and chronic);
 - Other transplant-related adverse events;
 - Overall survival; and
 - Quality of life (optional).
- 3. Standards of scientific integrity and relevance to the Medicare population

Note: Please include a specific reference to the page or pages in your application with your response to the following:

- a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
 - Describe how you will measure the outcomes listed in the NCD.
- b. The rationale for the study is well supported by available scientific and medical evidence.
 - Provide a brief review of pertinent published research that support your study hypotheses and methods.
- c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
 - Justify that your study adds to existing evidence.
- d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.

The response to this standard should contain the following:

- Introduction
- Hypotheses to be tested
- Specific aims
- Background and significance
- Trial design
- Target population and recruitment target
- Inclusion/exclusion criteria
- Power calculations
- e. The study is sponsored by an organization or individual capable of completing it successfully.
 - Provide CVs of investigators with a description of their contribution to the project.
 - Describe the capabilities of the study sites.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
 - Provide IRB approval letters from an IRB that is in compliance with 21 CFR Parts 50 and 56 for each site. Approvals should be updated before study initiation at each site. (Studies will be listed on the CMS website.)
- g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
 - Describe data safety monitoring procedures.
 - Describe stopping rules.
- h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
 - Required of all CED projects
- i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
 - Note: this standard is not relevant to this NCD. No answer required.
- j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
 - Plans to register the study if approved by CMS should be stated. (The ClinicalTrials.gov identifier is required for payment for platelet-richplasma for the treatment of chronic non-healing diabetic, pressure, and/or venous wounds.)

- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
 - Describe your approach to dissemination of the study results.
- I. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary. Address the following:
 - Inclusion and exclusion criteria and how they will affect enrollment.
 - Inclusion of women and minorities.
 - Inclusion of Medicare enrollees.
- m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.
 - Discuss how the methodology addresses the above issues.

Submit the study protocol, "Required Information," and "NCD/CED Coverage Requirements," electronically to: Cheryl.Gilbreath@cms.hhs.gov or hard-copy to:

Tamara Syrek Jensen, JD,
Director, Coverage and Analysis Group
Re: CED for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease) Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

Back to Top

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