September 21, 2009

Tamara S. Syrek Jensen, J.D.
Acting Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244

Re: National Coverage Determination Request – Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

Dear Ms. Syrek Jensen,

This letter, along with the enclosed supporting documentation, is a formal request for a National Coverage Determination (NCD) for allogeneic hematopoietic cell transplantation (HCT) for myelodysplastic syndrome (MDS) in the Medicare population. We believe that the body of evidence supports CMS issuing a coverage policy that ensures Medicare beneficiaries diagnosed with MDS have access to allogeneic HCT.

The services provided to Medicare beneficiaries diagnosed with MDS, and who require a transplant, include, but are not limited to, the statutorily defined benefit categories of inpatient hospital services and the physician services benefit categories (1861(b) and 1861(q), respectively).[1] Medicare patients age 65 and older represent 80 percent of the total population receiving an MDS diagnosis. For a number of these patients, allogeneic HCT is currently the only curative therapy for MDS, and the only treatment available that prevents certain death from this disease.

The National Marrow Donor Program (NMDP), American Society for Blood and Marrow Transplantation (ASBMT), AABB, American Cancer Society (ACS), American Cancer Society Cancer Action Network (ACS CAN), American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), Aplastic Anemia and MDS International Foundation, Blood & Marrow Transplant Information Network, National Bone Marrow Transplant Link, The Bone Marrow Foundation, and The Leukemia & Lymphoma Society submit this NCD request under Development Track #1. In addition, the American College of Physicians and the Intercultural Cancer Council support this NCD request and intend to submit their comments during the initial 30-day comment period provided by CMS following formal acceptance of this NCD request.

The current lack of an established Medicare national policy addressing allogeneic HCT for MDS has created coverage inequities for a small subset of Medicare patients for whom this treatment is the only established curative therapy. Although the National Government Services, Inc. (Medicare Contractor for Part A and B services for New York and Connecticut) recently developed a draft local coverage decision (LCD) for stem cell transplantation that includes MDS and myelofibrosis with myeloid metaplasia as locally covered indications, access to allogeneic HCT is not guaranteed for the majority of Medicare beneficiaries with MDS.[2] Without an explicit and well-defined national policy, hospitals have been reluctant to extend HCT services to

[1] Benefit categories for this request reflect benefit categories for existing NCD for Stem Cell Transplantation (111.8.1).
[2] National Government Services, Inc., Draft LCD for Stem Cell Transplantation (DL30183), http://www.ngsmedicare.com/NGSMedicare/lcd/DL30183_c_lcd.htm.

Medicare beneficiaries that would benefit. An NCD is essential to ensure that all Medicare beneficiaries with MDS receive appropriate and timely access to curative treatment.

For patients currently receiving HCT, established standards ensure a high level of safety and quality for all allogeneic HCT for MDS conducted in the United States. Both the NMDP and the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT (FACT-JACIE) have established provider and facility standards.[3] These established standards will ensure that the appropriately selected Medicare beneficiaries who receive this service will receive care by qualified providers.

Furthermore, federally mandated outcomes data collection efforts for allogeneic HCT for MDS capture data on the Medicare beneficiary population. Per the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129), a standard dataset for all U.S. allograft recipients must be submitted to the Center for International Blood and Marrow Transplant Research (CIBMTR). Through the CIBMTR, a worldwide network of HCT centers currently share data on HCT outcomes and maintain a clinical database with information for more than 280,000 HCT recipients.

In the section below, please find a listing of relevant clinical evidence, data collection capabilities, and facility standards supporting this formal coverage request.[4]

I. Summary of Supporting Documentation

Allogeneic HCT for MDS is the only curative therapy for MDS

MDS refers to a heterogeneous group of acquired bone marrow disorders characterized by dysplastic growth of hematopoietic progenitors and a hypercellular bone marrow with peripheral cytopenia. MDSs are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. Although some patients are asymptomatic, most present with signs or symptoms of anemia accompanied by infection or bleeding. MDS becomes more common as people age; the overall MDS incidence is 3.3 per 100,000, but the incidence in patients over 70 is between 15 and 50 per 100,000.[5] With a median age at presentation of 76 years, MDS patients within the Medicare population require full access to treatment options, including allogeneic HCT.

The only therapy with the potential to cure MDS is allogeneic HCT from either a related or an unrelated donor. There is no evidence of a survival advantage for patients receiving HCT from matched related donors versus unrelated donors.[6] Of the palliative treatment options for MDS -- including hematopoietic growth factors, hemotherapy, iron chelators, thalidomide and lenalidomide, and immune suppressants – chemotherapy has the best 5-year survival rate at 8 percent. The 5-year survival rates for MDS patients receiving allogeneic HCT can range

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[3] Tab D of supporting documentation binder includes both the NMDP Transplant Center Participation Criteria and the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fourth Edition. The basis for FACT or JACIE Accreditation is documented compliance with the current edition of these Standards. Although there are joint FACT-JACIE Standards, FACT and JACIE maintain separate and parallel accreditation processes. In this letter, accreditation is referred to as "FACT-JACIE."

[4] Appendix A includes a listing of all supporting documentation.

[5] Rollison, DE, et al. 2008. Epidemiology of Myelodysplastic Syndromes and Chronic Myeloproliferative Disorders in the United States, 2001-2004. *Blood.* No. 112:45.

[6] Ibid. 139, Table 3.

between 20 and 30 percent. While data on 5-year survival is not available in the 65 and over subset, the data show a 23% survival with a median follow-up of 36 months. These data are consistent with the overall MDS survival data for the same time period.[7]

In 1999, ASBMT began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of HCT. In February 2009, a multidisciplinary panel of experts completed an evaluation of current evidence on allogeneic HCT for MDS.[8] This systematic evidence-based review used specific criteria to search published scientific and medical literature and grade the quality and strength of evidence for allogeneic HCT for MDS. The review includes treatment recommendations based on the available evidence and identifies priority areas for future research in MDS. A main conclusion from the evidence review is that "there are sufficient data demonstrating a long-term curative outcome for related and unrelated allogeneic HCT]."[9]

Based on the treatment recommendations made by the MDS expert panel, early allogeneic HCT is fully recommended for patients with a bone marrow blast percentage over 10 and poor risk karyotype at diagnosis; who have a suitable donor; and who meet the transplant center's eligibility criteria. The expert panel also recommends early allogeneic HCT for MDS for selected patients with a bone marrow blast percentage of less than 10 and favorable risk karyotype at diagnosis who have additional poor prognostic features.

The only treatment providing or leading to or yielding long-term, progression-free survival for MDS is allogeneic HCT. Furthermore, age should not be a sole contraindication for allogeneic HCT. Recent advances in treatment have enabled successful allogeneic HCT among MDS patient populations over 65 years of age.[10] Allogeneic HCT for patients over the age of 60 is now common practice, and patients well above 70 have been transplanted successfully.[11,12,13] Below, new data are presented that further substantiate the effectiveness of allogeneic HCT for MDS among Medicare aged beneficiaries.

Tab A includes supporting clinical documentation on MDS and allogeneic HCT for MDS.

For background and descriptive information on MDS, please see:

- Greenberg, Peter, et al. 1997. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. *Blood.* No. 89, http://bloodjournal.hematologylibrary.org/cgi/reprint/89/6/2079?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=89&firstpage=2079&resourcetype=HWCIT (accessed February 16, 2009).

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[7] McClune, Brian, DO, et al. Effect of Age on Outcome of Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML in First Complete Remission and MDS. Draft Manuscript, which is described in greater detail below.

[8] Oliansky D, et al. 2009. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of MDS: An Evidence-Based Review. *Biology of Blood and Marrow Transplantation.* No. 15:137-172.

[9] Ibid., p. 139, Table 3.

[10] Finke J, Nagler A. 2007. Viewpoint: What Is the Role of Allogeneic Hematopoietic Cell Transplantation in the Era of Reduced-Intensity Conditioning – Is There an Upper Age Limit? *Leukemia.* No. 21: 1357-1362.

[11] Ibid.

[12] Barrett AJ, Savani BN. 2006. Stem Cell Transplantation with Reduced-Intensity Conditioning Regimens: A Review of Ten Years Experience with New Transplant Concepts and New Therapeutic Agents. *Leukemia.* No. 20: 1661-1672.

[13] Spyridonidis A, Bertz H. 2005. Hematopoietic Cell Transplantation from unrelated donors as an effective therapy for Older Patients (>60 years) with Active Myeloid Malignancies. *Blood.* No. 105: 4147-4148.

- Haferlach, Torsten, et al. 2003. Morphologic Dysplasia in De Novo AML Is Related to Unfavorable Cytogenetics but Has No Independent Prognostic Relevance Under the Conditions of Intensive Induction Therapy: Results of a Multiparameter Analysis From the German AML Cooperative Group Studies. *Journal of Clinical Oncology.* No. 21, http://jco.ascopubs.org/cgi/reprint/21/2/256 (accessed February 16, 2009).
- Ma, Xiaomei, et al. 2007. Myelodysplastic Syndromes: Incidence and Survival in the United States. *Cancer.* No. 109, http://www3.interscience.wiley.com/cgi-bin/fulltext/114174049/PDFSTART (accessed February 16, 2009).
- Plesa, Claudiu, et al. 2008. Prognostic Index for Older Adult Patients with Newly Diagnosed Acute Myeloid Leukemia: The Edouard Herriot Hospital Experience. *Clinical Leukemia.* No. 3, http://cigjournals.metapress.com/content/121024/?k=plesa (accessed February 16, 2009).
- Nimer, S., et al. 2008. Myelodysplastic syndromes. *Blood.* No. 111:4841-51, http://bloodjournal.hematologylibrary.org/cgi/content/full/111/10/4841 (accessed September 15, 2009).
- Rollison DE, Howlader N, Smith MT, et al. 2008. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004. *Blood.* No. 112:45-52, http://bloodjournal.hematologylibrary.org/cgi/content/full/112/1/45 (accessed September 15, 2009).

For information on treatment options for MDS, including allogeneic HCT, please see:

- Barrett AJ, Savani BN. 2006. Stem Cell Transplantation with Reduced-Intensity Conditioning Regimens: A Review of Ten Years Experience with New Transplant Concepts and New Therapeutic Agents. *Leukemia.* No. 20:1661-1672.
- Cheson, Bruce, D., et al. 2000. Report of an international working group to standardize response criteria for myelodysplatic syndromes. *Blood.* No. 96, http://bloodjournal.hematologylibrary.org/cgi/reprint/96/12/3671?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=96&firstpage=3671&resourcetype=HWCIT (accessed February 16, 2009).
- Cutler, Corey S., et al. 2004. A Decision Analysis of Allogeneic Bone Marrow Transplantation for the Myelodysplastic Syndromes: Delayed Transplantation for Low-Risk Myelodysplasia Is Associated with Improved Outcome. *Blood.* No. 104, http://bloodjournal.hematologylibrary.org/cgi/reprint/96/12/3671?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=96&firstpage=3671&resourcetype=HWCIT (accessed February 16, 2009).
- Finke J, Nagler A. 2007. Viewpoint: What Is the Role of Allogeneic Hematopoietic Cell Transplantation in the Era of Reduced-Intensity Conditioning – Is There an Upper Age Limit? *Leukemia.* No. 21: 1357-1362.
- Kantarjian, Hagop, et al. 2006. Decitabine Improves Patient Outcomes in Myelodysplastic Syndromes: Results of a Phase III Randomized Study. *Cancer.* No. 106, http://www3.interscience.wiley.com/cgi-bin/fulltext/112476875/PDFSTART (accessed February 16, 2009).
- Silverman, Lewis, et al. 2006. Further Analysis of Trials with Azacitidine in Patients with Myelodysplastic Syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *Journal of Clinical Oncology.* No. 24, http://jco.ascopubs.org/cgi/reprint/24/24/ (accessed February 16, 2009).
- Spyridonidis A, Bertz H. 2005. Hematopoietic Cell Transplantation from unrelated donors as an effective therapy for Older Patients (>60 years) with Active Myeloid Malignancies.

Blood. No. 105:4147-4148, http://bloodjournal.hematologylibrary.org/cgi/reprint/105/10/4147.pdf (accessed September 15, 2009).

For the recently completed evidence-based review of allogeneic HCT for MDS, please see:

- Oliansky D, et al. 2009. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of MDS: An Evidence-Based Review. *Biology of Blood and Marrow Transplantation.* No. 15:137-172.

Promising new data show that allogeneic HCT for MDS is an effective treatment for the Medicare population

A study recently presented by McClune et al. at the American Society of Hematology (ASH) 50th Annual Meeting and Exposition titled "Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML and MDS: Results from the CIBMTR" addresses age as a predictor of outcome among patients receiving allogeneic HCT for MDS. In the study, clinical experts retrospectively analyzed data reported to the CIBMTR from 1995-2005 on 551 patients with MDS. Researchers analyzed patient outcomes including transplant-related mortality (TRM), engraftment, incidence of acute and chronic graft-versus-host-disease (GVHD), Leukemia-free survival (LFS), and overall survival (OS). Patients were stratified according to age cohorts for comparison: 40-54, 54-59, 60-64, and ≥65 years.

Study results show clinical characteristics were balanced across age cohorts, with no statistically significant differences in TRM, no overall difference in occurrence of acute or chronic GVHD, and similar relapse rates. In addition, multivariate analysis revealed no statistically significant impact of age on TRM, relapse, LFS, or OS.

The CIBMTR study – currently undergoing peer-review prior to publication – concludes that the outcomes for older adults undergoing allogeneic HCT for MDS are not significantly different than those of younger adults, even after adjusting for multiple risk factors. As stated above, the data show a 23% survival with a median follow up of 36 months. Furthermore, the study concludes that age by itself should not be the limiting factor for proceeding with allogeneic HCT in older MDS patients. These key findings support our recommendation for coverage of allogeneic HCT for MDS among the Medicare population.

Tab B includes the draft of the CIBMTR study manuscript and the abstract from the 2008 ASH meeting.

- McClune Brian, DO, et al. 2008. Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML and MDS: Results from the CIBMTR. *American Society of Hematology.* Abstract 346.
- McClune, Brian, DO, et al. Effect of Age on Outcome of Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML in First Complete Remission and MDS. Draft Manuscript.

Federally mandated outcomes data collection will lead to continued research about the use of allogeneic HCT for MDS

In September 2006, the Health Resources and Services Administration (HRSA) awarded a contract to CIBMTR to administer the Stem Cell Therapeutic Outcomes Database (SCTOD).

SCTOD collects data on all allogeneic HCTs performed in the United States with the purpose of increasing the safety, efficacy, and availability of HCT. SCTOD data collection enables analysis of administrative program use, center-specific outcomes, donor registry, cord blood inventory size, and patient access to HCT.

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

Through use of TED forms and other data submission tools, researchers can use CIBMTR data to study a wide spectrum of treatment-related issues, including patient outcomes. Furthermore, CIBMTR provides broad database access to researchers, enabling robust data enterprise. In 2008 alone, 56 manuscripts were published in (38), submitted to (13), or accepted by (5) peer-reviewed journals. By October 2008, total CIBMTR-related publications exceeded 400 articles, with 213 active studies then in progress.[14]

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

Pre-Transplant TED	**Post-Transplant TED** (100 day, 6 month, and annually)
• Disease Classification • Transplant History • Donor Type • Preparative Regimen • Comorbid Conditions • Graft-Versus-Host Disease Prophylaxis (allogeneic transplants only) • Post-Transplant Care Plan	• Outcomes » Absolute Neutrophil Count Recovery » Initial Platelet Recovery • Post-Transplant Therapy • First Relapse/Progression after Transplant and Use of Additional Treatment • Emergence of a New Malignancy (different from disease for which transplant was performed) • Presence and Classification of Acute or Chronic Graft-Versus-Host Disease • Survival Rates

We believe the federally mandated data collection effort of CIBMTR and SCTOD represent adequate platforms to capture continued outcomes data for Medicare beneficiaries undergoing allogeneic HCT for MDS.

Tab C contains the CIBMTR 2008 Progress Report, which contains full background information on CIBMTR and SCTOD, including outcomes data collection capabilities. Tab C also includes the complete Pre- and Post-Transplant Essential Data CIBMTR data form and the Myelodysplasia/Myeloproliferative Disorders Pre-HSCT CIBMTR data form.

[14] CIBMTR 2008 Progress Report, p. 15.

Well-defined and accepted standards for conducting allogeneic HCT for MDS currently exist

Access to the NMDP registry of unrelated donors and cord blood units is regulated by formal Participation Agreements, which require that transplant centers meet certain standards. The NMDP standards are specific to unrelated allogeneic transplantation and apply to all donor recruitment, donor screening, collection, storage, processing, release, transportation, and administration of hematopoietic cells facilitated through the NMDP. Documented compliance and periodic inspection is included in the requirements for participation. Separately, FACT-JACIE provides accreditation of transplant centers through a process of inspection and certification that is available to all centers conduction of allogeneic HCT. Appendix B includes tables of key NMDP criteria and FACT-JACIE standards for accreditation.

Tab D includes the complete NMDP and FACT-JACIE transplant center standards.

- NMDP 20th Edition Standards and Glossary. March 30, 2009. http://www.marrow.org/ABOUT/Who_We_Are/NMDP_Network/Maintaining_NMDP_Standards/Standards_PDF/NMDP%2020th%20Ed.%20Stds.pdf (accessed April 8, 2009).
- NMDP Transplant Center Participation Criteria. February 2009. http://www.marrow.org/ABOUT/Who_We_Are/NMDP_Network/Maintaining_NMDP_Standards/TC_Participation_Criteria_PDF/criteria_tc.pdf (accessed April 8, 2009).
- FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fourth Edition. October 2008. http://www.factwebsite.org/uploadedFiles/News/4th%20Ed.%20Standards%20for%20Web.pdf (accessed April 8, 2009).

II. Formal Request

Based on the evidence presented above, we formally request a National Coverage Determination (NCD) to ensure that Medicare beneficiaries have access to allogeneic HCT for the treatment of MDS. The curative potential of allogeneic HCT for MDS is well documented as it induces long-term, disease-free survival for people with MDS. For the specific purpose of providing national coverage for allogeneic HCT transplant, beneficiaries would either be at high risk for progression to leukemia or be at risk for MDS complications that place them at high risk for death or prevent the future possibility of a transplant. The diagnosis of MDS would be confirmed in two steps:

1. Histopathologic examination of a beneficiary's bone marrow biopsy

2. Classifying the beneficiaries as one of the following:
   A. Beneficiaries at high risk for progression with one or more of the following:
      i) Bone marrow blast counts ≥ 5%
      ii) Poor prognosis cytogenetics, such as abnormalities of chromosome 7 or complex multiple cytogenetic abnormalities
      iii) MDS developed as a consequence of prior chemotherapy or radiation therapy treatments
   B. Beneficiaries at risk for early death with cytopenias resulting in:
      i) Severely low blood counts making the beneficiary prone to infection, such as those with an absolute neutrophil count <1000/µl or those requiring red cell or platelet transfusion support

ii) Severe or life-threatening MDS complications that result in bleeding or infections, or hospitalizations due to MDS complications

C. Beneficiaries diagnosed with chronic myelomonocytic leukemia (CMML)[15]

In addition to confirmation of the MDS diagnosis, eligible beneficiaries must have a suitable and available source of allogeneic hematopoietic donor cells and must be evaluated and approved at a transplant center with sufficient expertise and experience to perform allogeneic transplantation. The documentation of transplant center experience and expertise must include either NMDP or FACT-JACIE accreditation for allogeneic transplantation. Per the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129), transplant centers must submit outcomes data to CIBMTR for all Medicare beneficiaries receiving allogeneic HCT.

Tab E includes clinical evidence supporting the diagnostics characteristics of MDS in the formal coverage request.

- Greenberg P, Cox C, LeBeau MM, et al. 1997. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* No. 89:2079-2088.
- Vardiman JW, Harris NL, Brunning RD. 2002. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* No. 100:2292-302.
- Kuendgen A, Strupp C, Aivado M, et al. 2006. Myelodysplastic syndromes in patients younger than age 50. *Journal of Clinical Oncology.* No. 24:5358-5365.
- Alessandrino EP, Della Porta MG, Bacigalupo A, et al. 2008. WHO classification and WPSS predict post-transplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Blood.* No. 112:895-902.
- Malcovati L, Della Porta MG, Cazzola M. 2006. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica.* No. 91:1588-1590.
- Malcovati L, Germing U, Kuendgen A, et al. 2007. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *Journal of Clinical Oncology.* No. 25:3503-3510.
- Cutler CS, Lee SJ, Greenberg P, et al. 2004. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* No. 104:579-585.
- Sorror ML, Sandmaier BM, Storer BE, et al. 2007. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *Journal of Clinical Oncology.* No. 25:4246-4254.

III. Conclusion

We believe that the body of evidence supports CMS issuing a national coverage policy that ensures that Medicare beneficiaries diagnosed with MDS have access to allogeneic HCT. Such a policy will ensure appropriate beneficiary access. In addition, a change in Medicare coverage policy would support efforts to continue to collect and analyze data on the benefits of allogeneic HCT for MDS for Medicare beneficiaries, as all data on the procedures must be collected according to the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129). The SCTOD (described above) is federally supported and is a component of the CW Bill Young

[15] Beneficiaries with CMML should be eligible for allogeneic HCT for MDS under this policy because CMML was once classified as a subtype of MDS, but is now classified as a myeloproliferative disorder. In addition, CMML clinically acts like MDS and progresses within one to two years to leukemia.

Transplant Program. It exists to receive, analyze, and report on recipients of allotransplantation in the United States.

We look forward to working closely with CMS throughout the NCD process and to providing any additional information that CMS may require. For further assistance, please contact Michael Boo, Chief Strategy Officer, National Marrow Donor Program, at 612.627.5855 or mboo@nmdp.org; or Dr. James Gajewski, Chair, ASBMT Committee on Reimbursement, at 503.494.4606 or gajewski@ohsu.edu.

Sincerely,

[SENT VIA E-MAIL]

Michael Boo, JD	National Marrow Donor Program
Claudio Anasetti, MD	American Society for Blood and Marrow Transplantation
Theresa Wiegmann, JD	AABB (formerly the American Association of Blood Banks)
Otis Brawley, MD	American Cancer Society
Daniel Smith	American Cancer Society Cancer Action Network
Nancy Berliner, MD	American Society for Hematology
Douglas Blayney, MD	American Society of Clinical Oncology
John Huber	Aplastic Anemia and MDS International Foundation
Susan Stewart	Blood & Marrow Transplant Information Network
Myra Jacobs	National Bone Marrow Transplant Link
Christina Merrill	The Bone Marrow Foundation
Mark Pascu	The Leukemia & Lymphoma Society

Appendix A: Supporting Documentation Binder

Tab A: Description of MDS, allogeneic HCT treatment for MDS, and other treatment options for MDS:

- Barrett AJ, Savani BN. 2006. Stem Cell Transplantation with Reduced-Intensity Conditioning Regimens: A Review of Ten Years Experience with New Transplant Concepts and New Therapeutic Agents. *Leukemia.* No. 20: 1661-1672.
- Cheson, Bruce, D., et al. 2000. Report of an international working group to standardize response criteria for myelodysplatic syndromes. *Blood.* No. 96, http://bloodjournal.hematologylibrary.org/cgi/reprint/96/12/3671?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=96&firstpage=3671&resourcetype=HWCIT (accessed February 16, 2009).
- Cutler, Corey S., et al. 2004. A Decision Analysis of Allogeneic Bone Marrow Transplantation for the Myelodysplastic Syndromes: Delayed Transplantation for Low-Risk Myelodysplasia Is Associated with Improved Outcome. *Blood.* No. 104, http://bloodjournal.hematologylibrary.org/cgi/reprint/96/12/3671?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=96&firstpage=3671&resourcetype=HWCIT (accessed February 16, 2009).
- Finke J, Nagler A. 2007. Viewpoint: What Is the Role of Allogeneic Hematopoietic Cell Transplantation in the Era of Reduced-Intensity Conditioning – Is There an Upper Age Limit? *Leukemia.* No. 21: 1357-1362.
- Greenberg, Peter, et al. 1997. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. *Blood.* No. 89, http://bloodjournal.hematologylibrary.org/cgi/reprint/89/6/2079?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&volume=89&firstpage=2079&resourcetype=HWCIT (accessed February 16, 2009).
- Haferlach, Torsten, et al. 2003. Morphologic Dysplasia in De Novo AML Is Related to Unfavorable Cytogenetics but Has No Independent Prognostic Relevance Under the Conditions of Intensive Induction Therapy: Results of a Multiparameter Analysis From the German AML Cooperative Group Studies. *Journal of Clinical Oncology.* No. 21, http://jco.ascopubs.org/cgi/reprint/21/2/256 (accessed February 16, 2009).
- Kantarjian, Hagop, et al. 2006. Decitabine Improves Patient Outcomes in Myelodysplastic Syndromes: Results of a Phase III Randomized Study. *Cancer.* No. 106, http://www3.interscience.wiley.com/cgi-bin/fulltext/112476875/PDFSTART (accessed February 16, 2009).
- Ma, Xiaomei, et al. 2007. Myelodysplastic Syndromes: Incidence and Survival in the United States. *Cancer.* No. 109, http://www3.interscience.wiley.com/cgi-bin/fulltext/114174049/PDFSTART (accessed February 16, 2009).
- Nimer, S., et al. 2008. Myelodysplastic syndromes. *Blood.* No. 111:4841-51.
- Oliansky D, et al. 2009. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of MDS: An Evidence-Based Review. *Biology of Blood and Marrow Transplantation.* No. 15:137-172.
- Plesa, Claudiu, et al. 2008. Prognostic Index for Older Adult Patients with Newly Diagnosed Acute Myeloid Leukemia: The Edouard Herriot Hospital Experience. *Clinical Leukemia.* No. 3, http://cigjournals.metapress.com/content/121024/?k=plesa (accessed February 16, 2009).

- Rollison DE, Howlader N, Smith MT, et al. 2008. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004. *Blood.* No. 112:45-52.
- Silverman, Lewis, et al. 2006. Further Analysis of Trials With Azacitidine in Patients With Myelodysplastic Syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *Journal of Clinical Oncology.* No. 24 (August 20), http://jco.ascopubs.org/cgi/reprint/24/24/ (accessed February 16, 2009).
- Spyridonidis A, Bertz H. 2005. Hematopoietic Cell Transplantation from unrelated donors as an effective therapy for Older Patients (>60 years) with Active Myeloid Malignancies. *Blood.* No. 105: 4147-4148.

Tab B: CIBMTR Study abstract and draft manuscript:

- McClune Brian, DO, et al. 2008. Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML and MDS: Results from the CIBMTR. *American Society of Hematology.* Abstract 346.
- McClune, Brian, DO, et al. Effect of Age on Outcome of Non-Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML in First Complete Remission and MDS. Draft Manuscript.

Tab C: Federally mandated data collection efforts, and Pre-TED and Post-TED forms:

- CIBMTR 2008 Annual Progress Report: http://www.cibmtr.org/ABOUT/Annual_Report/DOCS/2008_CIBMTR_Annual_R.pdf.
- Pre-Transplant Essential Data CIBMTR Data Form.
- Post-Transplant Essential Data CIBMTR Data Form.
- Myelodysplasia/Myeloproliferative Disorders Pre-HSCT CIBMTR Data Form.

Tab D: NMDP and FACT-JACIE facility and provider accreditation standards:

- NMDP 20th Edition Standards and Glossary. March 30, 2009. http://www.marrow.org/ABOUT/Who_We_Are/NMDP_Network/Maintaining_NMDP_Standards/Standards_PDF/NMDP%2020th%20Ed.%20Stds.pdf (accessed April 8, 2009).
- NMDP Transplant Center Participation Criteria. February 2009. http://www.marrow.org/ABOUT/Who_We_Are/NMDP_Network/Maintaining_NMDP_Standards/TC_Participation_Criteria_PDF/criteria_tc.pdf (accessed April 8, 2009).
- FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fourth Edition. October 2008. http://www.factwebsite.org/uploadedFiles/News/4th%20Ed.%20Standards%20for%20Web.pdf (accessed April 8, 2009).

Tab E: Clinical evidence supporting the Formal Coverage Request:

- Greenberg P, Cox C, LeBeau MM, et al. 1997. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* No. 89:2079-2088.
- Vardiman JW, Harris NL, Brunning RD. 2002. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* No. 100:2292-302.
- Kuendgen A, Strupp C, Aivado M, et al. 2006. Myelodysplastic syndromes in patients younger than age 50. *Journal of Clinical Oncology.* No. 24:5358-5365.
- Alessandrino EP, Della Porta MG, Bacigalupo A, et al. 2008. WHO classification and WPSS predict post-transplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Blood.* No. 112:895-902.

- Malcovati L, Della Porta MG, Cazzola M. 2006. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica*. No. 91:1588-1590.
- Malcovati L, Germing U, Kuendgen A, et al. 2007. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *Journal of Clinical Oncology*. No. 25:3503-3510.
- Cutler CS, Lee SJ, Greenberg P, et al. 2004. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* No. 104:579-585.
- Sorror ML, Sandmaier BM, Storer BE, et al. 2007. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *Journal of Clinical Oncology*. No. 25:4246-4254.

Appendix B: Key Standards for Conducting Allogeneic HCT

Key NMDP Transplant Center Participation Criteria

Category	Center Criteria
Facility Characteristics	• Accreditation by Joint Commission or the American Osteopathic Association's Healthcare Facilities Accreditation Program • Medical director who has NMDP responsibilities for all units and serves as the single point of contact for the NMDP on clinical matters
Personnel and Transplant Team	• NMDP director who: o Is a licensed physician o Is board certified in one of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology o Has at least two years experience in the past five years as an attending physician responsible for the management of allogeneic HCT recipients • Use an experienced team that has performed at least 10 transplants (with NMDP-acceptable survival rates)
Support Services	• Laboratories certified by CMS for clinical tests required by NMDP • Laboratories accredited by the American Society of Histocompatibility and Immunogenetics or the European Federation for Immunogenetics for HLA typing required by NMDP • Hematopoietic cell-processing laboratory registered with the U.S. Food and Drug Administration (FDA) as a manufacturer of human cells, tissues, and other cellular- and tissue-based products
Policies and Procedures	• Maintains written policies and/or procedures to address at least the following: o Donor or cord blood unit selection; o Financial approval; o Infection prevention and control; o Processing ABO incompatible hematopoietic cell products to reduce red cell content; o Hematopoietic cell infusion; and o Blood component transfusion to include transfusion of blood components when the donor and recipient are ABO-mismatched. • Participates in the NMDP/CIBMTR Research Sample protocol and the Research Database protocol
Administrative	• Complies with applicable World Marrow Donor Association Standards • Adheres to established continuous Process Improvement criteria • Provides annual documentation that it continues to meet

Category	Center Criteria
	NMDP Participation Requirements • Completes and submits NMDP and CIBMTR data forms as required
Applicant Centers	• Applicant center must have performed primary allogeneic transplants for at least 10 different patients per year during the previous 24 months or primary allogeneic transplants for 20 different patients in the last 12 months to qualify as a Transplant Center. Applicant centers that perform allogeneic transplants for fewer than 10 different patients per year are eligible to apply as a Low Volume Transplant Center • Applicant center must submit a "Hematopoietic Stem Cell Transplant History" form documenting all allogeneic transplants for the previous 24 months, to include the day +100 status for each patient. Experience must demonstrate that applicant center achieved appropriate allogeneic recipient survival rates

Key FACT-JACIE Clinical Program Standards

Category	Standards
General	• Transplant Center Clinical Programs with allogeneic HPC transplantation accreditation must meet the numeric requirement of 10 new allogeneic patients per year. Clinical Programs requesting accreditation must meet this requirement during the twelve month period immediately preceding the application • Clinical Programs using more than one clinical site must meet an annual numeric requirement of 5 new allogeneic patients per site for accreditation • Clinical Programs that care for both pediatric and adult patients must perform a minimum of 5 allogeneic HPC transplants for each population annually
Personnel	• Clinical Program Director who: o Is a licensed physician o Is board-certified in one of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology o Has at least one year of clinical training in HPC transplantation • Uses a team of physicians with a minimum of one year of supervised training in HPC transplant medicine and patient management, as well as a clinical transplant team trained in patient management
Quality Management	• Quality Management Plan that incorporates o Information from clinical, collection, and processing facility quality management • Policies and procedures for personnel training and

Category	Standards
	competency assessment • Policies and Procedures for documentation and review of outcome analysis and product efficacy • Policies and Procedures for detecting, evaluating, documenting, and reporting errors, accidents, adverse events, biological product deviations, and complaints
Policies and Procedures	• Maintains Quality Management Plan procedures in addition to the procedures outlined in the Standard Operating Procedures Manual • Maintains archived policies and procedures for a minimum of 10 years
Clinical Research	• Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms in accordance with applicable laws and regulations • Maintains documentation of the following: o Audits o Approval by the Institutional Review Board, Ethics Committee, or equivalent o Correspondence with regulatory agencies o Adverse outcomes • Obtains informed consent from each research subject in compliance with applicable laws and regulations
Data Management	• Clinical Program collects all data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT