



STUDY PLAN

PART I OF AN ASSESSMENT OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN MEDICARE BENEFICIARIES WITH MYELODYSPLASTIC SYNDROME AND RELATED DISORDERS

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1.0 INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) is the only potentially curative therapy available to patients with myelodysplastic syndromes (MDS). Until recently, however, concerns regarding morbidity and mortality of this intensive procedure limited its application in older patients with MDS. The introduction of reduced intensity conditioning (RIC) regimens greatly expanded the utility of HCT in older and sicker patients by reducing the risk of regimen-related toxicity^{1,2}. Although several small studies indicate safety and efficacy of HCT in older patients,^{3,4} there are no large prospective studies evaluating outcomes in patients older than 65 years. The aim of this study is to prospectively examine post-HCT outcomes in CMS beneficiaries with MDS to determine whether these outcomes are similar to those in younger patients where the experience with HCT is more extensive and where HCT is an accepted medical therapy.

2.0 HYPOTHESIS:

The outcome of HCT for MDS and related disorders in ≥ 65 years of age is similar to outcomes in adults 55-64 years of age.

3.0 SPECIFIC AIMS

3.1. To prospectively determine the following outcomes in Medicare beneficiaries who undergo HCT for MDS and related disorders and compare these outcomes with those of non-Medicare beneficiaries, aged 55-64:

- Early (100-day) mortality
- Acute and chronic graft-versus-host disease (GVHD)
- Relapse and progression
- Disease-free survival
- Progression-free survival
- Overall survival

3.2. To prospectively determine whether there are disease- or patient-related factors that predict outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- World Health Organization (WHO) classification
- International Prognostic Scoring System (IPSS) score
- WHO-based Prognostic Scoring System (WPSS)
- Cytopenias
- Cytogenetics
- Primary versus secondary MDS
- Disease duration and prior therapy
- Recipient age
- Performance score
- Sorror co-morbidity index

3.3. To prospectively evaluate what transplant characteristics are associated with outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- Preparative regimen
- Graft source
- GVHD prophylaxis
- Use of hematopoietic growth factors

3.4. To prospectively evaluate treatment facility characteristics associated with outcomes of HCT for MDS and related disorders in Medicare beneficiaries, including:

- Transplant volume
- Years of operation
- Academic affiliation

3.5. This study is Part 1 of a comprehensive evaluation of HCT in Medicare beneficiaries. It will evaluate outcome of allogeneic HCT, with monitoring to ensure that there is not undue early mortality in adults ≥ 65 years of age. The intent is to assemble a high quality data set of 240 patients, whose data will be analyzed to provide information pertinent to design of Part 2 of this evaluation, a study directly comparing HCT with non-HCT therapies in this patient population for relapse and progression, progression-free survival, disease-free survival and overall survival.

4.0 BACKGROUND:

Myelodysplastic syndromes are a group of clonal hematological disorders characterized by progressive cytopenias and leukemic transformation. More than 15,000 patients are diagnosed with MDS each year in the United States, and 80% of those patients are older than 65 years of age. The median age at diagnosis is 70 years in western countries and incidence increases with increasing age. The incidence is 0.22/100,000 in those <49 years, 4.8/100,000 between the ages of 50 and 70 years and 22.8/100,000 in those older than 70 years⁵.

MDS is classified using several systems. For many years, MDS subtypes were classified by morphology using the French-American-British (FAB) classification; this has now largely been superseded by the WHO classification, which also incorporates cytogenetic abnormalities (5q-). Several prognostic scoring systems are also available. The International Prognostic Scoring System (IPSS) is the most widely accepted. The IPSS uses percentage of blasts, cytogenetic abnormalities and cytopenias to separate patients into 4 different prognostic groups: Low, intermediate-1, intermediate-2 and high risk. Median survivals vary from 0.4 years to 5.7 years for untreated patients with high and low risk disease respectively⁶. More recently, a prognostic system using the WHO classification, transfusion requirement and IPSS cytogenetic risk, the WPSS⁷ is suggested to provide better prognostic discrimination.

Recently the Food and Drug Administration approved three new drugs for therapy of MDS: azacytidine⁸, decitabine⁹ and lenalidomide¹⁰. Both azacytidine and decitabine are hypomethylating agents while lenalidomide is a thalidomide analogue. The response rates to those drugs range from 30-70%, however none are curative.

The only available therapy with the potential to cure MDS is HCT and HCT is the treatment of choice for younger patients¹¹. Prior to the introduction of RIC regimens, regimen-related morbidity and mortality limited the utility of HCT in older patients and in those with significant co-morbidities. RIC regimens now allow HCT to be offered more safely to those patients but use of HCT in the older population still remains limited. This was evident in a recent study by the CIBMTR where only 10% of patients who underwent RIC HCT were older than 65 years. In that study, age had no significant impact on outcome in multivariate analysis in a cohort of patients between 40 and 70 years.¹² The 100 day mortality rate was about 20% and the 2 year probability of survival was about 40%.

There are multiple reasons that older patients do not undergo transplantation. Older patients may have co-morbidities that compromise their ability to tolerate an intensive therapy like HCT. Some oncologists are reluctant to refer older patients for HCT, even if there are no clinical contraindications, because of perceived worse outcomes in older patients. Some transplant centers have arbitrary upper age limits for HCT candidates. Finally, some third party payers will not cover HCT in older patients until there is transformation to acute leukemia. Until recently, coverage of HCT for MDS by the US Centers for Medicare and Medicaid Services (CMS) depended on local coverage determinations¹³. CMS is the primary health insurer for most US adults 65 years of age or older. Recently, CMS made a National Coverage Determination (NCD) regarding MDS, indicating that data regarding efficacy in a CMS beneficiary population were currently insufficient but that coverage would be provided for patients enrolled in a clinical study appropriately designed to generate data necessary to make a determination about efficacy and effectiveness. This decision acknowledged that “the available evidence suggests that allogeneic HSCT for MDS is reasonable and necessary under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED).”

The aim of this study is to prospectively examine post-HCT outcomes in CMS beneficiaries with MDS to determine whether these outcomes are similar to younger patients where the experience with HCT is more extensive and where HCT is an accepted medical therapy. The study will also evaluate patient, disease and treatment factors which might modify transplant outcomes. The objectives and methods of the study comply with the CMS-specified requirement that a “clinical study seeking Medicare payment ... pursuant to Coverage with Evidence Development (CED) must address one or more aspects” of three questions outlined in its Decision Memo (CAG-00415N). The analyses in this Study Plan are for Part 1 of this evaluation and will directly address questions 2 and 3 in that Memo and will provide data to plan Part 2 of the evaluation, a study directly addressing question 1 in that Memo, which will compare outcomes after HCT to outcomes with non-HCT therapy.

5.0 STUDY POPULATION:

Eligible patients are persons ≥ 65 years old (or < 65 years of age and a CMS beneficiary) with myelodysplastic syndromes and related disorders, including chronic myelomonocyte leukemia (CMML), who are eligible to receive an allogeneic HCT from either an HLA-identical sibling or unrelated donor in a US transplant center and who agree to (sign

Informed Consent; Appendix A) submission of comprehensive clinical data on their pre- and post-transplant clinical status and outcomes to the Center for International Blood and Marrow Transplant Research (CIBMTR). Eligibility for HCT will be according to local institutional practices. Patients younger than 65 years of age who are CMS beneficiaries are included but will be analyzed separately. The object is to capture data on the broad range of patients in whom the therapy is used; there is no exclusion for race, gender or prior therapy.

6.0 OUTCOMES:

6.1. Primary outcome

6.1.1. 100 day mortality.

100 day mortality is chosen as the primary outcome because this is a preliminary study designed to provide data necessary to plan a prospective comparative study of transplant and non-transplant therapy. The timeline for designing and implementing the comparative study (Part 2 of the evaluation) is expected to be less than 30 months, so an early primary endpoint for Part 1 is desirable. The rationale for use of HCT for MDS in patients ≥ 65 years old is that outcomes are thought to be similar to those in adults 55-64, where HCT is an accepted therapy, given similar non-age-based eligibility criteria are met¹¹. This study will determine, in a large cohort of patient ≥ 65 years old, whether early mortality is indeed in the range expected and will also provide information on prognostic factors for outcome that will aid in designing the comparative study. The latter study will focus on long-term outcomes.

6.2. Secondary outcomes

6.2.1. Acute GVHD: Occurrence of grade II, III and/or IV skin, gastrointestinal or liver abnormalities fulfilling the IBMTR criteria for acute GVHD.

6.2.2. Chronic GVHD: Occurrence of symptoms in any organ system fulfilling the criteria of chronic GVHD.

6.2.3. Relapse: disease recurrence or persistent disease for patients not in CR at transplant. Those who survive without recurrence or persistent disease are censored at the date of last contact.

6.2.4. Progression: increase in marrow blasts to $>20\%$; patients without progression are censored at time of most recent marrow examination.

6.2.5. Disease-free survival: survival without death or relapse. Those who survive without recurrent or persistent disease are censored at the date of last contact.

6.2.6. Progression-free survival: survival without increase in marrow blasts to $>20\%$; patients without progression are censored at time of most recent marrow examination.

6.2.7. Overall survival: Surviving patients are censored at the date of last contact.

7.0 DATA COLLECTION:

All data necessary for this study will be collected using the existing mechanisms of the CIBMTR under, operating under the “NMDP and CIBMTR Protocol for a Research Database for

Hematopoietic Stem cell Transplantation and marrow Toxic Injuries”, version 6.0, (NCT01166009) (Appendix A). The Informed Consent for this protocol is also found in Appendix A. These data collection mechanisms support the reporting required for the Stem Cell Therapeutic Outcomes Database (SCTOD), and the research endeavors of the CIBMTR. Existing data instruments and procedure manuals can be found at www.cibmtr.org/DataManagement. Registration of patients and submission of data will follow standard CIBMTR procedures.

8.0 STUDY DESIGN:

This study will target accrual of 240 patients older than age 65. 100 day mortality will be used as the primary endpoint. Sample sizes are based on an inferiority test of the hypothesis that the 100 day mortality rate in the ≥ 65 year old cohort is higher than 20%, the approximate 100-day mortality rate in a 55-64 year old cohort. The study is designed to have approximately 80% power to detect a 6.5 % or greater increase in 100 day mortality rate in the ≥ 65 year old cohort. Table 1 below shows the power of the test for various 100 day mortality rates.

We will perform 3 interim analyses after each group of 60 patients has their 100 day survival assessed and a final analysis when 240 patients reach the 100 day survival assessment. Each of the four tests will be conducted at a 0.0183 type I error level to ensure an overall 5% alpha. The study will stop and 100 day mortality rate in the ≥ 65 year old cohort declared too high if there are ≥ 18 deaths in the first 60 cases; ≥ 33 deaths in the first 120 cases; ≥ 47 deaths in the first 180 cases or ≥ 60 deaths in the first 240 cases. Table 1 shows the power of the test to reject the null hypothesis (100-day mortality is $\leq 20\%$) given a range of true mortality rates from 21 to 29%.

True 100 day mortality rates	Power
0.21	10%
0.22	20%
0.23	32%
0.24	46%
0.25	60%
0.26	73%
0.27	83%
0.28	90%
0.29	94%

At each of the four evaluations points, we will prepare descriptive tables of the covariates. Kaplan-Meier estimates of mortality and disease free survival will be constructed for the entire cohort and by sub-groups defined by the fixed covariates such as IPSS score. Cumulative incidence curves will be constructed to estimate acute GVHD incidence, relapse progression rates. These analyses will be conducted when 60, 120, 180 or 240 patients have at least 100 days of potential follow-up. As they are descriptive in nature, no p-values are computed until the entire cohort has been observed.

When accrual to the study is complete and all patients followed for at least 100 days, the association between outcomes and the variables listed in Section 5.0 will be examined in either a logistic regression model or a Cox proportional hazards model depending on the outcome of interest. Forward stepwise model selection techniques will be used in this approach. These analyses will include a cohort of patients ages 55-64 years transplanted for MDS and related disorders in the same centers as the CMS beneficiaries included in this analysis. Based on current rates of accrual, we expect to include at least 400 such patients in the analysis. Interactions between age <65 and ≥ 65 and other covariates will be tested in all models.

Follow-up of this cohort will continue, through standard CIBMTR mechanisms, after completion of these analyses. Evaluation of all secondary endpoints will be repeated when all patients have been followed for a minimum of two years.

8.1. Variables to be analyzed for their association with primary and secondary outcomes

8.1.1. Patient related:

- Age: in five year increments (or appropriate cutpoint based on data analysis)
- Gender: male vs. female
- Race: Caucasian vs non-Caucasian
- Karnofsky performance status: <80% vs. $\geq 80\%$
- Sorror co-morbidity Index

8.1.2. Disease related:

- WHO Disease classification at diagnosis and just prior to HCT
- FAB classification
- Pretransplant WBC and untransfused platelet count and hemoglobin concentration
- IPSS score immediately prior to transplantation
- WPSS score immediately prior to transplantation
- Cytogenetics
- Primary versus secondary MDS
- Time from diagnosis to transplant: <1 year vs. ≥ 1 year (or more appropriate cutpoint based on data analysis)
- Agents used for prior therapy

8.1.3. Transplant related:

- Conditioning regimen: more versus less intensive; specific regimens to be evaluated if numbers of patients sufficient
- Donor age
- Donor-recipient CMV status: -/- vs. -/+ vs. +/- vs. +/+
- Donor-recipient HLA match: HLA matched sibling vs. 8/8 locus (HLA- A, B, C, DRB1) matched unrelated donor vs. 7/8 locus matched unrelated donor

- Stem cell source: bone marrow vs. peripheral blood
- GVHD prophylaxis: Cyclosporine or Tacrolimus + Methotrexate vs. ex vivo T-cell depletion vs. other
- Donor-recipient gender match: male-male vs. male-female vs. female-male vs. female-female
- Transplant center characteristics: transplant volume, years of operation, academic affiliation

9.0 SCIENTIFIC INTEGRITY AND RELEVANCE TO THE MEDICARE POPULATION

As required in Decision Memo CAG-00415N, this clinical study will adhere to the following standards of scientific integrity and relevance to the Medicare population:

9.1. *The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.*

The principle purpose of the proposed study is to test whether HCT leads to MDS-free survival in a large proportion of patients with acceptable rates of early mortality and GVHD-related morbidity.

9.2. *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.*

Allogeneic HCT is an accepted therapy for MDS with extensive data in young patients and moderate amounts of data in patients 65 and older. The National Comprehensive Cancer Center Network (NCCN) Guidelines recommend allogeneic HCT at an initial treatment for transplant-eligible patients with IPSS Int2-High Risk disease and as a salvage therapy for other patients who do not respond to non-HCT therapy¹¹.

9.3. *This research study does not unjustifiably duplicate existing studies.*

There are currently no existing prospective data addressing the outcome of HCT for patients with MDS who are 65 or older. Some data on this population are available but include small numbers and procedures done in an earlier era. As noted in the Decision Memo, CMS feels that there are “*limitations of the evidence base on the use of HSCT for MDS as described in our Analysis section*”. The proposed study addresses many of the current data limitations and will not be duplicative of existing studies.

9.4. *The research study design is appropriate to answer the research question being asked in the study.*

The proposed study has 80% power to detect an early mortality rate that is 6.5% higher than the rate that is well-documented in a 55-64 year old patient cohort and includes sufficient numbers of patients to evaluate key prognostic factors in this population. The Methods

described in Section 6.0 have been used successfully in hundreds of CIBMTR studies of similar data (see below).

9.5. *The research study is sponsored by an organization or individual capable of executing the proposed study successfully.*

This study will be performed through the CIBMTR, which has performed hundreds of similar analyses over its >30 year history. The CIBMTR is a clinical research program which receives HCT outcomes data from a network of more than 450 transplant centers worldwide. Data are collected and analyzed by the Statistical Center, located at the Medical College of Wisconsin in Milwaukee, WI, and the National Marrow Donor Program located in Minneapolis, MN. The CIBMTR database includes information on about 330,000 transplant recipients and receives information on about 15,000 new transplants annually. CIBMTR data and statistical and scientific expertise have resulted in hundreds of peer-reviewed publications (www.cibmtr.org/ReferenceCenter/PubList/index.html).

As of December 2007, all United States transplant centers are required to report data on their related and unrelated donor transplants to the CIBMTR; participation of non-U.S. centers is voluntary. Computerized checks for errors, review of submitted data by physicians and on-site audits of participating centers are used to monitor the quality of the data. The CIBMTR collects data on two levels. All centers register basic data (Pre- Transplant Essential Data) for all patients. Centers provide comprehensive data (Report Forms) for a subset of registered patients. Patients are selected for comprehensive data reporting using a randomization program that weights cases for selection in order to provide adequate numbers of cases for current and future studies and to ensure adequate representation of all transplant types and indications. The selection program is modified as needed to select cases for specific studies such as the one described in this protocol. CIBMTR centers are asked to provide follow-up on all patients for as long as they are able to maintain contact. Completeness rates for one and two year survival data are >95%. These data sets have been used to conduct numerous studies of transplant outcomes, including studies of conditioning regimens. The most recent versions of the CIBMTR study forms can be found at http://www.cibmtr.org/DATA/Data_Mgmt_Forms/index.html.

Additionally, we have assembled a team of HCT and MDS experts to guide development, implementation and completion of this study. Biosketches are included in Appendix B.

All participating centers will be NMDP and/or FACT accredited. See list in Appendix C.

9.6. *The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.*

The data collection and analyses for this protocol will be done in full compliance with the specified Federal regulations. Signing an Informed Consent (Appendix A) for participation is required. The most recent NMDP and transplant center IRB approvals for this protocol are found in Appendix D.

9.7. *All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <http://www.icmje.org>).*

The CIBMTR adheres to all appropriate standard of scientific integrity. An interim monitoring procedure for this study is described in Section 8.0. At the time of each interim analysis, the interim analysis, and summary data on patient demographics, all secondary outcomes and causes of death will be reviewed by the CIBMTR Data Monitoring Board. The primary function of the Monitoring Board is to perform ongoing assessment and monitoring of CIBMTR prospective studies relative to scientific merit/validity, safety and efficacy. The Monitoring Board is comprised of an interdisciplinary membership with expertise in hematopoietic stem cell transplantation, biostatistics, ethics and the conduct of clinical trials. Key responsibilities of the Monitoring Board are to:

- Offer advice concerning the continued scientific merit and/or validity of each ongoing study.
- Provide continual assessment and monitoring of study participant safety; particularly with respect to the magnitude and impact of any adverse or severe adverse events.
- Provide ongoing assessment and monitoring of all study specific prescribed treatment protocols.
- Review and assess study specific site performance data such as study recruitment and accrual, protocol adherence and data quality.
- Recommend the continuation, amendment or termination of each ongoing study based upon regularly scheduled review of interim data results.
- Ensure study subject confidentiality as well as that of all study data and the conclusions reached as a result of the monitoring process

The Monitoring Board can recommend stopping the study if warranted by their review of the interim data.

9.8. *The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.*

This document serves as the written study plan, which, in combination with the master protocol, A Database Study for Hematopoietic Stem Cell Transplantation and Marrow Injuries, (NCT01166009, Appendix A), addresses, or incorporates by reference, the standards listed.

9.9. *The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.*

The outcomes of this study include measures of efficacy as well as toxicity.

9.10. *The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.*

This study falls under the auspices of NCT01166009 which is registered by the CIBMTR on ClinicalTrials.gov.

9.11. *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 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 three (3) years after the end of data collection.*

Regardless of the outcomes, the results of this study will be incorporated into a manuscript and submitted to a peer-reviewed journal within 24 months of receipt the 240th patient's 100 day report. Results will likely be made public via an abstract prior to that time, submitted to the American Society of Hematology meetings, the BMT Tandem Meetings or similar appropriate national meeting.

9.12. *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.*

Our protocol does not limit the inclusion of underrepresented groups. CIBMTR members must report data on *all* HCT recipients at their center regardless of gender, race or age. All patients meeting the broad eligibility criteria (HCT recipient, MDS, CMS beneficiary, informed consent) in Section 5.0 will be included. The association between outcomes and race, gender and age will be explored as indicated in Section 8.1.1.

9.13. *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.*

This study is expected to include most, if not all, of the CMS beneficiaries who receive HCT for MDS or a related disorder during the period of study, ensuring generalizability. The separation of the beneficiaries into two age groups (64 years and younger vs. 65 years and older) allows for comparison, while the inclusive design ensures applicability to the full population of Medicare beneficiaries.

10.0 TIMELINE

Approval by CMS	Month 0
Activation	Month 1
Enrollment	Month 1 – 26
Interim analysis 1	Month 13
Interim analysis 2	Month 19
Interim analysis 3	Month 25
Completion of follow-up for primary endpoint	Month 29
Completion of 100-day analyses	Month 33
Submission of primary manuscript	Month 36
Completion of ≥ 2 years of Follow-up in all patients	Month 50
Completion of 2-year analyses	Month 56

This timeline assumes that about 10 eligible patients per month will be enrolled after an initial ramp-up period. Higher or lower rates of HCT for MDS in CMS-eligible patients could substantially affect this timeline.

11.0 REFERENCES:

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12.0 LIST OF APPENDICES

- A. NMDP AND CIBMTR PROTOCOL FOR A RESEARCH DATABASE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION AND MARROW TOXIC INJURIES and INFORMED CONSENT DOCUMENT**
- B. BIOSKETCHES FOR STUDY TEAM MEMBERS**
- C. LIST OF PARTICIPATING CENTERS WITH IRB APPROVAL DATE AND ACCREDITATION STATUS**
- D. MOST RECENT INSTITUTIONAL REVIEW BOARD APPROVALS**