

Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis

Study Plan

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Executive Summary

- Title:** Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation (alloHCT) in Patients with Myelofibrosis (MF)
- Co-Chairs:** Wael Saber MD, MS, Medical College of Wisconsin
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- Eligibility Criteria:** Patients with primary MF (PMF), post-essential thrombocythemia (ET) MF, or post-polycythemia vera (PV) MF, with intermediate-2 or high-risk disease as determined by the DIPSS, and aged ≥ 55 at the time of DIPSS assessment are eligible for this study. For the alloHCT arm of the HLA-Matched Donor HCT Study, donors must be either 6/6 HLA-matched related donors, defined by Class I (HLA-A and -B) intermediate resolution or high resolution DNA-based typing and Class II (HLA-DRB1) at high resolution DNA-based typing (but not monozygotic twins), OR an 8/8 HLA-A, -B, -C, and -DRB1 at high resolution DNA-based typing matched unrelated donors; both peripheral blood stem cells and bone marrow grafts are allowed, and all conditioning regimen intensities and GVHD prophylaxis regimens are allowed. For the Haploidentical Donor Study, donors must be haploidentical.
- Accrual Objective:** This study will target accrual of 650 patients receiving alloHCT, including approximately 225 receiving myeloablative conditioning. Participating centers are expected to provide data for approximately 2,400 patients to form the non-HCT historical control cohort.

HLA-Matched Donor HCT Study

- Primary Objective:** Compare the five-year survival probabilities from DIPSS assessment between the two study arms: alloHCT recipients (arm 1) and non-HCT therapies (ruxolitinib / best supportive care) recipients (arm 2).
- Secondary Objectives:** Compare leukemia-free survival at five years from DIPSS assessment. Identify patient-, disease-, and HCT-related factors associated with poor HCT outcomes in the alloHCT arm.
- Estimate the cumulative incidences of acute and chronic graft-versus-host disease, transplant related mortality, and relapse starting at HCT in the alloHCT arm.
- Study Design:** This observational study will compare outcomes of a prospectively-enrolled cohort of HCT recipients with outcomes of a cohort of age-matched historical non-HCT controls. Patients undergoing alloHCT will receive HCT in a US transplant center and be reported to the Center

for International Blood and Marrow Transplant Research (CIBMTR) using well-established CIBMTR report forms and data collection procedures as well as a study-specific supplemental form. Data on the historical non-HCT controls will be collected at 14 US academic centers. These centers will provide data on all consecutive patients with PMF, post-ET MF, or post-PV MF referred to their institutions between 2000 and 2012.

Haploidentical Donor Study

Primary Objective: Estimate the five-year overall survival probabilities with haploidentical HCT from DIPSS assessment.

Secondary Objectives: Estimate five-year leukemia-free survival with haploidentical HCT from DIPSS assessment.

Identify patient-, disease-, and HCT-related factors associated with poor outcomes post haploidentical HCT, starting at HCT.

Estimate the cumulative incidences of acute and chronic GVHD, relapse, and transplant related mortality, starting at HCT.

Study Design: This is a descriptive prospective study of long-term outcomes of a cohort of MF patients that undergo haploidentical HCT.

CMS Coverage with Evidence Development Requirements

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.

Study objectives are listed in **Section 3.1**. The study enrollment plan (**Sections 2.0 and 3.0**) will monitor how many patients get enrolled by age (<65 versus ≥65) to ensure sufficient numbers of patients will be available in each group for a secondary analysis that will examine impact of age on HCT outcomes (**Section 3.5.5.3**). This will allow the study to address the needs of beneficiaries with advanced disease that are deemed to be HCT eligible. The planned comparison with non-HCT controls will be critical in determining the true value of HCT.

b. The rationale for the study is well supported by available scientific and medical evidence.

HCT is currently the only potentially curative therapy for MF, and long-term survival is well-documented in several studies discussed above. Although these studies were not limited to a Medicare population, based on similar studies, and as explained in **Sections 1.1-1.3**, age alone is not expected to be a major factor in outcomes.

- c. The study results are not anticipated to unjustifiably duplicate existing knowledge.*

To the best of our knowledge, there has not been a study of similar methodology applied to the age-group cohort specified in this study.

- 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 HLA-Matched Donor HCT Study design has 86% power to detect a 10% improvement in 5-year survival between the overall alloHCT arm and the non-HCT arm. It also has 80% power to detect a 15% improvement in 5-year survival between the MAC intensity alloHCT arm and the non-HCT arm. The Haploidentical Donor Study design has 80% power to detect a 10% difference in day 100 TRM. It also has 80% power to detect a 15% improvement day 100 TRM. The methods described in **Sections 3.5 and 4.3** have been used successfully in hundreds of CIBMTR studies of similar data.

- e. The study is sponsored by an organization or individual capable of completing it successfully.*

This study will be performed through the CIBMTR, which has performed hundreds of similar analyses during its >40-year history. The CIBMTR is a clinical research program that receives HCT outcomes data from a network of approximately 400 treatment centers worldwide. Data are collected and analyzed by the Coordinating Center, located at the Medical College of Wisconsin (MCW) in Milwaukee, WI, and the National Marrow Donor Program in Minneapolis, MN. The CIBMTR Research Database includes information for >440,000 transplant recipients and receives information for about 15,000 new transplants annually. CIBMTR data and statistical and scientific expertise have resulted in >1,000 peer-reviewed publications.

- 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.*

The data collection and analyses for this study will be done in full compliance with the specified Federal regulations. Signing a patient-

level informed consent is required for all standard patient transplant data collected and stored in the Research Database (**Appendix G**). The most recent approval of the CIBMTR Research Database Protocol v7.4 was in July 2016 (**Appendix H**). The NMDP Institutional Review Board will review this Study Plan when final.

- g. All aspects of the study are conducted according to appropriate standards of scientific integrity.*

Data safety monitoring procedures and stopping rules are described in **Sections 3.5.4.2 and 4.3.3**.

- h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.*

This study clearly demonstrates adherence to the standard Medicare requirements, as explained in study rationale (**Section 1**) and design of the matched donor (**Section 3**) and haploidentical donor (**Section 4**) studies. This document serves as a written study plan, which in combination with the master protocol, A Database Study for Hematopoietic Stem Cell Transplantation and Marrow Injuries (NCT01166009) (**Appendix C**) addresses, or incorporates by reference, the standards listed.

- 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.*

Not applicable to this study.

- 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).*

This study is registered on the ClinicalTrials.gov website NCT02934477, titled Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis.

This study falls under the auspices of NCT01166009, which is registered by the CIBMTR on the ClinicalTrials.gov website. The CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies, and Marrow Toxic Injuries is registered on the AHRQ Registry of Patient Registries.

- 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 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 accessible 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).*

Regardless of the outcomes, the results of this study will be incorporated into a primary manuscript and submitted to a peer-reviewed journal within 12 months of receiving the 595th reduced-intensity conditioning patient's and 315th myeloablative conditioning patient's 5-year follow-up data. In addition to these publications, results will be made public via an abstract submitted to the American Society of Hematology Annual Meeting, the BMT Tandem Meetings, or a similar, appropriate national meeting.

- l. 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.*

Our study will be an accurate reflection of the population of patients receiving alloHCT for MF in the United States (US) as well as similar patients receiving non-HCT therapy. The CIBMTR does not limit the inclusion of underrepresented groups and Centers reporting data to the CIBMTR 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, non HCT recipient, MF, CMS beneficiary, informed consent) in **Section 2.0** will be included.

- 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.*

The study design targets an older adult population with intermediate to high-risk MF. We expect the study results to be generalizable to those beneficiaries that are clinical candidates for transplantation based on

their overall health and disease status. This does not preclude generalizability to the subpopulations described previously.

Study Glossary

Acronym	Meaning
AML	acute myelogenous leukemia
ATG	anti-thymocyte globulin
BCM	below costal margin
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CED	Coverage with Evidence Development
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplantation
CMS	Centers for Medicare and Medicaid Services
CPI	Continuous Process Improvement
CRF	Comprehensive Report Form
DIPSS	Dynamic International Prognostic Scoring System
EBMT	European Society for Blood and Marrow Transplantation
EMH	extramedullary hematopoiesis
ET	essential thrombocythemia
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HCT-CI	Hematopoietic Cell Transplantation - Comorbidity Index
HLA	human leukocyte antigen
HSCT	hematopoietic cell transplantation
int	intermediate (risk category of DIPSS)
IPSS	International Prognostic Scoring System
IRR	incidence rate ratio
IV	Intravenously
IWGMRT	International Working Group for Myelofibrosis Research and Treatment
LFS	leukemia-free survival
MAC	myeloablative conditioning
MF	myelofibrosis
MPN	myeloproliferative neoplasms
NMDP	National Marrow Donor Program (Be The Match)
OS	overall survival
PMF	primary myelofibrosis
PreTED	Pre-Transplant Essential Data Form
PTCy	post-transplant cyclophosphamide
PV	polycythemia vera
RIC	reduced intensity conditioning
TRM	transplant related mortality
US	United States
WHO	World Health Organization

1.0 Background and Rationale

1.1 Introduction

Myeloproliferative neoplasms (MPN) is a category in the World Health Organization (WHO) classification of myeloid tumors. A subcategory is “BCR-ABL1-negative MPN”, which includes PMF, post-ET MF, and post-PV MF. These disorders are characterized by stem cell-clonal myeloproliferation.¹

In PMF, clonal myeloproliferation is associated with reactive bone marrow fibrosis, extramedullary hematopoiesis (EMH), and abnormal cytokine expression. Ineffective hematopoiesis and EMH lead to marked hepatosplenomegaly while abnormal cytokine expression leads to constitutional symptoms.²

PMF is a rare disorder. Using data from 18 cancer registry areas of the Surveillance, Epidemiology and End Results Program (SEER-18) for 2001-2012, the estimated incidence rate of PMF was 3.1 per one million person-years [age-adjusted using the 2000 US population standard]. The median age at diagnosis was 70 years.³ In this population-based analysis, PMF incidence rate was higher among men (incidence rate ratio (IRR) of 1.82 [95% confidence interval (CI), 1.69–1.96], and compared to Whites, was lower among Hispanics [IRR 0.69 (95% CI, 0.59-0.80)], Blacks [IRR 0.73 (95% CI, 0.63-0.84)], and Asians / Pacific Islanders [IRR 0.73 (95% CI, 0.63-0.85)].³

Using data from the Rochester Epidemiology Project medical record linkage system for residents of Olmsted County, Minnesota, Mesa et al.⁴ estimated an annual incidence of PMF of 1.46 cases / 100,000 population. The median age at diagnosis was 67, and there appeared to be no gender predilection.⁴ A recent report suggests a higher rate of PMF among Blacks compared to Whites but only among those aged 35-49 years of age.⁵ Across all other age groups, Blacks demonstrated lower incidence of PMF compared to Whites.⁵

MF can develop in patients with pre-existing ET or PV. The criteria for diagnosing post-ET MF or post-PV MF are published and include a prior diagnosis of PV or ET and the subsequent development of two or more features, including bone marrow fibrosis; leukoerythroblastosis; new anemia; splenomegaly; or constitutional symptoms, like night sweats, fevers, or inappropriate weight loss.⁶

The natural history of PMF is characterized by progressive marrow failure and, in some, transformation to acute myelogenous leukemia (AML). The median life expectancy is four to five years, but the prognosis varies considerably.⁷ Transformation to AML is associated with dismal prognosis with 98% mortality expected at a median of 2.5 *months* after transformation.⁸

Several validated prognostic systems exist to classify patients into groups with distinct outcomes [overall survival (OS) and leukemia-free survival (LFS)].⁹⁻¹² The most common risk-stratification protocols, International Prognostic Scoring System (IPSS) and the Dynamic International Prognostic Scoring System (DIPSS), were both developed prior to the availability of modern therapies, like ruxolitinib. The IPSS, published in 2009 by the International Working Group for Myelofibrosis Research and Treatment (IWGMRT),¹³ calculates risk for patients aged >65 years based on factors at diagnosis: the presence of significant symptoms, a hemoglobin of <10 g / dL, a leukocyte count of >25 x 10⁹ / L, or circulating blast cells. In the absence of any of these features, their data show a diagnosis of PMF carries a median OS of >11 years. Patients with low-risk disease by the IPSS, meaning they have a single one of the above risk factors, have a median OS of 95 months or just over 8 years.

The dynamic IPSS, or DIPSS,¹¹ is able to provide a slightly more clinically useful risk calculation by allowing application of the calculation at any time during the course of disease rather than only at the time of diagnosis. In the 2010 DIPSS study, the IWGMRT additionally described a model that could be applied to patients under the age of 65 years – the age-adjusted DIPSS. Again, these factors reliably predict a category of low and intermediate (int)-1 risk patients who have relatively prolonged life expectancy with a median OS that was not reached in low-risk patients and 14.2 years in int-1 risk patients. In the age-adjusted model, median survival was not reached in low-risk patients and was 9.8 years in int-1 risk patients. It is important to note that patients in the population in which this score was developed did not receive contemporary therapies, and almost none underwent alloHCT.¹¹

By incorporating three additional variables (need for red cell transfusions, unfavorable karyotype, and thrombocytopenia), using data from single institution, the DIPSS was further refined and the DIPSS-plus risk score was developed.¹² For OS, DIPSS-plus stratified patients into four risk groups: low-risk, int-1, int-2, and high-risk. The median survivals for low, int-1, int-2, and high groups were 185 months, 78 months, 35 months, and 16 months, respectively. DIPSS-plus was only prognostic for OS and not for LFS.¹²

An increasing number of somatic mutations are described in association with MF. These include JAK2, CALR, MPL, LNK, CBL, TET2, ASXL1, IDH, IKZF1, EZH2, DNMT3A, TP53, SF3B1, SRSF2, or U2AF1. However, none thus far show sufficient pathogenetic specificity.^{2,14-16} Studies are ongoing to further elucidate the mechanistic and prognostic role these mutations play.

1.2 Non-HCT therapies for PMF / post-ET MF / post-PV MF

As outlined above, PMF, post-ET MF, and post-PV MF are rare conditions. Consequently, it is difficult, if not impossible, to conduct large randomized studies of all potential therapies. The scarcity of randomized data means that many treatment practices are based on smaller, single-arm studies and consensus opinion. Historically, clinicians focused on symptom palliation due to the absence of any disease-modifying therapy.¹⁷⁻¹⁹

The discovery, in 2005, of the key role of the JAK-STAT signaling pathway in myeloproliferative neoplasms led to an acceleration, over the last decade, in translational research in these diseases. In 2011, data from Phase III randomized trials in intermediate and high-risk MF led to the approval of ruxolitinib, a first-in-class Janus Kinase (JAK)-1/2 inhibitor. Long-term follow-up of patients from these studies indicates that ruxolitinib treatment provides durable reduction in spleen volume and improvement in quality of life, and suggests a continued survival advantage for ruxolitinib.²⁰⁻²² However, the drug does not induce complete remission or cure the disease.

Ruxolitinib was tested in the US in a double-blind placebo-controlled randomized trial dubbed the COMFORT (COntrolled MyeloFibrosis Study with ORal JAK Inhibitor Therapy) I study. A parallel trial, COMFORT II, in which the comparator arm was best available therapy, was performed in Europe. Eligibility for both studies included adults with PMF, post-ET MF, or post-PV MF according to the 2008 WHO criteria and int-2 or high-risk disease as determined by the IPSS. Efficacy was defined as a reduction in spleen volume of 35% or more at 24 weeks. Symptom assessment was a key secondary endpoint.²⁰⁻²²

In the US study, 42% of the 155 patients on the Ruxolitinib arm achieved the primary endpoint of spleen response compared while <1% in the placebo arm. The investigational arm also showed benefit in secondary endpoints, with significant improvements noted in left sided abdominal pain, early satiety, night sweats and pruritis.²¹ Published simultaneously, the European study provided comparable initial results.²² Of the 146 patients randomized to receive Ruxolitinib in the latter study, 28% achieved a 35% reduction in spleen volume from baseline. No subjects receiving best available therapy met this endpoint. Quality of life endpoints were also significantly improved with the therapy.

The latest data from the European study demonstrates that, after 3.5 years of patient follow-up, ruxolitinib is associated with a 42% reduction in risk of death [hazard ratio (HR) 0.58; 95% CI, 0.36-0.93] compared with best-available therapy. Probabilities of survival were 54% and 71% in the best available therapy and ruxolitinib arms, respectively. Additionally, ruxolitinib was superior to best available therapy in improving

MF-related symptoms, which improved the quality of life in responding patients.²⁰⁻²³ Longer-term results from the US study have been published.²⁴ With a median follow-up of 3 years, 59% of patients originally randomized to ruxolitinib achieved the defined outcome of splenic response, and the hazard ratio for overall survival continued to favor patients originally randomized to ruxolitinib compared with those originally randomized to placebo [HR 0.69 (95% CI, 0.46–1.03); P=0.067].

With these data, most consensus guidelines recommend initiation of ruxolitinib in eligible patients for control of splenic enlargement and improved quality of life with the expectation that it may also prolong life expectancy. There are limitations to the use of the medication, however, including worsening of baseline anemia and thrombocytopenia, increased risk for infection, and the necessity to wean off the medication slowly, rather than rapidly, as rebound symptoms can occur with abrupt discontinuation.¹⁹

With the success of ruxolitinib, other JAK-STAT inhibitory agents are now being developed. The one closest to approval, pacritinib, was recently placed on FDA clinical hold due for increased number of deaths in the investigational arms of early phase studies.²⁵ Another agent, momelitonib, remains under investigation.²⁶ Research on another agent, fedratinib, was suspended after reports of Wernicke's encephalopathy emerged during clinical testing.²⁵ Alternative approaches to disease control, for example inhibition of telomerase activity, are promising but very early in the developmental pipeline. Although these developments are important, to date, no medical agents, even if effective in modifying symptoms, reliably reverse the underlying pathophysiology of the disease.²⁷

For patients in the low-risk or intermediate risk categories described in the previous section, the absence of disease-altering therapy means that observation alone may be a reasonable treatment approach.²⁶ Among the most important current research questions is whether or not patients who are considered low risk by DIPSS but harbor high-risk molecular features should be taken to HCT early.²⁸ This is currently decided on a case-by-case basis considering patient characteristics and the risk of HCT-related mortality. Of note, some low-risk patients have debilitating symptoms, such as fatigue, bone pain, or pruritis. The symptom burden in PMF, post-ET MF, and post-PV MF can be significant, requiring therapy to improve quality of life.^{23,29}

Management of symptoms related to anemia includes the application, in specific situations, of danazol, steroids, or erythroid-stimulating agents as well as, occasionally, the repletion of cyanocobalamin, iron, and folic acid. Gouty flares, common with the condition, can be ameliorated with anti-uric acid agents, such as allopurinol.²⁹ For a subset with unrelenting symptoms, despite disease classification of low or int-1 risk,

initiation of therapy with interferon, ruxolitinib, or a JAK-STAT agent in the setting of a clinical trial can be recommended.^{17,23}

Patients with int-2 or high-risk disease, according to the DIPSS, have significantly reduced life expectancy, with median survivals of 4 years for inter-2 patients and 1.5 years for high-risk patients.^{11,13} Most consensus reviews recommend consultation for HCT shortly after diagnosis for these individuals regardless of symptoms.¹⁷⁻¹⁹ For those deemed good HCT candidates, treatment with a JAK inhibitor prior to transplant is a common approach. For those without a suitable donor or with comorbidities indicating high risk of HCT complications, treatment ruxolitinib can be initiated or a suitable clinical trial discussed rather than proceeding with transplantation.²³

1.2.1 Discontinuation rates of ruxolitinib

Despite the demonstrated benefits of these novel agents in clinical trials as discussed above,²⁰⁻²² it remains critical to appreciate the overall rate of treatment failure using these agents in routine practice. Treatment failure definition is complex and not well developed with use of ruxolitinib.³⁰ Patients can stop ruxolitinib because of lack of optimal response or loss of response (true treatment failure). Patients can also stop therapy (or undergo dose modification) because of loss of insurance coverage or development of side effects, such as infections, severe myelosuppression leading to transfusion dependence, or intolerance. Given these challenges in defining treatment failure, especially in routine practice, rate of discontinuation of therapy provides a useful indirect estimate of treatment failure.³⁰

Long-term analysis of COMFORT-II demonstrated that only 45% of patients who were randomized to ruxolitinib remained on their therapy at 3 years.³¹ Similarly, 3-year discontinuation rate in COMFORT-I was quite high at 50%.²⁴ When one looks at discontinuation rates based on US claims database, the rate is even higher.³² Silver et al. examined the IMS Health® database, which contains National Council for Prescription Drug Programs pharmacy-dispensed prescription claims, and the MarketScan® database containing patient-level data from approximately 100 health plans and from Medicare Supplemental data. Discontinuation rates in the IMS database were 73% at 6 months. In the MarketScan database, discontinuation rates were 48% for patients with at least 6 months follow-up.³²

These discontinuation rates provide a “practical” insight into the current challenges faced by patients with PMF, post-ET MF, or post-PV MF and indeed highlight the importance of having effective and enduring alternative therapeutic strategies, especially for those with high-risk disease.

1.3 Outcomes of alloHCT in patients with PMF / post-ET MF / post-PV MF

AlloHCT is the only curative therapy for PMF, post-ET MF, and post-PV MF. However, prospective studies evaluating the role of alloHCT in reasonable numbers of patients with this rare disorder were only recently reported.

The European Society for Blood and Marrow Transplantation (EBMT) reported outcomes of 103 patients (PMF / post-ET MF / post-PV MF: 63/40) who underwent alloHCT with reduced intensity conditioning (RIC) from 2002-2007 in a prospective multicenter study.³³ Median age was 55 years (range, 32-68). The distribution of risk profiles according to the Lille score was: low risk with constitutional symptoms, 17%; intermediate risk, 53%; and high risk, 30%.⁹ All patients received busulfan, 10 mg/kg orally (or busulfan, intravenously, in equivalent doses) given in 10 doses (1 mg/kg) over 3 days; fludarabine, 180 mg/m², given as 30 mg/m² over 6 days; and antilymphocyte-globulin (Fresenius), 3x10 mg/kg (for related donor transplantation) or 3x20 mg (for unrelated donor transplantation). In 21 patients, donors were mismatched for at least one human leukocyte antigen (HLA) allele or antigen: A locus, n=3; B locus, n=1; C locus, n=6; DRB1 locus, n= 2; DQB1 locus, n= 6; locus A plus C, n= 2; and locus A plus DQB1, n= 1. One hundred patients received peripheral blood grafts, and three received bone marrow. With a median follow-up of 33 months (12-76), the 5-year survivals by Lille score were 94% in low-risk patients versus approximately 60% in the intermediate and high-risk groups. In multivariate analysis, mismatched donors and older age were associated with inferior survival.³³

The Myeloproliferative Disorders Research Consortium prospectively evaluated 66 patients that underwent alloHCT with RIC from 2007-2011.³⁴ Sixty percent were PMF. Median age was 55.5 years (range, 30-65). Ninety-five percent had intermediate or high-risk MF according to the Lille score. Eighty-six percent received peripheral blood grafts, and 14% received bone marrow. Among those with related donors (n=32), 30 were HLA-identical, and 2 were mismatched at one HLA locus. Among those with unrelated donors (n=34), 25 were HLA identical, and 9 had were mismatched at one or two loci. Pre-transplant conditioning was with fludarabine 30 mg/m² per day intravenously (IV) for 5 days (day 26 to day 22) and melphalan 70 mg/m² per day IV for 2 days (day 22 to day 21). Thymoglobulin (rabbit antithymocyte globulin; Genzyme) at a 4.5-mg/kg total dose was used as additional graft-versus-host disease (GVHD) prophylaxis only in patients receiving a graft from an unrelated donor. With a median follow-up of 25 months, 75% and 32% in the sibling donor and unrelated donor groups were alive, respectively. Primary graft failure occurred at a higher rate in with unrelated (24%) versus related donors (3%). Corresponding secondary graft failure rates were 12% versus 3%.³⁴ It is important to mention, the study was not originally designed to

compare donor sources but rather as two parallel arms (related and unrelated). The authors felt the results with related donors using the melphalan-based regimen were comparable to the results from EBMT using busulfan.³³ However, the survival results (largely driven by graft failure) in the unrelated donor group suggested the busulfan-based regimen might be preferable.³³ The authors postulated the difference could be attributed to the regimen itself, the type of ATG used, or lack of measurement of donor-specific HLA antibodies.³⁴

A recent report retrospectively evaluated the outcomes of 100 patients who received JAK 1/2 inhibitors before undergoing alloHCT from 2009-2014. Median age was 59 years. Ninety-three patients received peripheral blood, and seven received bone marrow grafts. Forty-four received full rather than reduced intensity regimens. In multivariate analysis, disease status prior to initiation of JAK 1/2 inhibitors (determined by DIPSS), response to the JAK 1/2 inhibitors [group A: clinical improvement (defined as $\geq 50\%$ improvement in palpable spleen length for spleen palpable by ≥ 10 cm, or complete resolution of splenomegaly for palpable spleen < 10 cm); B: stable disease; C: intolerance to therapy, increase in blasts to 10-19%, new onset transfusion requiring anemia; D: disease progression (new splenomegaly palpable ≥ 5 cm below costal margin (BCM) or $\geq 100\%$ increase in palpable distance BCM for baseline splenomegaly of 5 cm to 10 cm BCM, $\geq 50\%$ increase in palpable distance BCM for baseline splenomegaly of ≥ 10 cm BCM, loss of spleen response, or symptomatic splenomegaly requiring splenectomy); E: transformation to AML), and HLA-mismatched donors (but not well matched unrelated donor) compared to identical sibling group, were significant predictors for mortality.³⁵ Regimen intensity was not associated with OS in multivariate analysis. The 2-year OS in groups A-E were 91% (95% CI, 69% to 98%), 54% (95% CI, 32% to 72%), 54% (95% CI, 24% to 76%), 60% (95% CI, 30% to 80%), and 32% (95% CI, 8% to 59%), respectively.³⁵

Despite the finding in the latter study³⁵ of no difference in OS between myeloablative conditioning (MAC) and RIC regimens, the impact of dose intensity on HCT outcomes remains an important one. Popat et al.³⁶ prospectively studied 46 patients with advanced PMF / post ET MF / post-PV MF who underwent busulfan / fludarabine based alloHCT. Median age was 58 (range, 27-74). Median follow-up was 5 years (range, 1-8). Because of a high relapse rate in the first 15 patients, the dose of busulfan was increased in the next 31 patients from 130 mg/m² for 2 days to a dose calculated to achieve target AUC of 4000 umol/min/day for 4 days. The 3-year event-free survival and OS were 48% (95% CI, 35-65) and 69% (95% CI 57-84). The 3-year relapse and transplant related mortality (TRM) rates in low dose busulfan were 53% (95% CI 27-80) and 10% (95% CI 0-20). Corresponding rates for high dose busulfan were 32% (95% CI, 15-49) and 20% (95% CI, 0-40). The 3-year event-free survival for low dose busulfan and high dose busulfan were 27% (95% CI 12-62) and 58% (95% CI 43-78),

respectively. In multivariate analysis, the high dose busulfan was associated with lower relapse rate (HR 0.44; P=0.07) compared to low dose busulfan. Similarly, high dose busulfan was associated with higher event-free survival (lower treatment failure) in multivariate analysis (HR 0.5; p=0.09). None of these findings reached statistical significance, but this was presumed to be due to small sample size. The authors concluded, “Allogeneic transplantation results in long-term survival in patients with myelofibrosis with better outcome seen in earlier phase of the disease. PK guided myeloablative busulfan (AUC 16,000 $\mu\text{mol}\cdot\text{min}$) appears promising in reducing relapse rate without increasing non-relapse mortality.”³⁶

A review of the literature on alloHCT in PMF, post-ET MF, and post-PV MF was recently published.⁷

1.4 When to consider alloHCT

In a recent retrospective cohort analysis, investigators compared survival of 188 patients with PMF post alloHCT to survival of 255 patients who only received conventional treatments. The analysis was restricted to those younger than 65, and it predated the introduction of ruxolitinib. Researchers matched patients at an equivalent time from diagnosis to HCT or non-HCT therapy. The comparison was stratified by DIPSS score. The analysis suggested that proceeding immediately to HCT is associated with superior survival for patients with higher risk disease (int-2 and high-risk DIPSS); whereas a strategy of delaying HCT can confer a survival advantage for those with low-risk disease (low-risk and int-1 DIPSS).³⁷

A recent review paper suggested a strategy of early HCT could be recommended for those with high-risk disease (int-2 and high-risk DIPSS) and for a subset of int-1 patients. The latter group is defined by poor-risk molecular profile (triple negative: JAK2, CALR, MPL; or presence of any of the following: ASXL1, SRSF2, EZH2, IDH1/2), severe thrombocytopenia, severe anemia, high peripheral blood blasts percentage, or high-risk cytogenetic findings.²⁸ Furthermore, the authors suggested that careful evaluation of “MF-related co-morbidities”, such as portal and pulmonary hypertension, can also impact the decision whether to proceed to HCT or not.²⁸ Finally, they suggest that given the relatively small numbers of patients who underwent haploidentical HCT for PMF reported in the literature,³⁸ and the high graft failure rates associated with use of umbilical cord blood grafts,³⁹ alternative donor HCTs should only be considered for those who are at very high risk of AML transformation and those who stopped JAK2 inhibitor treatment due to loss of response or intolerance.²⁸

CIBMTR data suggest, among patients older than 55 with DIPSS int-2 / high, who underwent alloHCT from either an identical sibling or well matched unrelated donor, the 100-day TRM is expected to be 17% (95% CI, 9-27), with rates of 14% (95% CI, 4-28)

for MAC and 19% (95% CI, 8-34) for RIC. Gray's test p-value is 0.64 for the difference. These data are critical in counseling patients regarding risks and benefits of alloHCT. Although there are indeed higher probabilities of upfront morbidity and mortality with HCT, given that HCT remains the only curative therapeutic option, and given the high demonstrated discontinuation rates of JAK-1/2 inhibitor therapy in routine practice (up to 50% in first 6 months of therapy in US claims databases³²) (**Section 1.2.1**), long-term outcomes should be weighed against short-term risk.

1.4.1 Is age at HCT an important prognostic factor for survival among those who make it to HCT?

This question was evaluated in two recent retrospective analyses.^{35,40} Shanavas et al. retrospectively compared outcomes of HCT among 100 patients with PMF / post-ET MF / post-PV MF. The median age at HCT was 59 years (range, 32-72). In univariate analysis, those who were older than 60 years of age (n=46) had similar survival compared to those younger than 60 (n=54) (p=0.07). In multivariate analysis, age was not a significant covariate.³⁵

Similarly, in a retrospective analysis of 233 patients [median age 55 (range, 19-79)] who underwent RIC alloHCT and were reported to the CIBMTR, the adjusted relative risk of OS for patients >60 years (n=64), compared with the risk for patients 41 to 60 years of age (n=157), was 0.77 (95% CI, 0.52 to 1.12; P = 0.17), and the relative risk for progression-free survival was 1.02 (95% CI, 0.72 to 1.45; P = 0.90).⁴⁰

Given these data, we conclude that other patient-, disease-, and HCT-related variables could play a more important prognostic role than stated chronological age.

1.5 Haploidentical HCT

A major obstacle to successful alloHCT is the frequent lack of suitable HLA-matched donors. Only one-quarter of siblings will be an HLA-match. There is only a 50% chance overall, and a much lower chance for African Americans (19%) and ethnic minorities, of finding a matched unrelated donor.⁴¹ Time is also a factor. It can take months to coordinate an HLA-identical unrelated donor transplant even when a matched donor is identified.⁴² There are currently three alternative options: an unrelated donor with limited HLA mismatch, banked umbilical cord blood, or a haploidentical related donor.

Haploidentical donors share identity with the recipient for one HLA haplotype on chromosome 6 and are variably matched for HLA on the unshared haplotype. As each individual inherits one HLA haplotype from each parent and passes on exactly one HLA haplotype to each child, any patient with a living parent or child has a potential

haploidentical donor; each sibling or half-sibling has a 50% chance of sharing one HLA haplotype with the patient.

The advantage of haploidentical donors is that they can generally be identified quickly. The donors are highly motivated to donate for a family member, and, unlike cord blood donors, they can donate lymphocytes for cellular therapy of post-transplantation. Using haploidentical donors also avoids the higher graft acquisition costs for unrelated donor and umbilical cord blood products.⁴³

Given the potential for development of severe acute GVHD with a half-matched donor, efforts to eliminate alloreactive donor T cells were critical to making haploidentical transplantation a viable option. Initial efforts used ex vivo T cell depletion, most commonly by using immunomagnetic-based positive selection of CD34+ cells. High incidences of graft failure were improved by intensifying pre-transplant conditioning regimens, combining ex vivo and in vivo T cell depletion, and using “mega-doses” of CD34+ cells.⁴⁴ However, non-relapse mortality rates were up to 40%, primarily due to slow post-transplant immune recovery and opportunistic infections as well as decreased graft-versus-leukemia effects.⁴⁵

Based on initial experiments in mouse models, the Johns Hopkins group pioneered in vivo T cell depletion technique using early post-transplant cyclophosphamide (PTCy) to control GVHD by eliminating rapidly dividing alloreactive donor T cells.⁴⁶ PTCy spares the quiescent progenitor cells and memory T cells in the graft, which are less susceptible to cytotoxic chemotherapy.⁴⁶ The PTCy approach was initially developed using non-myeloablative conditioning and bone marrow grafts with a lower T cell content compared to peripheral blood. In the first Phase II study at Johns Hopkins using the PTCy approach in 68 patients, non-relapse mortality at one year was only 15% with a relapse rate of 51%; grade III-IV GVHD developed in only 6% of patients.⁴⁷ Similar results were seen in a multicenter Phase II study performed by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).⁴⁸ In the latter study,⁴⁸ neutrophil recovery occurred at a median of 16 days and platelet recovery at a median of 24 days post-HCT. Acute GVHD occurred in 32% with no instances of grade III-IV acute GVHD, and chronic GVHD incidence was only 13%. Outcomes included a non-relapse mortality of 7% and relapse of 45%, progression-free survival of 48% and overall survival of 62% at one year. Since these data were published, modifications have been proposed to decrease relapse, such as implementation of myeloablative regimens, using PBSC as a donor source, and better patient selection.⁴⁹⁻⁵²

Numbers of haploidentical transplants are increasing rapidly and are likely to continue to do so in the US and around the world given the ease of finding a donor and the low cost of collection.^{53,54} We anticipate, in the future, haploidentical donors will be a widely used donor source, especially for minorities. The CIBMTR recently published data comparing

haploidentical HCT for leukemia and lymphoma in comparison to more standard donor sources. These studies indicate outcomes similar to unrelated donor transplantation in terms of survival, relapse, and non-relapse mortality, though sample sizes were small in the haploidentical cohorts.^{55,56} These studies also indicated substantially lower chronic GVHD rates with haploidentical HCT using PTCy than standard unrelated donor HCT using calcineurin inhibitors for GVHD prevention.

While no haploidentical study has specifically addressed MF, centers such as Johns Hopkins and MD Anderson are using haploidentical HCT for MF with increasing frequency (personal communication). Moreover, the EBMT / European LeukemiaNet International Working Group recently concluded that alternative donor sources may indeed be effective in MF, but success rates and the incidence of complications, such as graft failure and GVHD, in MF patients remain to be determined.⁵⁷ They commented further that MF patients should be enrolled in prospective clinical trials and that data should be reported to outcomes registries.

1.6 CMS decision

On January 27, 2016, the US Centers for Medicare and Medicaid Services (CMS) issued the Final National Coverage Decision Memorandum for Stem Cell Transplantation (Multiple Myeloma, Myelofibrosis, Sickle Cell Disease), Administrative File CAG-00444R. In that memorandum, CMS stated it will modify the existing National Coverage Determinations Manual to cover alloHCT for these three indications under the Coverage with Evidence Development (CED) mechanism.

Per the decision memo, CMS requires eligibility for Medicare beneficiaries be limited to those with DIPSS-plus int-2 or high primary or secondary MF, while participating in an approved prospective clinical study. The study must address the following question:

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

- GVHD (acute and chronic);
- Other transplant related adverse events;
- Overall survival; and
- Quality of life (optional)

2.0 Eligibility

Patients fulfilling the following criteria will be eligible for inclusion in the study:

- PMF, post-ET MF, or post-PV MF.

- Int-2 or high-risk disease as determined by the DIPSS.
- Age ≥ 55 at the time of DIPSS assessment.
- For the alloHCT arm:
 - Donors must be a 6/6 HLA-matched related donors, defined by Class I (HLA-A and -B) intermediate resolution or high resolution DNA-based typing and Class II (HLA-DRB1) at high resolution DNA-based typing (but not monozygotic twins) OR an 8/8 HLA-A, -B, -C, and -DRB1 at high resolution DNA-based typing matched unrelated donor identified through the National Marrow Donor Program (NMDP)/Be The Match. Donors must meet institutional or NMDP/Be The Match selection criteria; there is no age restriction for sibling donors.
 - Both peripheral blood stem cells and bone marrow grafts are allowed.
 - All conditioning regimen intensities are allowed.
 - All GVHD prophylaxis regimens are allowed.
- Haploidentical donors are allowed in the Haploidentical Donor Study (**Section 3.0**).

Patients with the following criteria will be ineligible for entry into the study:

- AlloHCT using umbilical cord blood unit(s) or HLA-mismatched adult donors ($< 6/6$ HLA alleles for related and $< 8/8$ HLA alleles for unrelated).
- Overlap syndromes.

3.0 HLA-Matched Donor HCT Study

The study hypothesis is that use of alloHCT from either an identical sibling donor or well matched unrelated donor will improve the 5-year survival in patients ≥ 55 years old with int-2 / high-risk (DIPSS) PMF, post-ET MF, or post-PV MF when compared to non-HCT therapies (ruxolitinib / best supportive care). This observational study will compare outcomes of a prospectively-enrolled cohort of HCT recipients with outcomes of a cohort of age-matched historical non-HCT controls.

Patients undergoing alloHCT will receive HCT in a US transplant center and be reported to the CIBMTR using well-established CIBMTR report forms and data collection procedures. In addition to the standard CIBMTR data collection forms for MF HCT recipients,⁵⁸ a study-specific supplemental form is being developed to capture critical variables (e.g. DIPSS variables prior to JAK2 inhibitor initiation among prospectively enrolled HCT recipients) not routinely currently collected in the CIBMTR forms. The variables that will be captured on this supplemental form and the schedule of this new form are included in **Appendix A**. Data on the historical non-HCT controls will be collected at 14 US academic centers (**Appendix B**). These centers will provide data on

all consecutive patients with PMF, post-ET MF, or post-PV MF referred to their institutions between 2000 and 2012. If final numbers are large enough, it may be possible to include only those patients referred in the later years (but with sufficiently long follow-up) and with age distribution close to that of the HCT recipients to form the historical non-HCT control cohort. The starting time of the analysis will be at DIPSS assessment after referral and prior to therapy. In the alloHCT arm, this will be immediately prior to initiation of JAK2 inhibitor therapy. (We assume, in contemporary practice, nearly 100% of patients with PMF / post-ET MF / post-PV MF being referred for an alloHCT will have received JAK2 inhibitor therapy. If a patient has not received JAK2 inhibitor therapy, the DIPSS immediately prior to pre-transplant conditioning will be used.) In the control arm, the DIPSS assessment used will be the assessment immediately prior to the start of the very first medical therapy a patient received. Controls who underwent a strategy of “careful watching” and were never started on any therapy will not be compared to the HCT recipients. Patients in the control cohort who received an HCT will be censored at the time of HCT; this number is expected to be small. Given the preliminary data on the difference in event-free survival and relapse rates between MAC and RIC regimens,³⁶ and the differences in patients selected for those regimens, two co-primary analyses will be conducted, one for all alloHCT recipients versus historical non-HCT controls and one for the subset of MAC intensity alloHCT recipients versus historical non-HCT controls. Conversely, given the available data on similar outcomes between identical sibling and well-matched unrelated donor,^{35,59} these two donor types will not be analyzed separately for the comparison against the historical non-HCT controls. Similarly, given the available data on impact of age on outcomes,^{35,40} there will be no age-specific stratum analysis planned. However, the study team will monitor how many patients get enrolled by age (<65 versus ≥65) to ensure sufficient numbers of patients will be available in each group for a secondary analysis that will examine impact of age on HCT outcomes (**Section 3.5.5.3**).

The reasons we are using DIPSS¹¹ to identify high-risk patients and not DIPSS-plus¹² are:

- DIPSS has been widely used and validated in studies as a risk stratification tool for patients with MF undergoing alloHCT,^{37,40,59} whereas DIPSS-plus has not undergone this rigorous systematic evaluation in the HCT literature.
- DIPSS-plus requires successful marrow aspiration in order to evaluate cytogenetic abnormalities. Patients with long standing MF have a severely fibrotic marrow and the rate of “dry tap [unsuccessful marrow aspiration]” is high. In one of our prior publications, we attempted to stratify patients according to DIPSS-plus but faced this challenge (~30% missing cytogenetics due to dry taps) and ultimately resorted to using DIPSS.⁴⁰
- The historical control non-HCT patient dataset only includes variables for DIPSS.

- DIPSS-plus has not been validated for leukemia-free survival.

3.1 Study objectives

3.1.1 Primary

Compare the five-year survival probabilities from DIPSS assessment between the two study arms. Two co-primary analyses will be conducted, one for all alloHCT patients versus Arm 2 and one for the subset of patients receiving MAC prior to alloHCT patients versus Arm 2.

- Arm 1: AlloHCT recipients
- Arm 2: Non-HCT therapies (ruxolitinib / best supportive care recipients)

3.1.2 Secondary

- Compare LFS at five years from DIPSS assessment. Two co-secondary analyses will be conducted, one for all alloHCT patients versus Arm 2 and one for the subset of patients receiving MAC prior to alloHCT versus Arm 2.
- Identify patient-, disease-, and HCT-related factors associated with poor HCT outcomes in the alloHCT arm.
- Estimate the cumulative incidences of acute (II-IV and III-IV) and (limited and extensive) chronic GVHD, starting at HCT in the alloHCT arm.
- Estimate the cumulative incidence of TRM and relapse starting at HCT in the alloHCT arm.

3.2 Study treatments (alloHCT arm)

MF is a standard indication for alloHCT in US transplant centers. Institutional standards for both reduced intensity and myeloablative conditioning regimens and GVHD prophylaxis will be used, including standards for dose modifications for renal impairment or other factors. Ex vivo T cell depletion, or in vivo T cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab regimens are allowed when used routinely at an institution.

3.3 Study endpoints

3.3.1 Primary endpoint

The primary objective is to compare five-year survival probabilities between the two treatment arms. Survival is calculated for all patients from the date of DIPSS assessment (immediately prior to pre-alloHCT JAK-1/2 inhibitor therapy in alloHCT arm

and at time of first medical therapy initiation in the control arm) until death from any cause. Observation is censored at the date of the last follow-up for patients last known to be alive. Two co-primary endpoints are planned; first will be among all alloHCT patients versus Arm 2, and second will be among the subset of patients receiving MAC prior to alloHCT versus Arm 2.

3.3.2 Secondary endpoints

- **LFS:** Time from the date of DIPSS assessment (immediately prior to HCT in the alloHCT arm and at time of first medical therapy initiation in the control arm) to the date of progression to AML or death from any cause, whichever comes first. Observation is censored at the date of last follow-up for patients known to be alive without leukemia. Progression to AML is defined as >20% leukemic blasts in bone marrow or in the peripheral blood.

3.3.3 HCT specific endpoints

- **Hematopoietic recovery:** Time to neutrophils (ANC) $>0.5 \times 10^9/L$ (first of 3 consecutive days) and time to platelets $\geq 20 \times 10^9/L$ (first of 3 consecutive days and no platelet transfusions 7 days prior).
- **Incidence of acute GVHD:** Occurrence of grade II, III, and / or IV skin, gastrointestinal, or liver abnormalities fulfilling the Consensus criteria of acute GVHD. Patients are censored at last follow-up or second transplant.
- **Incidence of chronic GVHD:** Occurrence of symptoms in any organ system fulfilling the criteria of chronic GVHD. Patients are censored at last follow-up or second transplant.
- **TRM:** Death from any cause in the first 28 days post-transplantation, irrespective of relapse status. Death beyond day +28 will only be considered transplant related if the disease is in remission. This event will be summarized as a cumulative incidence estimate with relapse / persistent MF or AML as the competing risk.
- **Relapse:** Disease recurrence or persistence. This event will be summarized by a cumulative incidence estimate with TRM as the competing risk.

3.4 Data collection

3.4.1 Prospectively enrolled HCT recipients

All data on alloHCT recipients will be collected using the existing mechanism of the CIBMTR operating under the “CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries”, version 7.4 (NCT01166009) (**Appendix C**). The most recent versions of the CIBMTR study forms can be found at www.cibmtr.org.⁵⁸ In addition, a supplemental form will be developed to capture additional critical variables that are not currently collected (**Appendix A**). Transplant centers pre-register all transplant recipients within two weeks of starting pre-transplant conditioning. The Pre-Transplant Essential Data Form (PreTED) captures information regarding primary disease, type of graft, conditioning regimen, and GVHD prophylaxis. For the purposes of this study, centers will be asked to complete Comprehensive Report Forms (CRF) for each transplant patient.

Within the transplant cohort, initial follow-up forms are due three months post-transplant and include a 100 Days Post-HSCT Data Form, Pre and Post-HSCT Disease Insert, and a Product Form. These forms capture demographics; details of the patient’s pre-transplant disease course and treatment; the transplant regimen, including graft characteristics; and post-transplant supportive care and outcomes, including disease control, GVHD, infections, organ dysfunction, and survival. Follow-up report forms will be required annually through year six post-transplant and include a general follow-up form and a disease-specific follow-up form. Follow-up forms will be required biannually after year six post-transplant and include a general follow-up form and a disease-specific follow-up form.

Reminders of forms due for pre-registered patients and patients requiring follow-up report forms are sent to participating centers monthly. Standard CIBMTR procedures require that all contact with patients be done by the transplant center. **Appendix D** describes the CIBMTR procedures governing IRB oversight, consent, and privacy as they relate to the transplant centers and this study.

3.4.2 Historical non-HCT controls

The data dictionary and the data collection template for the variables being retrospectively collected on the non-HCT controls are included in **Appendix E**. The CIBMTR regularly collects supplemental data on comparison cohorts to support studies under its existing IRB-approved research protocol. This study will utilize standard supplemental data collection mechanisms.

3.5 Statistical analysis

3.5.1 Overview

The main objective of this study is to compare survival and LFS at five years with two co-primary analyses:

1. AlloHCT group with any conditioning regimens and the non-HCT group;
2. AlloHCT group with MAC and the non-HCT group.

Acute GVHD, chronic GVHD, TRM, and relapse will also be analyzed for the transplant group.

3.5.2 Accrual

This study will target accrual of 650 patients receiving alloHCT, including approximately 225 receiving MAC. Over the last 5 years, the annual average number of alloHCT done in the US for patients aged ≥ 55 years with MF is 130, 30-60 being ≥ 65 . Based on experience with myelodysplastic syndromes, the number of HCTs in patients ≥ 65 years is expected to increase with activation of this CED study. The study team will monitor how many patients get enrolled by age (< 65 versus ≥ 65) to ensure sufficient numbers of patients will be available in each group for a secondary analysis that will examine impact of age on HCT outcomes (**Section 3.5.5.3**).

3.5.3 Sample size and power calculation

Preliminary estimates provided by collaborating institutions (**Appendix B**) indicate that a sample size of at least 2,400 patients will be available to form the non-HCT historical controls. Using estimates from the literature on the distribution of DIPSS among patients referred to academic programs,¹² we assume that $\sim 50\%$ ($N=1,200$) of patients will have either int-2 or high-risk DIPSS score. These patients who are high risk will form the cohort from which controls will be selected. We will further select based on:

- **Treatment status.** Patients who were only observed with no active therapy will not be selected.
- **Years of referral.** Patients referred more recently will be targeted so that they had a chance to receive JAK-1/2 inhibitor therapy during their disease course but with adequate follow-up.
- **Age distribution.** We will select patients who have age distribution similar to the age distribution of the HCT recipients.

We assume in the power calculations below that we can get at least 450 comparable patients in the non-HCT arm, out of the 1,200 potentially available, for use in the

analysis. The power analysis was performed using comparisons of Kaplan-Meier estimates of OS at five years, with a two-sided 5% significance level split between co-primary comparisons so that 4% Type I error is allocated to the overall alloHCT versus non-HCT comparison and 1% Type I error is allocated to the comparison of the subgroup of MAC patients versus non-HCT patients. We assumed that 85 patients with RIC and 45 patients with MAC are enrolled per year on average based on recent CIBMTR data. The total accrual time was assumed to be 5 years with 3 years of follow-up on the last patient enrolled, for a total study duration of 8 years and a total enrolled sample size of 650 alloHCT patients (225 MAC alloHCT patients).

Power was assessed through a simulation study under the following assumptions. Survival was simulated from a Weibull distribution (with shape=0.5 in the alloHCT group and shape=1 in the non-HCT arm), and with scale chosen to result in the targeted 5-year survival (40% for alloHCT, 30% for non-HCT, and 45% for MAC alloHCT). Different Weibull shape parameters are used to more accurately match the expected shapes of the survival distributions in the cohorts, but since the comparison uses survival at a fixed time point of 5 years, there is minimal impact of the assumed shapes on the power calculations. We assumed independent exponential censoring with a 5% rate per year to reflect loss to follow-up. We also assumed interim analyses would be conducted annually starting one year after the last patient is enrolled, with Type I error controlled using an O'Brien-Fleming error spending function. The survival rate at 5 years of the non-HCT group is assumed to be 30%.

The proposed study design has 86% power to detect a 10% improvement in 5-year survival between the overall alloHCT arm and the non-HCT arm. It also has 80% power to detect a 15% improvement in 5-year survival between the MAC intensity alloHCT arm and the non-HCT arm.

Non-HCT arm (30% 5 year survival)	All alloHCT (40% 5 year survival)		AlloHCT with MAC (45% 5 year survival)	
N=450	N=650	Power = 85.8%	N=225	Power=80.5%

3.5.4 Interim analysis

3.5.4.1 Efficacy

All patients enrolled prior to the time of the interim analysis will be used to compare OS at five years. If the p-value of the test statistic is less than the nominal p-values as below, the study team will discuss whether the study should continue. We will conduct interim analysis on efficacy starting one year after the last patient is enrolled as well as approximately six, seven, and eight years after the beginning of the study. The overall

significance level will be split at 4% for the overall alloHCT comparison and 1% for the MAC intensity comparison. To control cumulative Type I error rate for each comparison at the targeted level, we will use the following nominal p-values to define significance for each interim analysis.

Critical value and power at each interim analysis for comparison of all alloHCT patients with non-HCT cohort

Calendar time since study start	Information fraction	Critical value	Nominal Type I error	Cumulative Type I error	Power to detect 30% vs. 40% for all alloHCT
6 years	0.80	2.29	0.022	0.022	71.6%
7 years	0.93	2.22	0.026	0.033	82.6%
8 years	1	2.20	0.027	0.040	85.8%

Critical value and power at each interim analysis for comparison of MAC alloHCT patients with non-HCT cohort

Calendar time since study start	Information fraction	Critical value	Nominal Type I error	Cumulative Type I error	Power to detect 30% vs. 45% for MAC only
6 years	0.73	3.02	0.002	0.002	48.9%
7 years	0.90	2.76	0.006	0.007	72.3%
8 years	1	2.67	0.008	0.010	80.5%

3.5.4.2 Stopping rules for safety

HCT is an aggressive therapy with known risks of early mortality. CIBMTR data suggest, among patients older than 55 with DIPSS int-2 / high who underwent alloHCT from either an identical sibling or well matched unrelated donor, the 100-day TRM is expected to be 17% (95% CI, 9-27), 14% (95% CI, 4-28) for MAC, and 19% (95% CI, 8-34) for RIC. Gray’s test p-value is 0.64 for the difference. However, substantial risks (up to 20%) of early HCT-related death are considered acceptable in situations in which HCT offers the only possibility for cure and long-term survival. The stopping rule for RIC and MAC was prepared based on the null hypothesis: 100-day mortality is <20%. RIC or MAC will stop if there are >20 deaths in the first 50 cases, >30 deaths in the first 100 cases, >40 deaths in the first 150 cases, or >50 deaths in the first 200 cases. If the true

TRM at 100 days is 20%, there is a 5% chance of triggering this stopping rule; if the true TRM at 100 days is 30%, there is an 80% chance of triggering this stopping rule.

3.5.5 Analysis plan

3.5.5.1 Analysis of the primary endpoint

The primary outcome of the trial is survival at five years after DIPSS assessment. The transplant cohort will be left-truncated at the time of transplant to account for the time delay between DIPSS assessment and transplant. Because this is not a randomized trial and there is the potential for bias in the non-randomized comparison, the comparisons of OS will be adjusted for the following pre-specified patient characteristics:

- Age;
- Race / ethnicity;
- Gender;
- Cytogenetics;
- Duration of disease (time from diagnosis to DIPSS assessment);
- DIPSS.

Separate co-primary analyses are planned for all alloHCT patients (with significance level of 4%) and for the subset of MAC intensity alloHCT patients (with significance level of 1%). The primary analyses will be performed using the pseudo-value approach at five years.⁶⁰ Significant covariates will be adjusted under the generalized estimating equation setting. Interaction between the main effect and significant covariates will be tested. The adjusted survival probabilities are also estimated using the Cox proportional hazards model stratified by treatment using the method of Zhang et al.⁶¹ A 95% confidence interval for the difference in adjusted OS at five years will be constructed. In addition to a point-wise comparison at five years, adjusted survival curves will be constructed and confidence bands for the difference between treatments will be generated to compare the survival probabilities across time.

3.5.5.2 Analysis of secondary endpoints

LFS at five years will be compared using the pseudo-value approach, described in Zhang et al., and will follow the analysis as described in **Section 3.5.5.1**.^{60,61}

3.5.5.3 Secondary analyses of alloHCT arm

The following secondary analyses will be conducted for patients enrolled in the alloHCT arm. The time to event for all outcomes in the following analyses starts at the time of transplant. The impact of the following factors on transplantation outcomes (i.e. OS,

disease-free or progression-free survival, relapse, TRM, acute / chronic GVHD) will be evaluated:

- Response to ruxolitinib therapy (as defined in Shanavas et al.³⁵);
- Patient age (<65 years of age versus ≥65);
- Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI);
- Disease duration;
- Cytogenetics;
- DIPSS;
- Donor type (HLA-matched sibling donor versus matched unrelated donor versus haploidentical donor).

Cox proportional hazards models will be separately performed for each of conditioning intensity in these analyses. The proportional hazards assumption will be tested. If testing indicates differential effects over time (non-proportional hazards), models will be constructed breaking the post-transplant course into two time periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The interaction between significant covariates will be examined.

4.0 Haploidentical Donor Study

If a matched related or unrelated donor (as defined in **Section 2.0**) cannot be identified, patients may proceed to alloHCT from a suitable haploidentical donor. The rate of haploidentical HCTs for a variety of hematologic malignancies is increasing,^{53,54} affording patients with no HLA-matched donors the opportunity to receive curative therapy. We believe the same trend will be observed for patients with MF. We acknowledge there are currently limited data on the long-term outcomes of haploidentical HCTs. Therefore, we propose conducting a descriptive prospective study of long-term outcomes of a cohort of MF patients that undergo haploidentical HCTs with built in early safety benchmarks. The early safety endpoint we intend to evaluate is the day 100 TRM rate. The size of the haploidentical HCT cohort will be large enough to have at least 80% power to detect 10% higher rate of day 100-TRM in the haploidentical HCT arm compared to the well-matched unrelated donor alloHCT cohort. Since a well-matched unrelated donor is usually sought for patients for whom a matched related donor could not be identified, we felt the appropriate comparator to haploidentical HCT cohort is the well-matched unrelated donor cohort.

This descriptive study of outcomes post haploidentical HCT, although not definitive since no comparison to non-HCT therapies is planned, would be extremely valuable to provide robust estimates of long-term outcomes for a technology that is viewed as extremely promising and is gaining increasing acceptance in the community as a whole.

4.1 Study objectives

4.1.1 Primary

Estimate the five-year survival probabilities with haploidentical HCT from DIPSS assessment (collected prior to JAK2 inhibitor therapy initiation).

4.1.2 Secondary

- Estimate five-year LFS with haploidentical HCT from DIPSS assessment (collected prior to JAK2 inhibitor therapy initiation).
- Identify patient-, disease-, and HCT-related factors associated with poor outcomes post haploidentical HCT, starting at HCT.
- Estimate the cumulative incidences of acute (II-IV and III-IV) and (limited and extensive) chronic GVHD, starting at HCT.
- Estimate the five-year cumulative incidences of relapse and TRM, starting at HCT.

4.2 Study treatments

Institutional standards for conditioning regimens will be used.

For GVHD prophylaxis regimens, institutional standard regimens will be used. Institutional guidelines for dose modifications for renal impairment or other factors are allowed. Ex vivo T cell depletion, or in vivo T cell depletion with ATG or alemtuzumab regimens are allowed when used routinely at an institution.

4.3 Statistical analysis

4.3.1 Overview

The main objective of this analysis is to describe outcomes post haploidentical HCT using descriptive statistics. Kaplan-Meier five-year estimates of OS and LFS will be reported. Cumulative incidence function estimates of acute and chronic GVHD, TRM, and relapse will also be reported.

4.3.2 Sample size and power

Power analysis was performed to compare TRM at day 100 of the haploidentical HCT cohort with the well-matched unrelated donor cohort. The Fisher's exact test at the significant level 0.05 was used. The TRM at day 100 for the well-matched unrelated donor was estimated to be 23% (based on CIBMTR data). The well-matched unrelated donor was assumed to have 400 patients. With 80% power, we need 287 patients to

detect a 10% difference (33% day 100 TRM among the haploidentical HCT cohort). If the day 100 TRM rate differs by 15% (38% day 100 TRM among the haploidentical HCT cohort), with 80% power we will need only 99 haploidentical HCT recipients to detect this delta.

4.3.3 Stopping rules for safety

Based on data in the CIBMTR Research Database, TRM at day 100 for patients with well-matched unrelated donor, DIPSS int-2 / high, and age ≥ 55 in RIC was 23%. The stopping rule for haploidentical HCT was prepared based on the null hypothesis: 100-day mortality is $< 23\%$. Haploidentical HCT will stop if 100 day mortality rate in the ≥ 55 year old cohort is declared too high as follows: if there are > 22 deaths in the first 40 cases, > 31 deaths in the first 80 cases, > 40 deaths in the first 120 cases, or > 49 deaths in the first 160 cases. If the true TRM at 100 days is 23%, there is a 5% chance of triggering this stopping rule; if the true TRM at 100 days is 33% there is an 80% chance of triggering this stopping rule.

4.3.4 Accrual

No reliable estimates of accrual rates could be provided; however, considering national and international trends observed in utilizing haploidentical HCTs, it is becoming the most popular alternative donor source.

5.0 Relevance to CMS Beneficiary Population

5.1 CMS CED Requirements

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.

The principal purpose of the study is to determine whether HCT meaningfully improves health outcomes for individuals ≥ 55 years old with MF. This study will compare the five-year OS probabilities from DIPSS assessment between the two study arms: alloHCT and non-HCT therapies (best supportive care). The five-year time point was chosen because despite the well-established early higher risk of morbidity with mortality with HCT, it remains the only curative approach, and long-term endpoints (such as 5-year OS) will capture fully the true value of HCT to patients with aggressive disease. An earlier time point may miss the long-term benefits of HCT. Further information regarding study objectives is provided in **Section 3.1**.

The study enrollment plan (**Sections 2.0 and 3.0**) will monitor how many patients get enrolled by age (<65 versus ≥65) to ensure sufficient numbers of patients will be available in each group for a secondary analysis that will examine impact of age on HCT outcomes (**Section 3.5.5.3**). This will allow the study to address the needs of beneficiaries with advanced disease that are deemed to be HCT eligible. The planned comparison with non-HCT controls will be critical in determining the true value of HCT.

b. The rationale for the study is well supported by available scientific and medical evidence.

HCT is currently the only potentially curative therapy for MF, and long-term survival is well-documented in several studies discussed above. Although these studies were not limited to a Medicare population, based on similar studies, and as explained in **Sections 1.1-1.3**, age alone is not expected to be a major factor in outcomes.

c. The study results are not anticipated to unjustifiably duplicate existing knowledge.

To the best of our knowledge, there has not been a study of similar methodology applied to the age-group cohort specified in this study.

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 HLA-Matched Donor HCT Study design has 86% power to detect a 10% improvement in 5-year survival between the overall alloHCT arm and the non-HCT arm. It also has 80% power to detect a 15% improvement in 5-year survival between the MAC intensity alloHCT arm and the non-HCT arm. The Haploidentical Donor Study design has 80% power to detect a 10% difference in day 100 TRM. It also has 80% power to detect a 15% improvement day 100 TRM. The methods described in **Sections 3.5 and 4.3** have been used successfully in hundreds of CIBMTR studies of similar data.

Although a randomized trial would be preferable, such a study was not deemed feasible in this rare disease. See the following sections for specific details:

- Introduction – **Section 1.1**
- Hypothesis to be tested – **Section 3.1**
- Specific aims – **Section 3.1**
- Background and significance – **Sections 1.1-1.6**
- Trial design – **Sections 3 and 4**
- Target population and recruitment target – **Sections 2.0 and 3.5.2**

- Inclusion and exclusion criteria – **Section 2.0**
- Power calculations – **Section 3.5.3**

e. The study is sponsored by an organization or individual capable of completing it successfully.

This study will be performed through the CIBMTR, which has performed hundreds of similar analyses during its >40-year history. The CIBMTR is a clinical research program that receives HCT outcomes data from a network of approximately 400 treatment centers worldwide. Data are collected and analyzed by the Coordinating Center, located at the Medical College of Wisconsin (MCW) in Milwaukee, WI, and the National Marrow Donor Program in Minneapolis, MN. The CIBMTR Research Database includes information for >440,000 transplant recipients and receives information for about 15,000 new transplants annually. CIBMTR data and statistical and scientific expertise have resulted in >1,000 peer-reviewed publications (www.cibmtr.org/ReferenceCenter/PubList/index.html). In 2010, the CIBMTR launched the CMS-approved study, “Assessment of Stem Cell Transplantation in Medicare Beneficiaries with Myelodysplastic Syndrome and Related Disorders.” In this study, >100 centers are participating, and approximately 1,300 patients ≥ 65 years old, >800 patients 55-64 years old, and >200 patients <54 years old are enrolled. A follow-up study to this ongoing CMS study of HCT outcomes is now collecting comparison data for a cohort of patients receiving non-HCT therapy for myelodysplastic syndromes.

As of December 2007, all US transplant centers are required to report data on their related and unrelated donor transplants to the CIBMTR. 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 (PreTED) for all patients. Centers provide comprehensive data (CRF) 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 document. 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 >90%. These data sets have been used to conduct numerous studies of transplant outcomes, including comparisons of HCT to best supportive care. The most recent versions of the CIBMTR study forms can be found on the CIBMTR website (http://www.cibmtr.org/DATA/Data_Mgmt_Forms/index.html).

The CIBMTR will utilize its existing center network and data collection infrastructure to obtain data for the non-HCT therapies (ruxolitinib / best supportive care) arm of the study through a supplemental data collection mechanism (**Appendix E**). **Appendix B** lists the academic centers who have agreed to provide data for these patients.

Additionally, the CIBMTR has assembled a team of HCT and MF experts to guide development, implementation, and completion of this study. Curriculum vitae for the study team members, listed below, are included in **Appendix F**.

- Wael Saber, MD, MS (Medical College of Wisconsin) – Study Co-Chair
- Laura C. Michaelis, MD (Medical College of Wisconsin)– Study Co-Chair
- Kwang Woo Ahn, PhD (Medical College of Wisconsin)
- Andrew Artz, MD, MS (University of Chicago Hospitals)
- Karen Ballen, MD (Massachusetts General Hospital)
- H. Joachim Deeg, MD (Fred Hutchinson Cancer Research Center)
- Stephanie Farnia, MPH (NMDP/Be The Match)
- Aaron Gerds, MD, MS (Cleveland Clinic Foundation)
- Kristina Gowin, DO, MD (Mayo Clinic Arizona and Phoenix Children’s Hospital)
- Vikas Gupta, MD (Princess Margaret Hospital)
- Parameswaran Hari, MD, MS (Medical College of Wisconsin)
- Zhen-Huan Hu, MPH (CIBMTR)
- Ruben Mesa, MD (Mayo Clinic Arizona and Phoenix Children’s Hospital)
- Jeanne Palmer, MD (Mayo Clinic Arizona and Phoenix Children’s Hospital)
- Uday Popat, MD (MD Anderson Cancer Center)
- Rachel Salit, MD (Fred Hutchinson Cancer Research Center)
- Patricia Steinert, PhD, MBA (CIBMTR)
- Roni Tamari, MD (Memorial Sloan Kettering Cancer Center)

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.

The data collection and analyses for this study will be done in full compliance with the specified Federal regulations. Signing a patient-level informed consent is required for all standard patient transplant data collected and stored in the Research Database (**Appendix G**). The most recent approval of the CIBMTR Research Database Protocol

v7.4 was in July 2016 (**Appendix H**). The NMDP Institutional Review Board will review this Study Plan when final.

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.

Data safety monitoring procedures and stopping rules are described in **Sections 3.5.4.2 and 4.3.3**.

h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.

This study clearly demonstrates adherence to the standard Medicare requirements, as explained in study rationale (**Section 1**) and design of the matched donor (**Section 3**) and haploidentical donor (**Section 4**) studies. This document serves as a written study plan, which in combination with the master protocol, A Database Study for Hematopoietic Stem Cell Transplantation and Marrow Injuries (NCT01166009) (**Appendix C**) addresses, or incorporates by reference, the standards listed.

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.

Not applicable to this study.

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).

This study is registered on the ClinicalTrials.gov website NCT02934477, titled Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis.

This study falls under the auspices of NCT01166009, which is registered by the CIBMTR on the ClinicalTrials.gov website. The CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies, and Marrow Toxic Injuries is registered on the AHRQ Registry of Patient Registries.

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 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 accessible 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).

Regardless of the outcomes, the results of this study will be incorporated into a primary manuscript and submitted to a peer-reviewed journal within 12 months of receiving the 595th RIC patient's and 315th MAC patient's 5-year follow-up data. In addition to these publications, results will be made public via an abstract submitted to the American Society of Hematology Annual Meeting, the BMT Tandem Meetings, or a similar, appropriate national meeting.

1. 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.

Our study will be an accurate reflection of the population of patients receiving alloHCT for MF in the US as well as similar patients receiving non-HCT therapy. The CIBMTR does not limit the inclusion of underrepresented groups, and centers reporting data to the CIBMTR 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, non HCT recipient, MF, CMS beneficiary, informed consent) in **Section 2.0** will be included. Specifically:

- **Inclusion and exclusion criteria.** Patients aged ≥ 55 years with intermediate or high-risk MF are eligible. As the study is comparing survival and other outcomes after transplantation to non-HCT therapies, study eligibility requires all patients enrolled on the study meet functional and organ function criteria that would allow them to proceed to transplantation if a suitable donor is identified.
- **Gender.** Both women and men are eligible.

- **Minorities.** The study allows the use of haploidentical donors, which promotes increased participation by minorities as these subpopulations have decreased numbers of fully matched donors available.
- **Medicare beneficiaries.** Most, if not all, enrolled individuals will be Medicare beneficiaries, particularly those aged ≥ 65 years.
- **Retention of study participants.** Academic centers will follow study participants using standard CIBMTR forms and follow-up schedule. This schedule includes follow-up visits at regular intervals post-transplantation: three months, six months, annually during years one through five, and every other year starting in year six. More than 95% of data collected by the CIBMTR is submitted electronically via FormsNet, a comprehensive electronic data submission system containing >240 forms related to capturing clinical outcomes. The system's flexible ID assignment form allows the CIBMTR to collect data on patients who receive treatment other than HCT. Robust data collection is critical to the success of the CIBMTR. The CIBMTR has in place a Continuous Process Improvement (CPI) program to ensure timeliness and completeness of data submission. Treatment centers receive CPI reports three times per year (January, May, and September), listing the number of follow-up forms that were due in the previous trimester. A form is not officially submitted until all errors are resolved and all applicable information is submitted and approved.

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.

The study design targets an older adult population with intermediate- to high-risk MF. We expect the study results to be generalizable to those beneficiaries that are clinical candidates for transplantation based on their overall health and disease status. This does not preclude generalizability to the subpopulations described previously.

6.0 List of Appendices

- **Appendix A.** Variables proposed to be captured on supplemental form for HLA-Matched Donor HCT Study
- **Appendix B.** Academic centers collecting data on historical non-HCT controls
- **Appendix C.** CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries, version 7.4 (NCT01166009)

- **Appendix D.** CIBMTR procedures governing human subjects research and HIPAA compliance
- **Appendix E.** Data dictionary and data collection template for variables to be collected on historical non-HCT controls
- **Appendix F.** Biosketches for study team members
- **Appendix G.** Patient-level informed consent required for all patient transplant data collected by the CIBMTR and stored in the Research Database
- **Appendix H.** NMDP Institutional Review Board approval of CIBMTR Research Database Protocol, version 7.4 (July 2016)

7.0 References

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