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A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome

(Posted on clinicaltrials.gov as NCT02016781)

BMT CTN PROTOCOL 1102
VERSION 5.0

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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute

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PROTOCOL SYNOPSIS - BMT CTN PROTOCOL 1102

A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome

Study Chairpersons: Ryotaro Nakamura, M.D. and Corey Cutler, M.D., M.P.H., F.R.C.P.(C)

Study Design: This study is designed as a multicenter trial, with biological assignment to one of two study arms; Arm 1: Reduced intensity conditioning allogeneic hematopoietic cell transplantation (RIC-alloHCT), Arm 2: Non-Transplant Therapy/Best Supportive Care.

Primary Objective: The primary objective is to compare the three-year overall survival (OS) probabilities between two treatment arms.

Secondary Objectives: Patients will also be assessed for the following:

1. Compare leukemia-free survival (LFS) at 3 years from patient consent.

2. Compare Quality of Life (QOL) measures between treatment arms

3. Compare Cost-Effectiveness measures between treatment arms (see Appendix F for ancillary cost-effectiveness protocol)

Accrual Objective: The trial will accrue a total of 338 patients if the ratio of HCT vs. nonHCT is 6:4 and 400 patients if the ratio of HCT vs. nonHCT is 7:3.

Accrual Period: The estimated accrual period is 2.5-3.5 years.

Study Duration: Patients will be followed for three years after biological assignment; total time from start of accrual will be approximately 5.5-6.5 years.
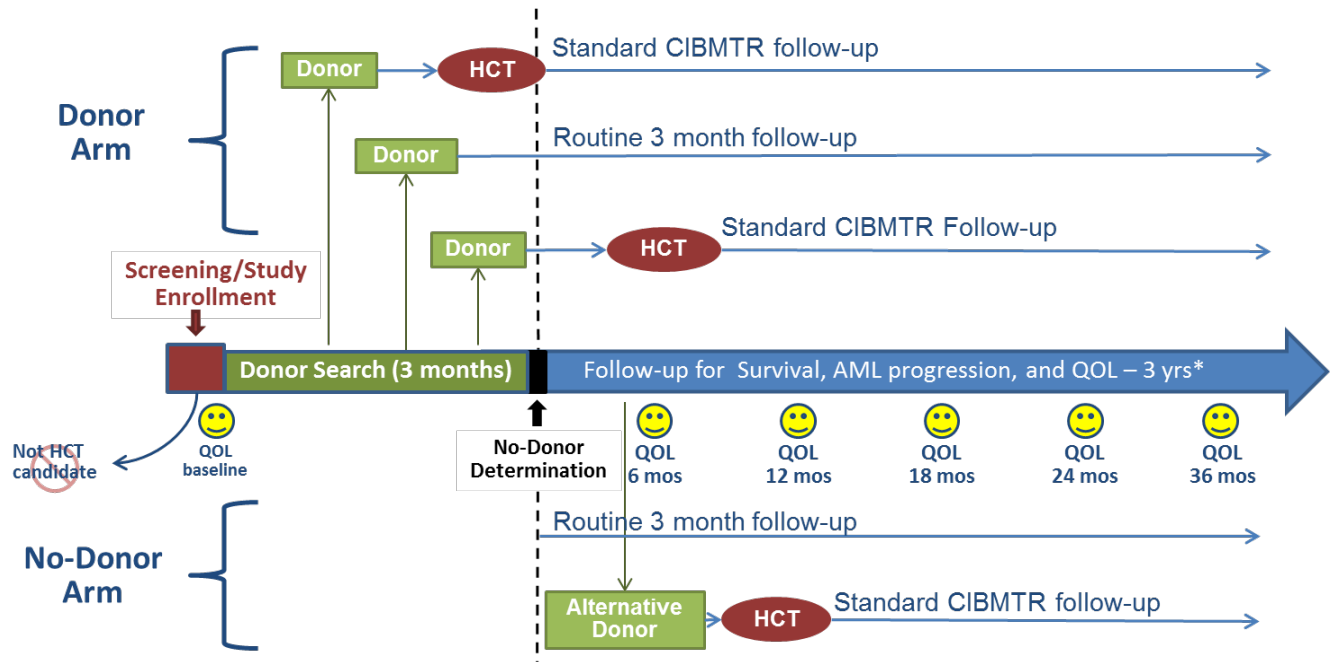
Eligibility Criteria: Patients 50-75 years of age with a history of de novo intermediate-2 or high-risk myelodysplastic syndrome (MDS) by the International Prognostic Scoring System (IPSS) with < 20% marrow blasts. MDS must be of an acceptable subtype. Patients must be considered to be suitable RIC alloHCT candidates at the time of initial evaluation based on medical history, physical examination, and available laboratory tests. Specific testing for organ function is not required for eligibility but, if available, these tests should be used to judge eligibility.

Patients and physicians must be willing to comply with treatment assignment:

1. No intent to proceed with alloHCT using donor sources not specified in this protocol, including HLA-mismatched related or unrelated donors (< 6/6 HLA related matched or < 8/8 HLA unrelated matched) or umbilical cord blood unit(s)

2. No intent to use myeloablative conditioning regimens

3. Intent to proceed with RIC alloHCT if a matched sibling or matched unrelated donor is identified. There is no requirement as to the timing of the transplantation.

To be biologically assigned to the alloHCT arm, patients must have either a 6/6 HLA-matched related donor, defined by Class I (HLA-A and -B) intermediate resolution or high resolution DNA-based typing and Class II (HLA-DRBI) at high resolution DNA-based typing OR an 8/8 HLA-A, -B, -C, and -DRB1 at high resolution DNA-based typing unrelated donor identified within 90 days from the date of consent.

STUDY SCHEMA

TABLE OF CONTENTS

LIST OF APPENDICES

CHAPTER 1

1.   BACKGROUND AND RATIONALE

1.1.   Background

A subject of clinical urgency for researchers, clinicians, patients, and health care underwriters such as Medicare, is the role of allogeneic hematopoietic cell transplantation (alloHCT) in the treatment of older patients with higher risk myelodysplastic syndromes (MDS). The use of reduced intensity conditioning (RIC) regimens has extended HCT to the care of older patients with acute myelogenous leukemia (AML) and lymphoma and a number of retrospective and phase II trials for patients with MDS now show the curative potential of RIC alloHCT in selected patients.[1, 2, 3, 4, 5, 6, 7] Concomitantly, new drugs have been developed for nontransplant therapy of MDS, including hypomethylating agents, which result in improved hematopoietic function and delayed transformation to acute leukemia.[8] While it is believed that RIC alloHCT provides a survival advantage over hypomethylating therapy because of its curative potential, RIC alloHCT also carries the risk of early transplant-related mortality and the relative effectiveness of the two approaches is uncertain, particularly in older patients. This protocol is designed to evaluate the relative benefits of RIC alloHCT compared to non-transplant therapies focusing on overall survival. The hypothesis to be tested is that RIC alloHCT improves overall survival in patients with higher risk MDS compared to patients who receive only hypomethylating therapy or best supportive care. The study is a prospective, multi-center, biologic assignment trial of hypomethylating therapy or other best supportive care versus RIC alloHCT from HLA-matched related and unrelated donors in patients aged 50.0 to 75.0 years with higher-risk MDS.

1.2.   Myelodysplastic Syndrome

MDS is a clonal disorder of hematopoietic precursors and stem cells, which may evolve to a terminal phase resembling acute leukemia. Alternatively, patients may suffer progressive peripheral blood cytopenias and hematopoietic failure, eventually succumbing to complications of bleeding and infection. The international prognostic scoring system (IPSS) for MDS assesses patients' risk for transformation and survival at the time of diagnosis and is based on analysis of bone marrow blasts, karyotype, and cytopenias.[9] Median survival for patients with low-risk disease is approximately 5.7 years; it is 11.8 years for low-risk patients younger than 60. Among patients with intermediate-2 disease (composite score 1.5-2), median survival is 1.2 years for all patients and 1.8 years for those younger than 60. In patients with high risk disease, however, the prognosis is measured in months in both younger and older patients.[10] A newer iteration of the IPSS score was recently proposed but has not yet been used in clinical trials.[11]

1.3.   Allogeneic Hematopoietic Cell Transplantation for MDS

AlloHCT is the only curative treatment modality for MDS, but the use and timing of transplantation remain controversial, particularly in older patients. The relatively chronic course of MDS often leads to reluctance to accept the risks associated with HCT where non-relapse mortality (NRM) rates are in the range of 20-35%, related to organ toxicity, graft-versus-host

disease (GVHD), and infections. Recently, an HCT-specific co-morbidity index has provided a useful guide for HCT risk assessment of HCT and can be applied to transplantation candidates with a variety of disorders, including MDS.[12] The IPSS is also useful in determining the timing of transplantation in younger patients who have HLA-identical siblings.[13, 14, 15] Several studies indicate that patients in the intermediate-2 and high risk IPSS groups have longer life expectancy when transplanted early, with delay of HCT resulting in loss of life years. In contrast, patients in the low-risk group have the best life expectancy if HCT is delayed until there is evidence of disease progression. Optimal timing for patients in the intermediate-1 risk category is less clear.[14] A recent study extended a Markov decision model to elderly MDS patients and showed for de novo MDS patients aged 60–70 years with low/intermediate-1 disease, early transplantation was not the preferred strategy unless MDS-associated QOL impairment was substantial. For intermediate-2/high IPSS risk, early RIC alloHCT offered a life expectancy benefit, with quality adjusted survival benefit detectable earlier.[16] While no prospective controlled study has been published, a retrospective study comparing alloHCT and treatments with hypomethylating agents suggests a survival advantage for alloHCT compared with azacytidine therapy in medically fit patients with high-risk MDS age 60-70 years.[17]

Conventional high dose conditioning regimens include myeloablative doses of chemotherapy and/or radiation. These regimens are often poorly tolerated by older patients or those with significant comorbidities and are generally offered to patients under the age of 50 years with good performance status. The introduction of RIC regimens over the last decade has allowed expansion of the upper age for alloHCT, with patients above age 70 transplanted successfully. Unfortunately, though treatment-related mortality is lower, some studies suggest higher incidences of relapse with lower intensity regimens. Patients with the low disease burden tend to have the best success rates with this approach. For this reason, some have recommended the use of cytoreductive chemotherapy prior to RIC alloHCT, but no controlled trials of this strategy have been conducted.[18, 19].

Over the last several years, multiple groups have used RIC alloHCT to treat MDS with two to three-year overall survival rates ranging from 27% to 70% depending on cohort and regimen characteristics.[1, 3, 4, 5, 20] Lim *et al* analyzed a group of 1,333 patients reported to the European Group for Blood and Marrow Transplantation (EBMT), ages 50 to 74 (median 62); 62% received RIC. The four-year survival rate was 31%, the NRM rate was 39% and the relapse rate was 36%.[6] No significant impact of age or transplantation regimen on outcomes was noted. Advanced disease stage at transplantation was the major independent predictor of poor outcomes. McClune *et al* reported data on 181 patients to the Center for International Blood and Marrow Transplant Research (CIBMTR), aged 40 to $\geq$ 65 (median 67); 68% received RIC. The two-year survival rate for this group was 45%, the NRM rate was 35%, and the relapse rate was 29%.[7] As in the EBMT study, the CIBMTR data showed no significant impact of age on outcomes. These two recent registry-based studies of older patients transplanted for MDS reflect results in the community-at-large and support the safety of alloHCT for older patients with MDS.

More recently, a study from the CIBMTR evaluated the outcomes of 701 adult MDS patients who underwent allogeneic HCT between 2002 and 2006. This study focused its analyses on the type of HCT donors (matched-related donor [MRD], n=176; 8/8 HLA allele matched unrelated donor [MUD], n=413; 7/8 MUD, n=112). The median age was 53 years (range, 22-78). Sixty-five

percent had advanced disease at HCT and 19% had therapy-related MDS. Seventy-seven percent received peripheral blood stem cells, and 40% received RIC regimens. The 100-day cumulative incidence of grades B-D acute GVHD was significantly lower in MRD HCT recipients than 8/8 MUD and 7/8 MUD HCT recipients (42%, 54%, and 57%, respectively; p=.009). The corresponding adjusted three-year disease free survival (DFS)/survival estimates were 40%/47% for MRD, 35%/38% for 8/8 MUD, and 29%/31% for 7/8 MUD HCT recipients. In multivariate analysis, adjusting for patient-related (age, gender, KPS), disease-related (IPSS stage at diagnosis, WBC count at diagnosis, therapy-related MDS, and disease status at HCT), and HCT-related variables (time between diagnosis and HCT, donor-recipient CMV and gender match, graft type, conditioning and GVHD prophylaxis regimens), 8/8 MUD HCT recipients had similar DFS and survival rates compared to MRD HCT recipients (relative risk [RR] 1.11 (95% confidence intervals [CI] 0.89-1.39) and 1.24 (95% CI 0.98-1.56), respectively). 7/8 MUD HCT recipients had an inferior DFS and survival compared to MRD HCT recipients (RR 1.43 (95% CI 1.08-1.91) and 1.62 (95% CI 1.21-2.17), respectively), and 8/8 MUD HCT recipients (RR 1.29 (95% CI 1.00-1.65) and 1.30 (95% CI 1.01-1.68), respectively). Differences in outcome were largely related to excess TRM (RR 1.37 and 1.71 for 8/8 MUD and 7/8 MUD respectively, p < 0.05 for both comparisons). Unrelated donor status or mismatch was not associated with less relapse (overall p value=0.33). In patients with MDS, transplantation from 8/8 MUD and MRD donors produce similar survival; however, 7/8 MUD HCT is associated with inferior outcomes.[21]

1.4.   Hypomethylating Therapy for Treatment of MDS

Azacytidine (5-azacytidine) and decitabine (5-aza-2'-deoxycytidine) are two hypomethylating agents approved by the Food and Drug Administration for treatment of MDS. The rationale for hypomethylation therapy is the observation that aberrant DNA methylation is frequently seen in patients with MDS. These drugs indirectly deplete methylcytosine and cause hypomethylation of target gene promoters involved in disease initiation or progression, making them appropriate targets for pharmacologic therapy.

Azacytidine was first synthesized in 1963 and demonstrated activity in four AML trials in the 1970s, resulting in complete remission in 17% to 36% of patients.[22] The registration study leading to FDA approval for azacytidine for all MDS subtypes was a phase III trial in which transfusion-dependent MDS patients were randomized to receive azacytidine or supportive care. Patients in the supportive care arm were allowed to cross over to the treatment arm at time of disease progression.8 Ninety-nine patients were randomized to the treatment arm, in which azacytidine was administered at 75 mg/m^2 daily for 7 days of a 28-day cycle, and 92 to the supportive care arm, of whom 49 crossed over to receive active therapy. When these and other CALGB data were analyzed using international working group (IWG) criteria, Silverman *et al* reported response rates of 14% complete response (CR) + partial response (PR) and 30% hematologic improvement.8 There was a significant delay in transformation to AML or death, but not a significant prolongation of survival in the treatment arm. Major toxicities included cytopenias. Patients also reported nausea and injection site-related complications.

Azacytidine was next explored in a Phase III trial in which higher-risk patients with MDS were randomized to receive azacytidine, at the dose used in the registration study, versus conventional care including: best supportive care, low-dose cytarabine, or intensive AML-type induction

chemotherapy, as selected by investigators prior to randomization.[23] Of 358 patients, 179 were randomized to azacytidine and 179 to conventional care, with the majority (n=105) receiving best supportive care. Overall response rates (ORR) with azacytidine were significantly greater than with conventional care, 29% versus 21%. With a median follow-up of 21.1 months, median survival was 24.5 months for the azacytidine arm and 15 months for the conventional care arm (hazard ratio .58, *P* = .0001). The superior activity of azacytidine in this study, compared with both conventional care and previous azacytidine studies, is credited to an appropriately selected population of higher-risk patients with MDS and to a median duration of therapy of more than 9 months.

Decitabine, developed in 1964, was also first explored in AML populations. The Phase III registration trial for MDS randomized 89 patients to receive the drug, 81 to receive supportive care.[24] Patients received decitabine at a dose of 15 mg/m^2 every 8 hours over 3 days, with a cycle repeated every 6 weeks. Using IWG criteria, CRs occurred in 9%, PRs in 8%, and hematologic improvement in 13% of patients, for an ORR of 30%. As with 5-azacytidine, the major toxicities were hematologic. Unlike with azacytidine, there was not a significant delay in transformation to AML or death in this study. Since the two drugs are biologically similar, this difference is often attributed to variation in the patient population enrolled to each study (more early MDS patients in the decitabine study) and to an inadequate number of cycles of decitabine given (median of 2). Alternate dosing schedules, including once-daily dosing of decitabine over 5 days every 28-day cycle, were explored in higher-risk patients given a median of > 5 cycles of therapy, and yielded CR rates equivalent or better than those seen with azacytidine.[25, 26] A Phase III survival study in higher-risk patients with MDS was conducted in Europe, comparing 119 patients treated with decitabine at the registration study dosing schedule, to 114 patients randomized to best supportive care. While the CR+PR rate was 23% (similar to azacytidine), the study was unable to demonstrate a survival advantage, with patients randomized to drug living a median of 10.1 months and those randomized to best supportive care living a median of 5.8 months (hazard ratio 0.88, *P* = .38). Progression-free survival (PFS), but not acute myeloid leukemia (AML) -free survival (AMLFS), was significantly prolonged with decitabine versus BSC (median PFS, 6.6 v 3.0 months, respectively; HR, 0.68; 95% CI, 0.52 to 0.88; P = .004; median AMLFS, 8.8 v 6.1 months, respectively; HR, 0.85; 95% CI, 0.64 to 1.12; P = .24). AML transformation was significantly (P = .036) reduced at 1 year (from 33% with BSC to 22% with decitabine).

Combination therapy has also been explored. A phase II trial of azacytidine (75 mg/m^2/d x 5 days) in combination with lenalidomide (10 mg/d x 21 days (28-day cycle)) was conducted in patients with higher-risk MDS.[27] This study demonstrated the overall response rate (per modified MDS IWG criteria) of 72% (CR: 44%), median CR duration of 17+ months (range, 3-39+) and median overall survival of 37+ months (range, 7-55+) for CR patients, 13.6 months for the entire cohort (range, 3-55). Another phase I study evaluated the combination of azacytidine and vorinostat in MDS and AML patients. There were no serious non-hematologic toxicities, and responses were seen in up to 86% of patients.[28] The Southwest Oncology Group (SWOG) has recently begun accrual to a 3-arm randomized phase II study of a) azacytidine + lenalidomide versus b) azacytidine + vorinostat versus c) azacytidine alone for higher risk myelodysplastic syndromes.[29]

Although these results from hypomethylating therapy represent an important advance for patients with MDS, 40% to 50% of patients did not respond to therapy, and most responders experienced

disease progression within 2 years of response.[23] In a recent study,[30] 435 patients with high-risk MDS and former refractory anemia with excess blasts in transformation (RAEB-T) were evaluated for outcome after azacytidine failure. The cohort of patients included four data sets (i.e., AZA001, J9950, and J0443 trials and the French compassionate use program). With the median follow-up after azacytidine failure of 15 months, the median overall survival was 5.6 months, and the 2-year survival probability was 15%. Data on treatment administered after azacytidine failure were available for 270 patients, demonstrating a better outcome associated with allogeneic HCT and investigational agents compared with conventional clinical care.

1.5. Quality of Life

In the randomized trials comparing hypomethylating agents and best supportive care, both azacytidine and decitabine were associated with an improved self-reported QOL scales, evidenced by the reduction of transfusion requirements, decreased rate of infections and hospitalizations, as well as improvement of fatigue, dyspnea, and physical functioning in patients receiving azacytidine. Comparisons of QOL between alloHCT and hypomethylating agents/non-HCT therapy may be confounded by systematic differences in patients who undergo alloHCT versus non-alloHCT therapy. In a literature review,[31] three studies have reported worse QOL after alloHCT, including physical, cognitive, emotional, and social functioning as well as overall QOL. Four studies reported no statistically significant differences between alloHCT and standard-dose chemotherapy. QOL appears to be better after alloHCT than chemotherapy when patients with and without relapse are included. This pattern of findings suggests that differential rates of relapse in alloHCT and chemotherapy patients may influence QOL findings, with higher rates of relapse in the chemotherapy group potentially associated with worse QOL in that group. As MDS patients generally require continued treatment and supportive care, the QOL measurements may be improved with alloHCT despite the known adverse factor of GVHD.

1.6. Study Rationale

Advances in both the understanding of MDS and in the development of alternatives to standard leukemia induction therapy in the treatment of MDS, including hypomethylating therapy and RIC alloHCT for older patients, lead to questions about the appropriate role and timing of these therapies. This trial will compare RIC alloHCT with hypomethylating/best supportive care in patients with higher risk MDS who are referred for transplantation evaluation. The proposed trial is consistent with the National Comprehensive Cancer Center (NCCN) Treatment Guidelines for Myelodysplastic Syndromes[32] and with suggestions from a recent review article by Giralt *et al.* regarding clinical trials to provide evidence for Medicare coverage of allogeneic transplant for MDS.[33] The design will use assignment to transplantation, when a donor is available, or best supportive care (usually hypomethylating therapy) when a suitable matched related or unrelated donor is not available. Patients with an HLA-matched sibling or unrelated donor will proceed to allogeneic transplantation utilizing an institutionally-approved RIC regimen. Patients without a suitable donor will be offered hypomethylating therapy (or other best supportive care). The primary objective is to determine whether there is a meaningful benefit (overall survival advantage) among those who undergo RIC alloHCT when compared to those who continue on hypomethylating therapy/best supportive care.

CHAPTER 2

2.   STUDY DESIGN

2.1.   Study Overview

The study hypothesis is that use of RIC alloHCT will improve three year overall survival in patients with Intermediate-2/High risk MDS when compared to DNA hypomethylating therapy / best supportive care. This study is designed as a prospective, comparative biologic assignment trial of RIC alloHCT from related and unrelated donors versus hypomethylating therapy / best supportive care among patients with Intermediate-2/High risk MDS. Study subjects will be biologically assigned to one of the two treatment arms based on the availability of an HLA-matched related or unrelated donor (Figure 2.1). All subjects are initially assigned to the non-transplant arm. Subjects will be re-assigned to the transplant arm should a suitable donor be identified within 90 days of informed consent. Both the RIC alloHCT regimen and non-transplant therapy/best supportive care will be at discretion of the treating physician. Patients will be evaluated for survival, progression to acute leukemia, and quality of life (QOL).
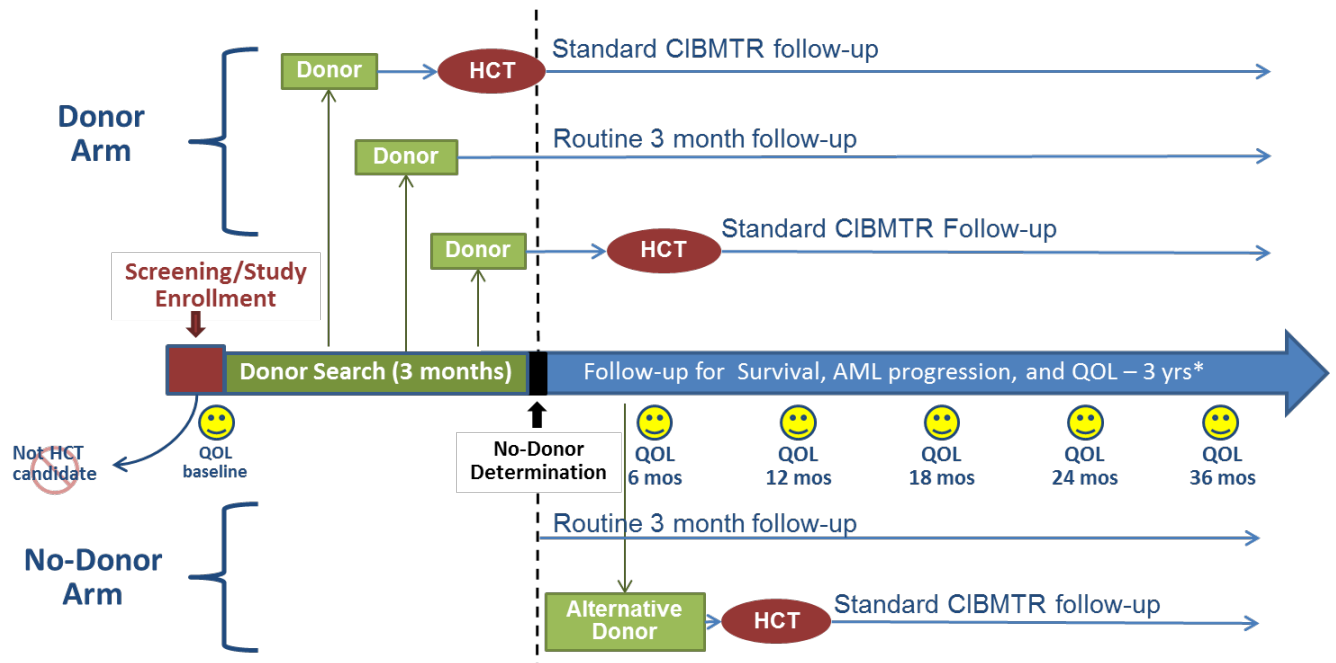
Figure 2.1: Study Schema

2.2.   Study Objectives

2.2.1. Primary Objective

Compare the three-year overall survival probabilities between the two study arms using an intent-to-treat analysis.

Arm 1: RIC alloHCT

Arm 2: Hypomethylating Therapy / Best Supportive Care

2.2.2. Secondary Objectives

1. Compare leukemia-free survival (LFS) at 3 years from patient consent

2. Compare QOL measures between treatment arms

3. Compare Cost-Effectiveness measures between treatment arms (see Appendix F for ancillary cost-effectiveness protocol)

2.3.   Patient Eligibility

Patients must meet specified eligibility criteria for entry into the study.

2.3.1. Patient Inclusion Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

1. Patients with de novo MDS who have, or have previously had, Intermediate-2 or High risk disease as determined by the IPSS (see Appendix E)[9]. Current Intermediate-2 or High risk disease is <u>NOT</u> a requirement.

2. Patients must have an acceptable MDS subtype:

   - Refractory cytopenia with unilineage dysplasia (RCUD) (includes refractory anemia (RA))

   - Refractory anemia with ringed sideroblasts (RARS)

   - Refractory anemia with excess blasts (RAEB-1)

   - Refractory anemia with excess blasts (RAEB-2)

   - Refractory cytopenia with multilineage dysplasia (RCMD)

   - Myelodysplastic syndrome with isolated del(5q) (5q–syndrome)

   - Myelodysplastic syndrome (MDS), unclassifiable

3. Patients must have fewer than 20% marrow blasts within 60 days of consent.

4. Patients may have received prior therapy for the treatment of MDS, including but not limited to: growth factor, transfusion support, immunomodulatory (IMID) therapy, DNA hypomethylating therapy, or cytotoxic chemotherapy prior to enrollment.

5. Age 50.0-75.0 years.

6. Karnofsky performance status ≥ 70 or ECOG ≤ 1 (see comparison scale in Appendix D).

7. Patients are eligible if no formal unrelated donor search has been activated prior to date of consent. A formal unrelated donor search begins at the time at which samples are requested from potential NMDP donors. Patients who have started a sibling donor search or who have found a matched sibling donor are eligible.

8. Patients and physicians must be willing to comply with treatment assignment:

    a) No intent to proceed with alloHCT using donor sources not specified in this protocol, including HLA-mismatched related or unrelated donors (< 6/6 HLA related matched or < 8/8 HLA unrelated matched) or umbilical cord blood unit(s).

    b) No intent to use myeloablative conditioning regimens.

    c) Intent to proceed with RIC alloHCT if a matched sibling or matched unrelated donor is identified. There is no requirement as to the timing of the transplantation.

9. Patients must be considered to be suitable RIC alloHCT candidates at the time of enrollment based on medical history, physical examination, and available laboratory tests. Specific testing for organ function is not required for eligibility but, if available, these tests should be used to judge eligibility.

10. Signed informed consent

2.3.2. Patient Exclusion Criteria

Patients with the following will be ineligible for enrollment onto this study:

1. Therapy-related MDS (defined as the occurrence of MDS due to prior exposure to systemic chemotherapy and/or radiation)

2. Current or prior diagnosis of AML

3. Chronic myelomonocytic leukemia or myelodysplastic/myeloproliferative neoplasm (unacceptable MDS subtypes); uncontrolled bacterial, viral or fungal infection (currently taking medication and with progression or no clinical improvement) at time of enrollment.

4. Patients with prior malignancies, except treated non-melanoma skin cancer or treated cervical carcinoma in situ. Cancer treated with curative surgery without chemotherapy/radiation therapy ≥ 5 years previously will be allowed. Cancer treated with curative surgery < 5 years previously will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs.

5. Prior autologous or allogeneic HCT

6. Human Immunodeficiency Virus (HIV) infection

7. Patients of childbearing potential unwilling to use contraceptive techniques

8. Patients with psychosocial conditions that would prevent study compliance

2.4.　　Donor Selection Guidelines

Donors must be a 6/6 HLA-matched related donor, defined by Class I (HLA-A and -B) intermediate resolution or high resolution DNA-based typing and Class II (HLA-DRBI) 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). Donors must meet institutional selection criteria, and there is no age restriction for sibling donors. Allogeneic transplantation using umbilical cord blood unit(s), mismatched adult donors (< 6/6 HLA alleles for related and < 8/8 HLA alleles for unrelated) or haploidentical donors is not allowed.

2.5.　　Study Treatments

Patients must receive either RIC alloHCT (bone marrow or peripheral blood stem cells) or non-transplant therapy according to their treatment assignment. The specific transplant or non-transplant treatment regimen will be at the discretion of the treating physician. The following are examples of *acceptable* regimens for non-transplant therapy, conditioning regimens, and GVHD prophylaxis regimens. Hypomethylating therapy is the accepted standard therapy of treatment-naïve patients with Int-2/High Risk MDS not undergoing transplantation. Participation in Phase II clinical trials of HCT or non-transplant therapy is allowed with the exception of experimental graft manipulation studies.

2.5.1. Hypomethylating Therapy – Examples of Standard Therapies

Azacytidine: 75 mg/m^2 by subcutaneous injection or IV for 7 days; 28 day cycles

Decitabine: 20 mg/m^2 IV daily for 5 days; 28 day cycles

Hypomethylating-based therapy on an Intergroup clinical trial (e.g., SWOG S1117)

2.5.2. Reduced Intensity Conditioning Regimens

Institutional standard regimens will be used. All regimens must be declared by the center as a preferred regimen in order to assure that alloHCT is performed according to the institutional standard. Deviations from the preferred regimen must be cleared with the study team. Institutional guidelines for dose modifications for renal impairment, obesity, or other factors are allowed. As a general consideration, the following limits on conditioning dose intensity delineate myeloablative regimens:

1. TBI doses of ≥ 500 (unfractionated) cGy and ≥ 800 cGy (fractionated)
2. Busulfan dose ≥ 9.5 mg/kg
3. Melphalan ≥ 150 mg/m^2

2.5.3. GVHD Prophylaxis Regimen

Institutional standard regimens will be used. All GHVD regimens must be declared for the center as a preferred regimen in order to assure that alloHCT is performed according to the institutional

standard. Deviations from the preferred regimen must be cleared with the study team. 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. Highly exploratory phase I trials of ex-vivo T cell depletion or other graft manipulations will not be allowed. The protocol team will review those studies.

2.6.   Supportive Care

2.6.1. Post-HCT

All supportive care will be given in keeping with the BMT CTN Manual of Procedures (MOP) and local institutional guidelines. All patients will receive prophylaxis against bacterial, fungal, and viral infections during the post-HCT period according to institutional standards.

2.6.2. Hypomethylating Therapy/Best Supportive Care

All supportive care will be given in keeping with local institutional guidelines.

2.7.   Participant Risks

AlloHCT recipients incur risks from conditioning and post-HCT complications, which must be weighed against the risk of complications in the absence of transplantation during hypomethylating therapy/non-HCT therapy. Major risks common to both transplantation and non-transplantation therapies include: 1) Infection, which can be bacterial, viral, parasitic, or fungal, occurs commonly after transplantation due to impaired immunologic reconstitution (in MDS, infection occurs due to neutropenia and granulocyte dysfunction); 2) Bleeding occurs after transplantation and with non-transplantation therapy due to thrombocytopenia; 3) Damage of all or any of the major organs may occur as a result of reactions to drugs (e.g., chemotherapy, antibiotics, anti-fungal medications), and as a result of destructive processes (e.g., infection); and 4) Relapse or progression may occur, especially in patients with advanced disease status at time of treatment. Major risks associated with alloHCT can be 1) Acute and chronic GVHD and 2) Graft failure, and both can result in significant organ dysfunctions and subsequent mortality. While expected treatment-related mortality (TRM) varies widely in non-HCT therapy depending on its intensity (negligible in transfusion support only but up to 5-10% in high-intensity induction therapy), the TRM is expected range about 20-30% with RIC alloHCT. Patients' QOL can be affected by these clinical complications in HCT/non-HCT therapies. QOL of MDS patients are also known to be reduced due to symptoms associated with pancytopenia (infections/bleeding/fatigues) as well as frequent need for transfusions.

CHAPTER 3

3.   STUDY OBJECTIVES AND ENDPOINTS

3.1.   Primary Objective and Endpoint

The primary objective for this study is to compare three-year overall survival probabilities between two treatment arms (Arm 1: RIC alloHCT and Arm 2: Hypomethylating therapy/best supportive care). Overall survival is calculated for all patients from date of patient consent until death from any cause. Observation is censored at the date of last follow-up for patients last known to be alive.

3.2.   Secondary Objectives and Endpoints

3.2.1. Three-year Leukemia-free Survival (LFS)

LFS is defined as the time from the date of patient consent 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.

3.2.2. Relapse for HCT Arm

Patients assigned to the HCT arm will be followed for relapse of their MDS.

Disease relapse for patients with MDS:

- Satisfying criteria for evolution into acute leukemia; or,

- Reappearance of pre-transplant morphologic abnormalities, detected in bone marrow specimens; or,

- Reappearance of pre-transplant cytogenetic abnormality in at least one metaphase on each of two separate consecutive examinations at least one month apart, regardless of the number of metaphases analyzed.

- Institution of any therapy to treat relapsed disease (institution of any therapy not meant for maintenance or prevention), including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse regardless of whether the criteria described above are met.

3.2.3. QOL Comparison Between Transplant and Non-Transplant Therapy

The following instruments will be used to assess QOL at study entry, and then serially 6, 12, 18, 24, and 36 months from enrollment. Only English- or Spanish-speaking trial participants will be included in the QOL studies.

The **FACT-BMT** version 4.0 instrument[34] is comprised of a general core questionnaire, the FACT-G that evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. In this protocol, only the FACT-G will be used, which consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning.

The **MOS SF-36** instrument[35, 36, 37] is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

The **EQ-5D** will collect data that may be used to calculate patient-reported utilities for cost-utility analyses. The EQ-5D contains a five item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D takes approximately 1 minute to complete (Agency for Healthcare Research and Quality, 2005).

3.2.4. Cost-Effectiveness Analysis

The primary endpoint for the CEA will be the cost per quality-adjusted life year (QALY) from the third party payer perspective with two time horizons: (1) within trial (at 3 years post-enrollment), and (2) lifetime using simulating modeling.

The secondary endpoint for the CEA is the cost per QALY from the societal perspective, a broader measure that captures health insurer direct medical care costs and patient out-of-pocket direct medical and direct non-medical costs. Patient productivity costs (captured as part of QALY calculations) will be reported separately.

CHAPTER 4

4.   PATIENT ENROLLMENT AND EVALUATION

4.1.   Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC^{SM}). The following procedures should be followed:

1. After the patient has given informed consent to participate on the study, an authorized user at the transplant center completes the BMT CTN 1102 Segment 0 Enrollment Form (patient demographic data, and the date that informed consent was signed). A study number will be generated for the patient with the submission of the BMT CTN 1102 Segment 0 Enrollment Form.

2. If the patient has bone marrow biopsy results from within the past 60 days, the BMT CTN 1102 Segment A Enrollment Form should be completed. If the patient does not have bone marrow biopsy results from within the past 60 days, a marrow should be obtained within 30 days after consent. The BMT CTN 1102 Segment A Enrollment Form will need to be completed once the bone marrow biopsy results are obtained. Segment A enrollment should occur no later than 30 days after Segment 0 enrollment.

3. Some of the post-transplant outcomes data for this study will be collected through the CIBMTR. If a suitable donor is identified, centers must obtain a CIBMTR Recipient Identification (CRID) number at the time of treatment assignment and enter it on the BMT CTN 1102 Segment A CIBMTR Recipient ID Form (see CIBMTR Data Collection below).

4.1.2. Evaluations and Research Samples at Enrollment

Since non-HCT patients may not return to the BMT CTN transplant centers after enrollment, the baseline demographics and research samples will be collected at this time point. Patients will have a history and physical examination, KPS/ECOG assessment, and baseline laboratory studies (CBC/differentials, comprehensive metabolic panel, serum ferritin level) performed as shown in Table 4.1.2.

1. Disease- and patient-specific data: A modified CIBMTR MDS/MPN Pre-HCT data form (CIBMTR Form 2014 MDS) will be used to collect the clinical data at enrollment. The pre-HCT data form (2400) will be used to derive the HCT co-morbidity index. However, it is anticipated that some data may be missing at the time of enrollment (i.e., DLCO, FEV1). Bone marrow data must be current (within 60 days of consent). If a marrow examination is not recent, a bone marrow examination will be repeated for trial entry. An attempt to ascertain the HIGHEST prior IPSS and IPSS-R score should be made by the investigator. Response to prior hypomethylating or other therapies will also be collected at the time of enrollment.

2. Laboratory tests: See Table 4.1.2.

3. OPTIONAL research samples: At consent (or within 3 months after consent), a peripheral blood sample (50 mL) and buccal swab will be collected for future unspecified research from those patients that provide consent to optional research samples. The BMT CTN clinical sites will collect the peripheral blood/buccal swab samples from consenting patients prior to receiving study treatment and ship to the BMT CTN repository on the day of collection without having to process and freeze (see Appendix C).

4. QOL data: The baseline QOL survey will be collected within 1 month after Segment A enrollment. QOL interviews will be conducted by the Survey Research Group (SRG). The transplant centers will contact the SRG once a patient is enrolled, either by e-mailing or faxing a form with the patient's contact information. A separate database will be created to house the contact information; no patient contact information will be stored in AdvantageEDC^{SM}; it will only contain the 3 QOL questionnaires (FACT-G, MOS SF-36 and EQ-5D). Interviewers will call the patient at a day and time that is convenient for them, and the interviewers will be trained to enter the data collected into AdvantageEDC^{SM}.

5. OPTIONAL cost-effectiveness analysis study data: At the time of enrollment, patients consenting to the ancillary Cost-Effectiveness analysis study (see Appendix F) will need to complete the HIPAA Authorization Form and Patient Contact Information Form/Optional Alternate Contact Information Form which will be submitted to the CEA study team at Fred Hutchinson Cancer Research Center.

TABLE 4.1.2: REQUIRED PATIENT EVALUATIONS AT TIME OF ENROLLMENT

Required Studies/Testing
Informed Consent
History, Physical Examination, Height and Weight*
Karnofsky/ECOG Performance Score
Assessment of HIGHEST IPSS and IPSS-R Score since diagnosis
CBC with Differential*
Serum Chemistry Panel with Liver Function Tests*
Serum Ferritin level*
HLA Testing
Bone Marrow Aspiration and Biopsy, Cytogenetic Analysis[1]
Patient and MDS Specific Data (CIBMTR Forms 2014 / 2400)
OPTIONAL Research Samples (Blood / Buccal Swab)
Quality of Life Assessments[2]
HIPAA Authorization Form and Patient Contact Information Form/Optional Alternate Contact Information Form for Cost-Effectiveness Analysis Study[2,3]

Notes:
[1] Review of recently obtained sample (obtained within 60 days prior to consent) is permitted
[2] To be performed by the Survey Research Group
[3] If the patient consents to the Cost-Effectiveness Analysis study
*Should be taken from the most recent values, preferably within 30 days prior to enrollment

4.1.3. Donor Search

The transplant coordinator at the transplant center should proceed with their institution's standard procedure to identify a sibling donor, if applicable. If an unrelated donor search is to be pursued, then the coordinator should inform the transplant center's assigned NMDP coordinator through the standard procedure for any unrelated donor.

4.2.   Treatment Group Assignment

The primary purpose of this study is to compare the outcomes of subjects assigned to transplantation with outcomes of those assigned to non-transplant therapy. Since this is not a randomized study, minimizing bias in treatment assignment is critical. Subjects will be assigned to the transplantation arm on the basis of a having an available 6/6 related or 8/8 unrelated matched (HLA-A, B, C, DRB1) donor as defined in section 2.4, found within 90 days.

On the date of transplantation evaluation, potential research subjects should be offered participation in this clinical trial. The date of consent should be as close to the date of initial transplantation consultation as possible, and optimally on the date of consultation. Enrollment should take place within 30 days from the date of consent. Once consent has been obtained, and the subject has been enrolled, the subject will be assigned to one of the two treatment arms within 90 days from the date of consent. **All subjects are initially assigned to the non-transplant arm. Subjects will be re-assigned to the transplant arm should a suitable donor be identified within 90 days of informed consent.** The primary outcome analysis will use the date of consent for survival analyses.

> *Example 1*. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject undergoes transplantation 70 days from consent.
>
> Analysis: Transplantation Arm
>
> *Example 2*. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject receives 4 cycles of hypomethylating therapy and undergoes transplantation 200 days from consent.
>
> Analysis: Transplantation Arm
>
> *Example 3*. Subject is consented and enrolled. A transplant donor is identified 30 days from consent. The subject receives 4 cycles of hypomethylating therapy and expires related to an infection prior to transplantation.
>
> Analysis: Transplantation Arm
>
> *Example 4*. Subject is consented and enrolled. The patient has an identified sibling donor on the date of consent. The patient eventually declines transplantation.
>
> Analysis: Transplantation Arm
>
> *Example 5*. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. The subject expires 80 days after consent without a donor being identified.

Analysis: Non-Transplantation Arm

Example 6. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. No donor is identified after a 90 day search. The subject continues on hypomethylating therapy.

Analysis: Non-Transplantation Arm

Example 7. Subject is consented and enrolled. A donor search is begun, and the subject begins hypomethylating therapy. No donor is identified after a 90 day search. The subject progresses and undergoes alternative donor transplantation 150 days from consent.

Analysis: Non-Transplantation Arm

4.3.   Methodology and Documentation of Study Events

4.3.1.   Approaching Patients, Eligibility, Screening, and Obtaining Consent

Subjects will be approached for this study when they are considered to be potential alloHCT candidates and the decision to proceed with a donor search is made. Transplant physicians will evaluate the patient eligibility. Eligible patients willing to participate in the study will sign an Institutional Review Board (IRB) approved consent form for this protocol. Transplant center personnel will record the documentation of patient consent in EMMES AdvantageEDC^{SM} (Electronic Data Capture, an Internet-based data entry system) and patients will be enrolled through the AdvantageEDC..

4.3.2.   Search Commencement

Transplant centers will initiate the donor search by testing patients and their siblings' HLA types when potential sibling donors are available. If no healthy siblings are available or no siblings are HLA-match, an unrelated donor search will be performed. Transplant center will initiate the unrelated donor search by submitting patient demographics, HLA, and disease information to the NMDP coordinating center using standard NMDP forms. The date of requesting sibling HLA typing and/or unrelated donor search will be recorded if informed consent and enrollment do not occur on the same day.

4.3.3.   Search End and Assignment to alloHCT versus non-HCT Arm (Donor versus no-Donor)

Search end is defined as the date when a 6/6 matched related or 8/8 matched unrelated donor as defined in section 2.4 is identified (confirmation of HLA match is completed). The assignment (biologic allocation) to alloHCT occurs on this date. If a 6/6 matched related or 8/8 matched unrelated donor has not been identified within 90 days of consent, the patient will be assigned to the non-HCT arm (no donor).

Patients must receive either RIC alloHCT or non-HCT therapy according to their treatment assignment. The specific transplant or non-transplant therapy will be at the discretion of the treating physician. Patients assigned to the alloHCT arm will receive more information about the specific transplant procedures and will be required to sign the institution's consent form which

outlines the risks and benefits of the transplant procedure they will undergo. Patients assigned to the non-HCT arm will receive more information about the non-transplant therapy options including hypomethylating therapy and will sign a consent form if deemed appropriate. Non-transplant patients may return to their primary hematologists for therapy.

4.4.   Study Monitoring

4.4.1. Follow-up Schedule for non-HCT Arm

Subjects who are assigned to the non-HCT donor arm will be followed by their primary hematologists. The HCT centers which enrolled and registered the patients will be responsible for periodic contact (every 3 months for Year 1 and 2: +/- 1 month; every 6 months in Year 3: +/- 2 months) with the primary hematologists. When feasible, a recent CBC/differentials and bone marrow report should be obtained at each time point. Documentation of transformation to AML should be obtained, when applicable, as well as treatment history. Vital status (death or alive), concurrent therapy (for the first year), and date of the last follow up or death will be recorded. The primary endpoint of this study is 3 year overall survival, which is not affected by ascertainment bias.

Should a subject on the non-HCT donor arm eventually undergo alternative donor transplantation, long-term outcome reporting will be per Section 4.4.2 using CIBMTR forms. All patients, including those assigned to the non-HCT arm will be registered with the CIBMTR and receive a CRID ID to be recorded in AdvantageEDC upon assignment to a study arm.

4.4.2. Follow-up Schedule for HCT Arm

Patients in the HCT arm will be followed according to each HCT center's institutional standard and data will be reported every 3 months for Year 1 and 2 (+/- 1 month) and every 6 months in Year 3 (+/- 2 months) in AdvantageEDC.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic cell transplantations done at their institution during their time of participation to the CIBMTR. Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US alloHCT recipients.) Intended enrollment on BMT CTN 1102 must be indicated on the SCTOD pre-transplant registration form. CIBMTR pre- and post-transplant comprehensive Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

In the event that patients with donors DO NOT undergo transplantation, the follow up will remain the responsibility of the transplant center, with a schedule of contact and required information as in Section 4.4.1.

4.4.3. Collection of QOL Data

QOL interviews will be conducted by the Survey Research Group (SRG). The transplant centers will contact the SRG once a patient is enrolled in Segment A, either by e-mailing or faxing a form with the patient's contact information. A separate database will be created to house the contact information; no patient contact information will be stored in AdvantageEDC^{SM}; it will only contain the 3 QOL questionnaires (FACT-G, MOS SF-36 and EQ-5D). Interviewers will call the patient at a day and time that is convenient for them, and the interviewers will be trained to enter the data collected into AdvantageEDC^{SM}.

The baseline QOL survey will be collected within 1 month after Segment A enrollment. For each subsequent interview, they may occur within the following windows, calculated from month since Segment A enrollment.

- 6 months: +/- 1 month

- 12 months: +/- 1 month

- 18 months: +/- 1 month

- 24 months: +/- 2 month

- 36 months: +/- 2 month

At the conclusion of each survey administration, patients will be reminded of the next date of contact and the procedures that will be followed. The clinical contact person associated with the patient will notify the SRG if a patient's contact information has changed or if a patient has died.

4.4.4. Locating Missing Patients

If patients cannot be located through the contact information provided, or through the transplant center, then Accurint, a government website accessible to only those with permission will be used by the SRG to locate the patient. Patients give their permission for the SRG to use this site when they sign the informed consent.

4.4.5. Adverse Event Reporting

Only adverse events related to the study consent process, collection of the optional research samples, or completing QOL Surveys will be reported. Since no other therapy is mandated in this study, adverse events associated with transplantation or non-transplantation will not be collected nor reported for this protocol.

4.4.6. Patient Evaluations prior to HCT Therapy

Pre-HCT testing will be performed per institutional standards. The CIBMTR MDS/MPN Pre-HCT data form (CIBMTR Form 2014 MDS) will be used to collect the clinical data pre-HCT. The

standard CIBMTR pre-HCT data form (2400) will also be used to derive HCT co-morbidity index at the time of transplantation.

4.5.   OPTIONAL Research Samples Pre-transplant and at Relapse (RIC alloHCT Arm only)

In addition to research samples at enrollment (Section 4.1.2) collected from consenting patients, a pre-transplant bone marrow sample (1 mL) will be collected for those assigned to the alloHCT arm (within 3 months prior to transplant). This sample is asked for only when a clinically indicated bone marrow aspirate is performed at BMT CTN centers. Additionally, at the time of disease relapse for those patients assigned to the alloHCT arm, an additional peripheral blood sample (50 mL, or specified amount based on weight if < 50 kg) and bone marrow sample (1 mL) will be collected if possible.

4.6.   OPTIONAL Cost-Effectiveness Analysis Information

Patients consenting to the optional Cost-Effectiveness Analysis ancillary study (see Appendix F) will be interviewed by the Survey Research Group (SRG) at 1, 7, and 19 months after enrollment to gather information about their out-of-pocket costs.

CHAPTER 5

5.   STATISTICAL CONSIDERATIONS

5.1.   Study Overview

This study is designed as a multicenter trial, with biological assignment to one of two study arms; Arm 1: Reduced intensity allogeneic hematopoietic cell transplantation (RIC alloHCT), Arm 2: non-transplant therapy / best supportive care. Patients with an HLA-matched related or unrelated donor found within 90 days will be assigned to the RIC alloHCT arm. Patients without a matched donor in that time period will be assigned to the non-transplant therapy arm.

The primary objective is to compare the three-year overall survival (OS) probabilities between the RIC alloHCT arm versus the non-transplant arm. The primary analysis will include all enrolled subjects, classified according to their biological treatment assignment, irrespective of treatment actually received (intent-to-treat analysis). (See Section 4.2.)

5.1.1. Accrual

The length of time required to accrue the targeted sample size for this study depends on the proportion of enrolled patients with a matched related or matched unrelated donor. Although this proportion is not exactly known, it is believed that 60% - 70% of patients will have a matched donor. To ensure the study is sufficiently powered to detect a 15% improvement in three-year overall survival, accrual will remain open until 135 patients are assigned to the non-transplant arm if the proportion of patients with a matched donor is 60% and until 120 patients are assigned to the nonHCT therapy arm if the proportion with a matched donor is 70%. The sample size and power calculations are given in Section 5.2.

Based on historical CIBMTR data, it is estimated that 420 MDS patients receive RIC alloHCT from a matched sibling or matched unrelated donor per year. Further assuming that at least 50% of these patients have had Intermediate-2 or high risk IPSS, approximately 210 patients will be eligible to enroll in the RIC alloHCT arm. Assuming an accrual rate of 40%, we expect annual enrollment of 84 patients to the RIC alloHCT arm. Table 5.1 provides estimated annual accruals for various proportions of donor availability.

Table 5.1: ESTIMATED ANNUAL ACCRUAL

	Donor Availability	
	60%	**70%**
Donor	84	84
No Donor	56	36
Total	**140**	**120**

Based on these assumptions, it is estimated that 2.5 - 3.5 years of accrual will be necessary to enroll the targeted sample size if 60% - 70% of patients have a matched donor.

5.1.2. Biologic Assignment and Randomization

This is a biologic assignment trial. There will be no randomization. All patients enrolled in the study are initially assigned to the non-transplant therapy arm. Patients with a matched related or matched unrelated donor as defined in section 2.4 will be assigned to the RIC alloHCT arm when a donor is identified. To prevent bias resulting from biological assignment, patients are eligible if no formal unrelated donor search has been activated prior to informed consent. Patients who have started a sibling donor search or who have found a matched sibling donor are eligible. Final assignment for all patients will be made within 90 days from study consent. Patients without a donor identified in the first 90 days will stay in the non-transplant arm. Patients without a donor identified who die before 90 days will be analyzed in the non-transplant arm, although this number is expected to be small.

There are many possible sources of heterogeneity in a multi-center clinical trial.[37] In a large randomized trial, chance ensures balance on average of both known and unknown risk factors across treatment arms. A non-randomized study is vulnerable to differential assignment of higher risk patients to one or the other treatment arm. Potential sources of heterogeneity include: degrees of compliance with biological assignment, differences in baseline characteristics such as age, race, gender, performance status, and disease risk status. To address these concerns, the DCC will monitor compliance rate throughout the study and the final analysis will adjust for baseline characteristics potentially affecting outcomes.

5.1.3. Intention-to-Treat Principle

In the primary analysis of overall survival at three years post-consent, patients will be classified according to their biologic assignment regardless of their actual treatment in accordance with the intent-to-treat principle. Secondary analyses using an as-treated principle will be considered.

5.2.   Sample Size and Power Calculations

The primary analysis will compare three-year OS probabilities between arms using adjusted survival estimates provided by the method of Zhang et al[38] to account for potential differences in baseline covariates. Without censoring or covariates, the three-year OS probabilities reduce to simple binomial proportions. A point-wise comparison of survival at three years is proposed for the primary analysis rather than the Cox proportional hazards model because of the potential for crossing hazards. The Cox model would have lower power to detect a difference between two groups in the presence of crossing hazards. The sample size calculations were based on a two-sample Z test of binomial proportions.

The targeted sample size is specified in terms of minimal number of patients without a matched donor whose final assignment is non-transplant therapy. Data from the CIBMTR suggests a three-year OS probability after transplant for high-risk MDS patients older than 50 to be approximately 35%-40%. Three-year OS for the non-transplant group based on data from European patients under a compassionate use program of AZA[39] are estimated to range between 20% and 25%. From these estimates, we propose a design with sufficient power to detect a 15% increase in three-year OS probability in the RIC alloHCT arm compared to the non-transplant arm. The sample size was

estimated assuming 10% loss to follow up at the end of three years. Table 5.2 give the estimated sample size and power to detect a 15% increase in three-year overall survival for various combinations of baseline survival probability and donor availability. If 60% of patients will have a matched donor, the study will require 135 patients in the non-transplant arm to provide sufficient power to detect a 15% increase in three-year survival probability in the RIC alloHCT arm. If 70% will have a matched donor, 120 patients in the non-HCT arm will

Donor Availability	Total Sample size (HCT, Non-HCT)	Three-year OS		Power
		HCT	Non-HCT	
60%	338	35%	20%	83%
	(203, 135)	40%	25%	80%
70%	400	35%	20%	84%
	(280, 120)	40%	25%	81%

provide sufficient power to detect a 15% increase in three-year survival probabilities as shown in Table 5.2.

TABLE 5.2: POWER TO DETECT 15% INCREASE IN OS PROBABILITY IN THE TRANSPLANT ARM FOR VARIOUS SURVIVAL PROBABILITIES AND PROPORTIONS OF DONOR AVAILABILITY

Donor Availability	Total Sample size (HCT, Non-HCT)	Three-year OS		Power
		HCT	Non-HCT	
60%	338	35%	20%	83%
	(203, 135)	40%	25%	80%
62%	343	35%	20%	85%
	(213, 130)	40%	25%	81%
64%	355	35%	20%	86%
	(227, 128)	40%	25%	81%
66%	368	35%	20%	84%
	(243, 125)	40%	25%	81%
68%	380	35%	20%	85%
	(258, 122)	40%	25%	81%
70%	400	35%	20%	84%
	(280, 120)	40%	25%	81%

5.3.   Interim Analysis and Stopping Guidelines

Since the true proportion of donor availability is not known, we recommend monitoring treatment assignment to assess the proportion of donor availability and to ensure enough patients will be enrolled in each arm to have sufficient power to detect the specified treatment effect. If the proportion of donor availability reaches 90%, an action plan will be developed to address future accrual. The DCC will also monitor compliance rate throughout the study to ensure patients will receive their assigned treatment. Noncompliance in the non-transplant arm is defined as a patient without a matched donor identified receiving alternative donor HCT within the first 90 days or a

patient not having a donor identified in the first 90 days after consent receiving a transplant within six months from the final assignment. Noncompliance in the transplant arm is defined as a patient with a matched donor identified not receiving a transplant within six months from the final assignment. If noncompliance in each arm exceeds 25%, an action plan will be developed to address future accrual.

In addition to monitoring for compliance and enrollment imbalance between assignment arms, we recommend monitoring the proportion of patients enrolled by age group (< 65 years of age vs. ≥ 65) to ensure sufficient number of patients will be available in each age group for secondary subgroup analysis.

We do not recommend interim analysis for futility for two reasons. First, we expect the risk of mortality in the early period to be higher after HCT and in the later period to be higher with non-transplant therapy, resulting in crossing hazards. Although we expect the survival curves to cross approximately two years after enrollment, no data exist to estimate the crossing point. If the survival curves happen to cross later than two years, we do not want to prematurely stop the study for futility. Secondly, the investigators are also interested in using the lower bound of the confidence interval of the survival difference at three years to learn about the magnitude of the survival difference. Stopping early for futility would result in substantially wider confidence intervals, leading to greater uncertainty about the magnitude of the survival difference when it is not likely to be as large as targeted.

We recommend interim analysis for efficacy after accrual is complete starting at 4 years from the beginning of the study and every year thereafter to allow the investigators to report the study results earlier when there is sufficient evidence to conclude one treatment results in superior three-year survival. Interim analysis for efficacy will be conducted at times that coincide with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately one year intervals. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis. These stopping guidelines serve as a trigger for consultation with the DSMB for additional review and are not formal "stopping rules" that would mandate automatic closure of the study enrollment.

5.3.1. Interim Analysis for Efficacy

Analyses will be performed as described below for the primary endpoint. At the time of each interim analysis, a two-sided test to detect either an increase or decrease in the proportion of patients surviving will be performed. The test statistic used at each interim analysis will be the difference between treatment arms in adjusted estimates of three year overall survival. All patients enrolled prior to the time of the interim analyses will be used to compute these adjusted probability estimates. If the test statistic exceeds the critical value, the DSMB will discuss whether the trial should continue.

In order the preserve the overall Type I error rate at 5%, the critical value for the test statistic will be inflated above 1.96, the value that would be used if no repeated testing were used. Equivalently, the nominal p-value at which an observed difference is declared significant will be reduced below

0.05. The actual critical values and nominal p-values will be computed using statistical methods for group sequential testing with Haybittle-Peto boundaries[40,41]. Because differences in adjusted survival estimates are not known to follow an independent increments structure asymptotically, a Bonferroni adjustment will be used to ensure that the overall type I error rate does not exceed 0.05. Letting K denote the total number of analyses and π_j the nominal type I error rate for the analysis performed at analysis j, the overall type I error rate will not exceed 0.05 if these are chosen such that $\sum_{j=1}^{K} \pi_j = 0.05$. The Haybittle-Peto design uses a critical value of 3.00 at each intermediate analysis, giving $\pi_j = 2[1 - \Phi(3)] = 0.0027$ for stages $j < K$ and $\pi_K = 0.05 - 2(K-1)[1 - \Phi(3)]$ for the final analysis, where Φ is the standard normal cumulative distribution function. The critical value for the final analysis, then, is $\Phi^{-1}(1 - \pi_K/2)$.

We recommend interim analyses starting four years after the beginning of the study and yearly thereafter, until the last patient has been followed for three years. Four years was chosen as the time of the first interim analysis to ensure enough patients have reached the primary endpoint to provide reasonable estimates of three-year survival. The number of subsequent analyses depends on the length of time required to complete accrual.

Assuming donor availability rate of 60%, the total accrual time is estimated to be 2.5 years. With 3 years of follow up, the study can be completed within 6 years. In this case, analyses will be conducted at the end of year 4, 5, and 6. Table 5.3.A shows the critical values, nominal Type I error, cumulative Type I error, and the probability of stopping to reject the null hypothesis at each analysis conducted at the end of year 4, 5, and 6. This is estimated using a simulation study with two different survival probability scenarios, uniform accrual over 2.5 years, and assuming exponential censoring with 10% rate by 3 years; we use an unadjusted test statistic for simulation study purposes, even though the primary analysis will use the difference in adjusted survival probabilities at 3 years. The power at each look is the probability of stopping and rejecting the null hypothesis at that look if the true increase in OS at three years is 15% in the HCT arm compared to the non-HCT arm. In particular, there is 32% power to detect a 15% improvement in three-year survival by the first look, 51% by the second look, and 83% by the final look if the true survival probabilities were 35% vs. 20%. There is 29% power to detect the same improvement by the first look, 46% by the second look, and 79% power by the final look if the true survival probabilities were 40% vs. 25%.

TABLE 5.3.A: CRITICAL VALUES AND OPERATING CHARACTERISTICS; DONOR AVAILABILITY RATE OF 60%

Calendar Time since Study Start	Critical Value	Nominal Type I Error Rate	Cumulative Type I Error Rate Upper Bound	Cumulative Probability of Stopping under H_a	
				35% vs. 20%	40% vs. 25%
4 years	3.00	0.0027	0.0027	0.3238	0.2892
5 years	3.00	0.0027	0.0054	0.5096	0.4562
6 years	2.01	0.0446	0.0500	0.8272	0.7906

Assuming donor availability rate of 70%, the total accrual time is estimated to be 3.5 years. With 3 years of follow up, the study can be completed within 7 years. In this case, analyses will be conducted at the end of year 4, 5, 6, and 7. Table 5.3.B shows the critical values, nominal and cumulative Type I error, and the power to reject the null hypothesis by each look conducted at the end of year 4, 5, 6, and 7. This is estimated using a simulation study with two different survival probability scenarios, uniform accrual over 3.5 years, and assuming exponential censoring with 10% rate by 3 years; we use an unadjusted test statistic for simulation study purposes, even though the primary analysis will use the difference in adjusted survival probabilities at 3 years. In particular, there is 46% power to detect a 15% improvement in three-year survival by the second look and 85% by the final look if the true survival probabilities were 35% vs. 20%. There is 41% power to detect the same improvement by the second look and 81% power by the final look if the true survival probabilities were 40% vs. 25%.

TABLE 5.3.B: CRITICAL VALUES AND OPERATING CHARACTERISTICS; DONOR AVAILABILITY RATE OF 70%

Calendar Time since Study Start	Critical Value	Nominal Type I Error Rate	Cumulative Type I Error Rate Upper Bound	Cumulative Probability of Stopping under H_a	
				35% vs. 20%	40% vs. 25%
4 years	3.00	0.0027	0.0027	0.2538	0.2226
5 years	3.00	0.0027	0.0054	0.4564	0.4058
6 years	3.00	0.0027	0.0081	0.5636	0.5124
7 years	2.03	0.0419	0.0500	0.8476	0.8084

5.3.2. Guideline for Safety Monitoring

Treatment-related mortality, a key safety endpoint for patients receiving RIC alloHCT, will be monitored up to 100 days post-transplant. A truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions for treatment-related mortality will be used as described below. This sequential testing procedure conserves type I error across all of the monitoring looks for TRM. The SPRT can be represented graphically. At each interim analysis, the number of patients received HCT is plotted against the total number of patients who have experienced TRM by day 100 post transplant. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive TRM. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more TRM than predicted by the number of HCT patients. Otherwise, the SPRT continues until enrollment reaches the target goal.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be slightly lower than the nominal level. The test to be used in this protocol was developed from the following SPRT:

- An SPRT contrasting 20% versus 30% TRM, with nominal type I and II errors of 5% and 20%, respectively.

- The slope of the parallel lines for monitoring TRM is 0.248 and the intercepts are –2.891 and 5.144.

Graph of the stopping boundary is given in Figure 5.3.
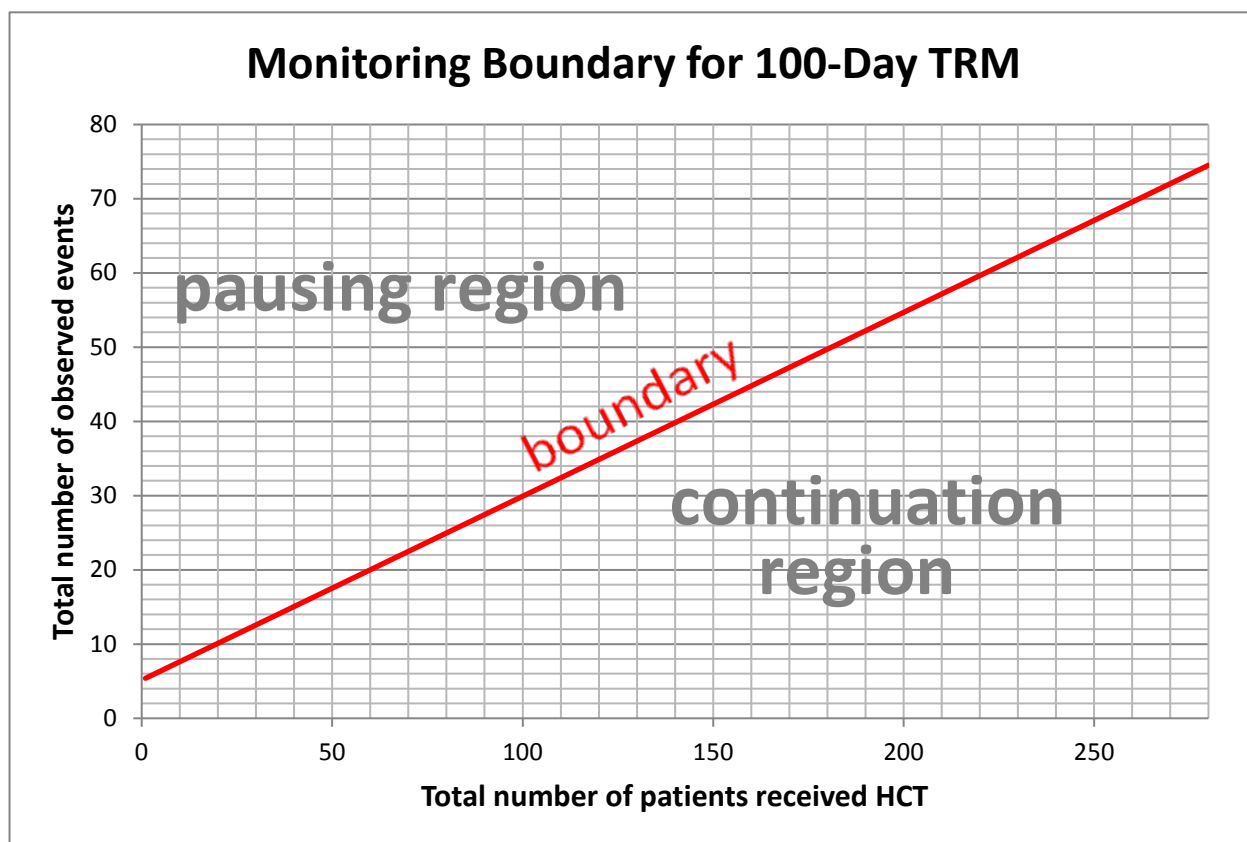
Figure 5.3: Stopping Boundary

The actual operating characteristics of the truncated test, shown in Table 5.3.C, were determined in a simulation study. The simulation assumed uniform accrual of 280 patients over a period of three and a half years.

**TABLE 5.3.C: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING
PROCEDURE FOR 100-DAY TRM FROM A SIMULATION STUDY
WITH 10,000 REPLICATIONS**

True 100-day rate	20%	25%	28%	30%
Probability reject the null hypothesis	0.05	0.49	0.84	0.95
Mean month stopped	42.0	31.9	22.5	17.5
Mean # endpoints	54.2	50.3	37.7	30.0
Mean patients with 100 days follow-up	271.1	200.8	134.8	99.9

Treatment-related mortality is monitored in all patients receiving RIC alloHCT. The SPRT rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day TRM is 20%, and 95% of the time when the true 100-day TRM is 30%. This corresponds to a type I error rate of α=0.05 and a type II error rate of β=0.05. When the true 100-day TRM rate is 30%, on average, the DSMB will be consulted 17.5 months after opening, when 30 events have been observed in 100 patients. Note that the SPRT procedure is adequately powered to distinguish between a TRM rate of 20% and 30%.

5.4.   Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, disease status, donor type, donor gender, all components of IPSS score, co-morbidity index, duration of disease, cytogenetics, prior treatment, and response to prior treatment.

5.5.   Analysis Plan

5.5.1. Analysis of the Primary Endpoint

The primary outcome of the trial is overall survival at three years after consent. The primary null hypothesis of the study is that there is no difference in overall survival between the treatment arms at three years post consent. In the primary analysis, the intent-to-treat principle will be used. Because of the potential bias resulting from biological assignment[42], the comparisons of overall survival will be adjusted for the following pre-specified patient characteristics: age, race/ethnicity, performance status, disease status, co-morbidity index, IPSS score, duration of disease (time from diagnosis to enrollment), cytogenetics, and response to prior therapy. The primary analysis will be performed using the difference in adjusted overall survival probabilities at three years, using the method of Zhang et al[38]. In this analysis, the time to event is the time from study consent to the time of death from any cause; surviving patients will be censored at last follow-up. The adjusted survival probabilities are estimated using the Cox proportional hazards model stratified by treatment. A 95% confidence interval for the difference in adjusted OS at three years will also be constructed. In addition to a point-wise comparison at three 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.

5.5.2. Analysis of Secondary Endpoints

5.5.2.1.   Overall survival at three years (as treated analysis)

In addition to the primary intent-to-treat analysis, three-year survival probabilities will be compared using the adjusted OS probabilities in several exploratory analyses. In the first one, the patients who die or drop out before 90 days without a donor identified will be removed from the non-transplant group. The second analysis will be an as treated analysis, where patients are classified by the treatment they actually received.

5.5.2.2.   Overall survival post three years

Overall survival post three years will be compared between arms using the linear combination test proposed by Logan et al[43]. This comparison directly compares the survival curves starting at three years, and accounts for patients enrolled early in the study having additional follow-up beyond three years.

5.5.2.3.   Leukemia-free survival at three years

Probabilities of leukemia-free survival three years post consent will be compared between treatment groups using the method of Zhang et al.[38] adjusting for age, race/ethnicity, performance status, disease status, co-morbidity index, IPSS score, duration of disease (time from diagnosis to enrollment), cytogenetics, and response to prior therapy. A 95% confidence interval for the difference in adjusted OS at three years will also be constructed. In addition to a point-wise comparison at three years, adjusted survival curves will be constructed and confidence bands for the difference between treatments will be generated to compare the leukemia-free survival probabilities across time. An as-treated analysis as described in Section 5.5.2.1 will also be conducted to compare leukemia-free survival probabilities at three years.

5.5.2.4.   Quality of Life

QOL will be described and compared between treatment arms utilizing the FACT-G, the MOS-SF36 Physical Component Score (PCS) and Mental Component Score (MCS), and the EQ-5D utility score. The questionnaires will be scored according to standard procedures. The self report questionnaires will be completed at enrollment and subsequently at six months, 12 months, 18 months, 24 months, and 36 months from enrollment. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial.

Differences in quality of life will be assessed in several ways. For the descriptive analysis only, QOL scores for survivors at specific time points will be compared between treatment arms using two-sample t-tests. In addition, pattern of missing QOL data will be examined using graphical techniques and logistic regression models. At each time point, the difference in QOL between the treatment arms conditional on being alive at that time point will be estimated using the inverse probability of censoring-weighted generalized estimating equations with independent working correlation model of Kurland and Heagerty[44].

5.5.3. Subgroup Analyses

Exploratory analyses will be performed to determine the impact of the following factors on treatment effect:

1. Response to hypomethylating therapy (response versus no response), where response is defined as achieving complete or partial response or hematologic improvement.

2. Patient age (< 65 years of age vs. ≥ 65),

3. Disease duration,

4. IPSS, and

5. Revised-IPSS.

Subgroup analyses will be conducted separately for each factor listed above using the pseudo-value approach of Klein et al[45]. Differential impact of each factor on the effect of transplant on three-year OS and three-year LFS will be tested for by including an interaction term between the factor and the treatment group in the pseudo-value regression models.

5.5.4. Secondary Analyses of RIC 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:

1. Response to hypomethylating therapy (complete response, partial response and no response),

2. Patient age (< 65 years of age vs. ≥ 65),

3. Disease duration,

4. IPSS,

5. Revised-IPSS, and

6. Donor type (HLA-matched sibling donor vs. matched unrelated donor).

Cox proportional hazards models will be performed in these analyses. The proportional hazards assumption will be tested. When test indicated 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.

QOL will be described and compared between age groups (< 65 years of age vs. ≥ 65) utilizing the FACT-G using the same approach described in Section 5.5.2.4.

5.5.5. Exploratory Analysis of Non-transplant Therapy Arm

Exploratory analysis of post-enrollment therapy will be conducted for patients assigned to the non-transplant therapy arm. Frequency and type of systemic therapy at each periodic contact will be summarized.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

1.   Subject Consent

Patients will be approached for this study when they are considered to be potential allo RIC HCT candidates based on medical history, physical examination and available laboratory tests. A conference will be held with the patient and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The Principal Investigator or another designated physician will conduct the conference. Potential risks associated with HCT should be discussed as objectively as possible. Informed consent for this study will be obtained using a form approved by the Institutional Review Board of the institution enrolling the patient.

If an appropriate matched related or unrelated donor is found within 90 days of consent, the patient will be assigned to the allo RIC HCT treatment arm. The treating physician will review the risks and benefits of the institutionally-approved allo RIC HCT regimen with the patient. Informed consent for the specific transplant study will be obtained using a separate consent form approved by the Institutional Review Board of the institution enrolling the patient.

Patients without suitable donors will be offered standard treatment (hypomethylating therapy) or other best supportive care. The treating physician will discuss the options and risks and benefits of each therapy. Informed consent for standard treatment will be obtained if required by local IRB of the institution treating the patient.

2.   Confidentiality

Confidentiality will be maintained by masking of individual names and assignment of a patient identifier code. The identifier code representing the patient's identity will be kept separately from the research file at the center. The ID code will be transmitted to the BMT CTN Data Coordinating Center upon enrollment.

3.   Participation of Women and Minorities and Other Populations

Women, ethnic minorities, and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on the incidence of MDS. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX B

INFORMED CONSENT

APPENDIX B

Informed Consent to Participate in Research

A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Age 50 or Older with Intermediate-2 and High Risk Myelodysplastic Syndrome

Your Name: _____

Study Title: A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Age 50 or Older with Intermediate-2 and High Risk Myelodysplastic Syndrome

Protocol: BMT CTN #1102

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**Transplant Center
Investigator:**   _____
(Insert contact information for PI at your site)

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. You are invited to join this study because:

1) You have **myelodysplastic syndrome (MDS)**, also called myelodysplasia;

2) Your MDS is at an advanced stage. This means that you are at medium (intermediate) to high risk for your MDS to become acute leukemia or cause death; and

3) Your doctor recommends that you have an **allogeneic stem cell transplant (transplant)** if a donor is found whose DNA or tissue type matches your DNA or tissue type.

We are doing this study because we want to find out if patients with MDS who have a matched donor and get a **reduced-intensity conditioning (RIC) transplant** do better than those who get drugs to treat their MDS (no transplant).

This study also wants to learn more about the cost-effectiveness of transplant and collect extra blood and tissue samples for future studies.

(See **Section 2. Study Background** for a definition of the bolded terms)

This study will take about 6.5 years and will include about 338 – 400 participants from around the United States. We will collect information on how you're doing (your

health condition and how you feel) for **3 – 4 years.**

This Consent Form tells you about the purpose of the study, the possible risks and benefits, other treatment options available to you, and your rights as a participant in the study. Please take your time to make your decision.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.

- You will not benefit from taking part on the study. Knowledge we gain from this study may benefit others.

- If you join the study, you can quit the study at any time.

- If you decide to quit the study, it will not affect your care at [*insert name of facility or institution*].

- Please ask the study staff questions about anything that you don't understand, or if you would like to have more information.

- You can ask questions now or any time during the study.

- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join,

please sign and date the end of the Consent Form.

You and your doctor will discuss how to best treat your MDS. Joining this study will affect your treatment decisions. If you don't want to participate in this study, we will not collect information on your health condition or how you're feeling.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN will direct the research study. The BMT CTN and the NIH will make decisions about how to manage the study.

Myelodysplastic Syndrome (MDS), also called myelodysplasia, is a disease where the bone marrow does not make enough normal blood cells for the body. This can lead to a fast-growing blood cancer called acute leukemia. It mostly affects people who are 50 or older.

There are different ways to treat MDS. Some treatments use blood transfusions and drugs. These treatments can improve MDS and slow it from becoming acute leukemia. However, drugs don't cure MDS.

Allogeneic stem cell transplant (transplant) is another treatment option for advanced stage MDS. A transplant uses blood-making cells from a family member or an unrelated donor to remove and replace your abnormal blood cells. It requires a close tissue match between you and the donor.

Your donor could be a sibling (a sister or brother) or an unrelated person. We use the Be The Match® Registry to find unrelated donors.

The best experience with transplant for MDS is with well-matched sibling or unrelated donors. If you do not have one of these donors there may be other potential donor options such as umbilical cord blood or mismatched donors. Since the outcome from transplant with these donors is not as good, only well-matched sibling and unrelated donors are being offered on this trial.

A transplant first uses chemotherapy and radiation to destroy the abnormal blood cells or stop them from growing. For your MDS and your condition, your doctor wants to use lower amounts of chemotherapy and radiation. This type of transplant is called **reduced-intensity conditioning (RIC)** or non-myeloablative. There are different combinations of RIC drugs and radiation. Your doctor will decide on the best combination for you.

Because of your age or health problems, you may have a higher chance of side effects and health problems from a standard transplant that uses very high doses of chemotherapy and radiation. The possible benefit of RIC is

a lower chance of side effects. The possible risk of RIC is that the transplant will not stop your disease from growing or cure it. Your doctor will explain all of the risks and side effects of your RIC treatment.

Transplant cures MDS <u>for some patients, but not all patients</u>. However, patients often have side effects after both standard and RIC transplants. The side effects can be very serious, sometimes even causing death. We don't know if patients with MDS in an advanced stage do better with transplant or with drug therapy only (no transplant). Both treatments are common.

If you don't find a donor whose DNA or tissue type is a close match, you might be able to get a transplant that uses a donor who isn't a close match or that uses an umbilical cord blood unit (CBU). However, other research studies showed that transplants that use a less-closely matched donor or a CBU don't treat the disease as well, so transplants with these donor types are not included in this study.

3. Study Purpose

We are inviting you to join this study because you have MDS and your doctor recommends reduced-intensity transplant as a treatment option for you (if you find or have a matched donor).

The main goal of this study is to learn if MDS patients who have a matched donor and receive transplant do better than other MDS patients who don't have a donor and only get drugs to treat their MDS (no transplant). We want to know how well you're able to do your normal activities after your treatment. We will ask you survey questions (health evaluations) by phone after you start your treatment.

We also want to learn more about the cost-effectiveness of transplant (see **Ancillary Cost-Effectiveness Analysis Informed Consent Form (Optional)**) and collect extra blood and tissue samples for future research (see **Section 17: Blood and Tissue Samples for Future Research**). These studies are optional. This means you can still be part of the main study (health evaluations by phone) if you say 'no' to these studies.

4. Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about the study or you want to leave the study, please contact:

[*insert contact info for site PI*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or to leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health condition before you start treatment and for 3 years after. You will not have to make any extra visits to your clinic or transplant center to be part of this study.

If you have not had a bone marrow biopsy within the last 60 days, you might need to have one before you join the study. Your doctor will tell you if you need a bone marrow biopsy.

Study Participation

If you join this study and you don't have a known sibling donor, your doctor will determine if you have a suitable matched donor. Your donor could be a sibling (sister or brother) or an unrelated person. If a donor is found within 90 days (about 3 months) of your consent to be on this study, you will have a transplant as soon as you and your doctor feel you are ready for it.

If we can't find a matched donor for you, you will continue to see your regular cancer doctor. Together, you and your doctor will decide on the standard treatment or a different treatment for your MDS. We will be in touch with you and your cancer doctor's office to collect information on how you're doing.

Once you and your doctor decide on your treatment, you will get more information about the treatment.

Health Evaluations

After you join the study, we will ask you questions about your health and how you're feeling over the phone.

We will also contact you by phone at:

- 6 months
- 1 year (12 months)
- 1 ½ years (18 months)
- 2 years (24 months), and
- 3 years (36 months)

These phone calls will take approximately 30 minutes each. These health evaluation follow-up phone calls are only for English- and Spanish-speaking participants.

Different treatments can work to treat MDS, but they can have different side effects. In this study, we want to find out how transplant makes people feel compared to how drug therapy only makes people feel.

We will use surveys to collect information on how you're doing. The surveys will ask you about:

- Your general health

- Any side effects you may have from your treatment

- How well you can do your normal activities

- Your feelings

You <u>do not</u> need to answer all of the questions or complete the surveys at all. It is okay to only answer the questions you feel comfortable answering. If any of the questions make you uncomfortable, you can skip them.

If your phone number changes, it's important that you let us know your new number so we can reach you. You can call:

[Insert contact information for site PI]

If we can't reach you by phone, we may use an Internet search service to find you. By agreeing to join this study, you are giving us your permission to use search firms to find your contact information. The service uses public and non-public information to reach you.

We will also give you the choice to provide a list of what you and your insurance company pay for your treatment (see **Ancillary Cost-Effectiveness Analysis Informed Consent Form (Optional)**) and extra samples of your blood and tissue for future research (see **Section 17: Optional Blood and Tissue Samples for Future Research**).

6. Risks and Discomforts

The risks and side effects of transplant are the same if you join this study or if you don't join this study. Your doctor will give you drugs to help ease side effects, such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or never go away.

a) Risks and side effects of transplant

If you have a matched donor, the following general problems might happen from your transplant. Your doctor will explain the possible risks and benefits for the drugs used with your transplant before you get your transplant.

<u>Anyone who has a transplant will experience the risks described below:</u>

1. Slow recovery of blood counts. You will need blood and platelet transfusions after your transplant because red blood cells, white blood cells, and platelets can be slow to recover. This will make you at risk for bleeding and infections.

2. Graft failure. The peripheral blood or bone marrow stem cells (the "graft") may fail to grow inside your body. There is a low chance of this happening (about 1 out of 10 people), and can result in low blood counts for a long time. If your counts don't recover, you might need another transplant. Graft failure can be fatal.

3. Graft-Versus-Host Disease (GVHD). This happens when the graft sees your body as foreign and attacks it. Sometimes GVHD

is serious or difficult to treat and may lead to death. In most cases, GVHD can be successfully treated.

Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, stomach pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To diagnosis acute or chronic GVHD, you may need to have a biopsy (a small sample of your tissue for testing) of your skin, gut, or liver.

4. Damage to the vital organs in your body. The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys and bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections, or the chemotherapy and radiation.

5. Serious infections. There is an increased risk of infections when your immune system is recovering. Most infections can be successfully treated, but some infections may result in death.

6. Relapse of MDS. Your MDS may come back even if the transplant is successful at first.

7. Risk to the unborn. Transplant has <u>not</u> been proven to be safe at any stage of pregnancy. If you are a woman and can become pregnant, it's very important that you aren't pregnant when you start the study

and don't become pregnant while in the study.

8. Reproductive Risks. The drugs used in transplant may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of transplant.

  ▪ **If you are a woman and can become pregnant:**

  You will need to take a pregnancy test before you start transplant. You should discuss ways to prevent pregnancy while you are going through transplant.

  ▪ **If you are a man:**

  Your body may not be able to make sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

  Please check with your doctor to understand more about these risks.

b) Risks and side effects of RIC drugs

Your doctor decided that a RIC transplant is the best treatment for you if you have a matched donor.

The drugs used in RIC transplants are likely to cause infection, bleeding, feeling tired (fatigue), feeling sick to your stomach (nausea), and throwing up (vomiting). You might also have diarrhea, feel numb in your

hands and feet, or notice changes in your eyesight.

Other side effects that are very rare (but serious if they happen) include a lung infection (pneumonia), feeling confused, coughing and trouble breathing, serious brain damage, and death. <u>Your doctor will tell you more about the side effects of the specific RIC drugs you will receive before you get your transplant</u>.

c) Risks and side effects of drug therapy for MDS (no transplant)

If you don't have a matched donor, you will be treated with drugs for MDS. Your doctor will discuss with you more details about the side effects, risks, and benefits of these drugs. Some of the drugs can cause low blood counts, nausea, and stomach upset. Drug treatments can improve MDS and slow it from becoming leukemia. <u>However, because drugs alone don't cure MDS, the risk of your disease coming back is very high</u>.

d) Risks of being in this study

The 3 main parts to this study are health evaluations, optional cost-effectiveness of transplant research, and optional blood and tissue samples for future research. Each of these studies has their own risks. These risks are described below:

1. **Health evaluations by phone** (see **Section 5**). You may feel uncomfortable about some of the questions on the surveys. If this happens, you can skip

these questions. You can also decide not to take the entire survey.

2. **Ancillary Cost-Effectiveness Analysis (Optional)** (see **Ancillary Cost-Effectiveness Analysis Informed Consent Form**). The risks to participating in the cost-effectiveness study are small. A possible risk is the loss of confidentiality of your medical information, but the chance that this information will be given to someone else is very small.

3. **Blood and Tissue Samples for Future Research (Optional)** (see **Section 17**). The risk of injury from having your blood taken is very small. If your blood samples are collected from your arm, you may bleed a little bit and/or develop a small bruise. Infection from blood draws is rare, but it may happen. If you are uncomfortable at the sight of blood, you may feel light-headed or faint. The risk of injury from having your bone marrow taken also is small. You may feel stiff or sore for several days afterwards. You may bleed a little bit and/or develop a bruise. The risk of injury from having a cheek swab from the inside of your mouth is very small.

4. **Unforeseen risks**. New risks might appear at any time during the study. We may learn new things that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to stay in the study.

7. Alternative Treatments

It is your choice to join this study. If you choose not to take part, you may still receive an allogeneic transplant to treat your MDS. Your treatment and evaluations could be very similar to what you would receive if you join this study.

The best experience with transplant for MDS is with well-matched sibling or unrelated donors. If you do not have a matched donor, you might be able to get a transplant that uses a donor who isn't a close match or that uses an umbilical cord blood unit (CBU). Since the outcome from transplant with these donors is not as good, only well-matched sibling and unrelated donors are being offered on this trial.

Your study doctor will talk with you about your options. If you decide not to join this study, your medical care will not be affected in any way.

8. Possible Benefits

You will not benefit from taking part in this study. Your participation in this study allows us to collect specific information about your treatment for MDS. You can still receive the same or similar treatments if you don't take part in this study.

Information from this study will help doctors learn more about treatments for MDS. This information could help people with MDS who may need a transplant in the future.

9. New Information Available During the Study

During this study, the study doctors may learn new information about the risks and benefits of the study. If this happens, they will tell you about the new information.

The new information may mean that you can no longer take part in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation and offer you all available care to meet your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure

that the personal information in your medical record will be kept private. However, we can't guarantee total privacy.

All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- */Institution/Transplant center*

- The National Institutes of Health (NIH)

- The National Heart, Lung, and Blood Institute (NHLBI)

- The National Cancer Institute (NCI)

- Office of Human Research Protection (OHRP)

- The Food and Drug Administration (FDA)

- Institutional Review Boards (IRBs) responsible for this study

- Data and Safety Monitoring Board (DSMB), not part of /Institution/

- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN

- Study investigators, Ryotaro Nakamura, MD and Corey Cutler, MD MPH FRCP(C)

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your privacy is very important to us. The study doctors will make every effort to

protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Data regarding your clinical situation, including follow-up after 3-4 years, may be obtained from the CIBMTR, which captures information on all US transplants.

For questions about access to your medical records, please contact *\/name\/at\/number.*

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study.

If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.

- You need a medical treatment not allowed in this study.

- The study doctor decides that it would be harmful to you to stay in the study.

- You are having serious side effects.

- You become pregnant.

- You cannot keep appointments.

- The study is stopped for any reason.

Even if you withdraw from the study, the information collected from your participation will be included in the study.

12. Physical Injury as a Result of Participation

It is important to tell your study doctor *[investigator's name(s)]* or study staff if you feel that you have been hurt or injured from taking part in this study. You can tell the doctor in person or call *[telephone number].*

You will get all available medical treatment if you are injured from taking part in this study.

You and/or your health plan will be charged for this treatment. The study will not pay for this treatment.

In case you are injured in this study, you don't lose any of your legal rights to receive payment by signing this consent form.

13. Compensation or Payment

You will not be paid for taking part in this study. You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

14. Costs and Reimbursements

The clinic visits for this study are standard medical care for transplant or the standard treatment. You and/or your health plan/insurance will need to pay for the costs of transplant or standard treatment in this study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. For More Information

If you want more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or study staff.

They can be reached at the telephone numbers listed here:

[*Insert contact information for site PI*].

16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about the project, or any questions about your rights as a research participant, you may contact:

[*Insert appropriate contact details*].

The ethical aspects of this research study have been reviewed and approved by [*name of IRB*].

For questions about your rights while taking part in this study, call the **_____***[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at **_____** *(telephone number).*

17. Blood and Tissue Samples for Future Research (Optional)

This section of the consent form is about future research studies that will use blood and tissue (blood, cheek cells, and bone marrow) samples from people who are taking part in the main study. You may choose to give blood and tissue samples for these future studies if you want to. You or your insurance will not be charged for these research samples.

You can still be a part of the main study (health evaluations by phone) even if you say 'no' to give blood and tissue samples for future studies.

The risk of injury from having your blood taken is very small. If your blood samples are collected from your arm, you may bleed a little bit and/or develop a small bruise. Infection from blood draws is rare, but it may happen.

If you are uncomfortable at the sight of blood, you may feel light-headed or faint. Only trained people will draw your blood.

The risk of injury from having your bone marrow taken is small. You may feel stiff or sore for several days after the aspiration. You may bleed a little bit and/or develop a bruise. Only trained people will collect your bone marrow.

The risk of injury from having a cheek swab from the inside of your mouth is very small.

If you agree to provide blood and tissue samples, this is what will happen:

a.) We will collect 1 extra blood sample at the same time you have routine blood tests done before you start your treatment. We will collect about 4 tablespoons (50 mL). If you weigh less than 110 pounds (50 kg), the amount of blood we collect will be based on your weight.

b.) We will also collect cells from your mouth by gently rubbing a cotton swab on the inside of your cheek.

c.) Additionally, if you are going to get a transplant, we will also collect about ¼ teaspoon (1 mL) of bone marrow fluid and cells through a needle put into your bone (aspiration, if you and your doctor choose to perform this procedure) before you get your transplant.

The skin will be cleaned with a special solution and a medicine (local anesthetic) will be used to numb the area. Then the aspiration needle will be put through your skin and into your bone to reach the bone marrow. During an aspiration, you may feel a quick, shooting pain as the sample is taken.

d.) If you get a transplant and your MDS comes back:

    a. We will collect another blood sample (no more than 4 tablespoons).

    b. We will collect another ¼ teaspoon (1 mL) of bone marrow fluid and cells through a needle put into your bone (if you and your doctor choose to perform this procedure).

e.) The blood and tissue samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores, and sends out samples for approved research studies. All research samples will be given a number that cannot be linked to you.

f.) Samples stored in the Repository will be used mainly by doctors and researchers in the BMT CTN network. In the future, the unused blood and tissue samples and health information will be made available outside of this network (see sections 'g' below).

g.) Researchers can apply to study the health information and blood and tissue samples in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

h.) DNA from your stored blood and tissue samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at millions of genetic changes at the same time.

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples although the results of genetic studies could theoretically include identifying information about you.

Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is small, but may grow in the future. Researchers have a duty to protect your privacy and to keep your information confidential.

Some general things you should know about letting us store your blood and tissue samples for research are:

- We will only store samples from people who give us permission.

- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.

- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and health information to make sure that your personal information will be kept private. It's very unlikely that your personal information will be given to someone else.

- Your blood and tissue will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

You can change your mind at any time about allowing us to use your samples and health information for research.

If you <u>do not</u> want us to use your blood and tissue samples or health information for research, we ask that you contact: *[Principal Investigator]* in writing. The mailing address is on the first page of this form.

However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at: *[contact information for site PI]*. _____.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Optional Blood and Tissue Research Samples

The purpose of storing blood and tissue samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood and tissue for research.

If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood, tissue, and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and clinical information may or may not be used in genome-wide association studies.

Blood and cheek samples

❑ I agree to allow my blood and cheek samples to be stored for research.

❑ I do not agree to allow my blood and cheek samples to be stored for research.

Bone marrow samples

❑ I agree to allow my bone marrow samples to be stored for research.

❑ I do not agree to allow my bone marrow samples to be stored for research.

_____   _____

Signature   Date

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Age 50 or Older with Intermediate-2 and High Risk Myelodysplastic Syndrome

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)

- Medical history (for example: diagnosis, complications with prior treatment)

- Findings from physical exams

- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*].

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1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

D. Parties Who May Receive or Use My Individual Health Information:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff:

    Dr. Ryotaro Nakamura, Co-Principal Investigator

    Dr. Corey Cutler, Co-Principal Investigator

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),

- Study sponsors: Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data and Coordinating Center

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study as required by law and would no longer be protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. This authorization does not have an expiration date.

TITLE: A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Age 50 or Older with Intermediate-2 and High Risk Myelodysplastic Syndrome

PROTOCOL NUMBER: BMT CTN 1102

PRINCIPAL INVESTIGATORS:

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Phone: (626) 656-4673

Corey Cutler, MD MPH FRCP(C)
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
Phone: (617) 632-3470

- I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I understand that I will have a transplant if a matched donor is found. If I don't have a matched donor, I will get the standard treatment.

- I have had the chance to ask questions, and I understand the answers I have been given. I understand that I may ask questions at any time during the study.

- I freely agree to take part in the study.

- I understand that I will not directly benefit from taking part in the study.

- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.

- I have had the chance to discuss my participation in this research study with a family member or friend.

- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.

- I understand that I will be given a copy of this signed Consent Form to keep.

Participant Name   Date

Signature   Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Name of Counseling Physician   Date

Signature of Counseling Physician   Date

Name of Interpreter   Date

Signature of Interpreter   Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

1. OPTIONAL RESEARCH SPECIMENS

Patients consenting to the optional future research will have samples collected for future, undefined research supporting the protocol. All research sample aliquots will be given unique bar code designations that cannot be linked back to the participant's name or other identifying information. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the protocol. Samples sent to researchers cannot be linked with any remaining samples at the repository.

Patient peripheral blood and buccal swab samples will be collected at enrollment for both arms. Peripheral blood (and bone marrow samples if available) will also be collected from patients assigned to the HCT arm who experience relapse at the time of relapse and stored to support future research studies. If available, bone marrow will be collected pre-transplant for the patients assigned to the HCT arm. All research samples will be collected and shipped same-day to the BMT CTN Repository for processing and sample aliquot storage. Sample collection and shipping procedures are detailed in the BMT CTN 1102 Laboratory Sample Guide.

BMT CLINICAL TRIALS NETWORK

RIC Allo vs. Hypometh./Best Supportive Care in MDS – Protocol 1102
Version 5.0 – November 28, 2018

Subject	Optional Research Samples						
	Research Sample Type	**Time Points [Total Blood Volume]**	**Sample Quantity**	**Stored Material**	**Sample Processing & Storage Site**	**Aliquots Stored**	**Purpose**
Non-transplant Therapy/Best Supportive Care **120 Patients**	Peripheral Blood	Enrollment **50 mL**	5 mL EDTA	Plasma	BMT CTN Repository	Maximum **5 aliquots** 0.5 mL aliquots; stored at -80º C	Undefined Future Research (Proteomic)
			6 mL EDTA	Whole Blood	BMT CTN Repository	Maximum **6 aliquots** 1.0 mL aliquots; stored at -80º C	Undefined Future Research (Genomic)
			29 mL Heparin	Viable PBMC	BMT CTN Repository	Maximum **6 aliquots** 1.0 mL aliquots containing ~ 2.5-5.0 x 10^6 PBMC; controlled-rate frozen and stored in LN2	Undefined Future Research (Cell-Functional & Gene Expression)
			10 mL PAXgene	Whole Blood	BMT CTN Repository	Maximum **4 aliquots** 2.5 mL-fill PAXgene tubes; stored at -80º C	Undefined Future Research (Gene Expression)
	Buccal Swabs	Enrollment	4 swabs	Buccal Cells	BMT CTN Repository	**4 cryovials** each containing a swab; stored at -80º C	Undefined Future Research (Genomic)

Subject	Research Sample Type	Time Points [Total Blood Volume]	Sample Quantity	Stored Material	Sample Processing & Storage Site	Aliquots Stored	Purpose
		Optional Research Samples					
Reduced Intensity Conditioning Allogeneic Transplant **280 Patients**	Peripheral Blood	Enrollment *280 patients** **and** Disease Relapse (event-driven) *84 patients** **50 mL**	5 mL EDTA	Plasma	BMT CTN Repository	Maximum **5 aliquots** 0.5 mL aliquots; stored at -80° C	Undefined Future Research (Proteomic)
			6 mL EDTA	Whole Blood	BMT CTN Repository	Maximum **6 aliquots** 1.0 mL aliquots; stored at -80° C	Undefined Future Research (Genomic)
			29 mL Heparin	Viable PBMC	BMT CTN Repository	Maximum **6 aliquots** 1.0 mL aliquots containing ~ 2.5-5.0 x 10^6 PBMC; controlled-rate frozen and stored in LN2	Undefined Future Research (Cell-Functional & Gene Expression)
			10 mL PAXgene	Whole Blood	BMT CTN Repository	Maximum **4 aliquots** 2.5 mL-fill PAXgene tubes; stored at -80° C	Undefined Future Research (Gene Expression)
	Buccal Swabs	Enrollment	4 swabs	Buccal Cells	BMT CTN Repository	**4 cryovials** each containing a swab; stored at -80° C	Undefined Future Research (Genomic)

Subject	Optional Research Samples						
	Research Sample Type	**Time Points [Total Blood Volume]**	**Sample Quantity**	**Stored Material**	**Sample Processing & Storage Site**	**Aliquots Stored**	**Purpose**
	Bone Marrow Aspirate	Pre-transplant (if available) *280 patients** and Disease Relapse (event-driven) *84 patients**	1-3 mL	Bone Marrow	BMT CTN Repository	Maximum **4 aliquots** 0.5 to 0.75 mL BM aliquots added to equal volume RPMI freezing solution; controlled-rate frozen and stored in LN2	Undefined Future Research (Genomic)

*Estimated patient numbers

APPENDIX D

KARNOFSKY AND ECOG
PERFORMANCE STATUS SCALES

APPENDIX D

KARNOFSKY AND ECOG PERFORMANCE STATUS SCALES

Karnofsky Scale %	Karnofsky Description	ECOG Scale*	ECOG Description	SWOG Scale
100	Normal, no complaints, no evidence of disease.	0	Fully active, able to carry on all pre-disease activities without restriction.	0
90	Able to carry on normal activity, minor symptoms or signs of disease.			
80	Normal activity with effort, some signs or symptoms of disease.	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work office work.	1
70	Cares for self, unable to carry on normal activity or to do active work.			
60	Requires occasional assistance, but is able to care for most of own needs.	2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours	2
50	Requires considerable assistance and frequent medical care.			
40	Disabled, requires special care and assistance.	3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours	3
30	Severely disabled, hospitalization is indicated although death is not imminent.			
20	Hospitalization necessary, very sick, active supportive treatment necessary.	4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair	4
10	Moribund, fatal processes			
Dead		Dead		5

*also known as Zubrod or WHO scale

APPENDIX E

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)
AND
REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM
(IPSS-R)

APPENDIX E

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)
AND
REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) FOR PATIENTS WITH MDS

International prognostic scoring system (IPSS)[*] for MDS:

Prognostic Variable	Score				
	0	0.5	1.0	1.5	2.0
BM blasts (%)	< 5	5 - 10	-	11 - 20	21 - 30
Karyotype[**]	Good	Intermediate	Poor		
Cytopenias[^]	0 or 1	2 or 3			

Score for risk groups are as follows:

Risk Group	IPSS Score
Low	0
Intermediate - 1	0.5 - 1.0
Intermediate - 2	1.5 - 2.0
High	≥ 2.5

*International Prognostic Scoring System [21]
***Good**: normal, -Y, del(5q), del(20q); *Poor*: complex ($\geq$3 abnormalities) or chromosome 7 anomalies; *Intermediate*: other abnormalities
^Red blood cells: Hemoglobin <10 g/dL (100g/L); White blood cells: Absolute neutrophil count <1800/microL; Platelets: Platelet count <100,000/microL

Revised international prognostic scoring system (IPSS-R) in MDS:

Prognostic Variable	Score						
	0	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**
Cytogenetics*	Very good	-	Good	-	Intermediate	Poor	Very poor
Bone marrow blasts (%)	≤ 2	-	> 2 to < 5	-	5 - 10	> 10	
Hemoglobin (g/dL)	≥ 10	-	8 to < 10	< 8			
Platelets (cells/microL)	≥ 100	50 - 100	< 50				
Absolute neutrophil count (cells/microL)	≥ 0.8	< 0.8					

Score for risk groups are as follows:

Risk Group	IPSS-R Score
Very low	≤ 1.5
Low	> 1.5 to 3.0
Intermediate	> 3 to 4.5
High	> 4.5 to 6
Very high	> 6

**Very good: -Y, del(11q); *Good*: Normal, del(5q), del(12p), del(20q), double including del(5q); *Intermediate*: del(7q), +8, +19, i(17q), any other single or double independent clones; *Poor*:-7, inv(3)/t3q)/del(3q), double including -7/def(7q), complex 3 abnormalities; *Very poor*: complex, ≥3 abnormalities

APPENDIX F

ANCILLARY COST-EFFECTIVENESS ANALYSIS PROTOCOL

**Ancillary Cost-Effectiveness Analysis to:
A Multi-Center Biologic Assignment Trial Comparing Reduced
Intensity Allogeneic Hematopoietic Cell Transplant to
Hypomethylating Therapy or Best Supportive Care in Patients Aged
50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome
BMT CTN 1102**

**BMT CTN PROTOCOL 1102
CEA VERSION 2.0**

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CEA Study Team
Adam Mendizabal, PhD
Alyssa Ramirez
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LIST OF ABBREVIATIONS

Abbreviation	Definition
alloHCT	Allogeneic hematopoietic stem cell transplant
BMT	Bone marrow transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CEA	Cost-effectiveness analysis
CIBMTR	Center for International Blood and Marrow Transplant Research
GVHD	Graft versus host disease
HMA	Hypomethylating agents
ICER	Incremental cost effectiveness ratio
MDS	Myelodysplastic syndromes
OS	Overall survival
PFS	Progression free survival
QALY	Quality adjusted life year
QoL	Quality of life
RIC	Reduced intensity conditioning
SRG	Survey Research Group

PROTOCOL SYNOPSIS

Myelodysplasic syndrome (MDS) is a heterogeneous group of acquired malignant bone marrow disorders with an annual incidence rate of approximately 4 per 100,000.[1,2] MDS most commonly occurs in older individuals, with 80% diagnosed at ≥65 years of age in the United States.[3] Allogeneic hematopoietic stem cell transplantation (alloHCT) is the only curative treatment modality for MDS, and with the introduction of reduced intensity conditioning (RIC) regimens, alloHCT is now a viable treatment option for many older patients. Hypomethylating agents ([HMA] azacitadine and decitabine) also on average improve progression free (PFS) and overall survival (OS) in patients with MDS and, unlike transplantation, these agents do not require the demanding preparation or carry the risk of graft versus host disease (GVHD) and other transplant related morbidity and mortality. BMT CTN 1102 is a controlled trial designed to evaluate the comparative effectiveness of alloHCT relative to treatment with HMA or best supportive care in patients with MDS aged 50-75. Although alloHCT is the only curative modality for MDS, clinical equipoise exists given the considerable mortality and long term morbidity risk associated with transplant. Moreover, the relative survival, quality of life, and cost impacts of these alternative treatment approaches in older adults remains uncertain.

This protocol describes an ancillary cost-effectiveness analysis to be conducted alongside BMT CTN 1102. Consenting patients will provide health insurance information to allow calculation of direct medical costs from reimbursement records, and will provide out-of-pocket costs, time costs, through paper-based surveys. These outcomes will inform a cost-effectiveness analysis comparing the outcomes of alloHCT and HMA or best supportive care from patient, payer, and societal perspectives. The results of this analysis will be the first to provide a comprehensive evaluation of the comparative effectiveness of these MDS treatment approaches from multiple perspectives.

Table of Contents

LIST OF TABLES AND FIGURES

1.   BACKGROUND AND RATIONALE

1.1   Background

MDS is a clonal disorder of hematopoietic stem cells, which may progress to acute myeloid leukemia (AML). Data from the Surveillance Epidemiology and End Results (SEER) national cancer registries estimate that approximately 10,000 new cases of MDS are diagnosed annually.[4] However, this may be a substantial underestimate given the diagnostic challenges of identifying MDS.[5] Using linked SEER-Medicare records, Cogle et al estimated an annual incidence of 75 per 100,000 among persons aged 65 and older, compared to an incidence of 20 per 100,000 for the same age group when only SEER records were used.[6] The median age at diagnosis is 67 years and incidence rises sharply with age.[4] MDS is more common among males than females, and while a significantly higher incidence has been observed in non-Hispanics than among Hispanics, significant differences by race have not been observed.[4]

The International Prognostic Scoring System (IPSS) is used to classify MDS into four risk groups (low, intermediate-1, intermediate-2, and high). Table 1 shows the median survival for each risk group, as published by Greenberg et al.[7] Low-risk MDS patients are often not treated until they become

Table 1. Median survival estimates based on the IPSS	
Risk Category	**Median Survival (y)**
Low	5.7
Intermediate-1	3.5
Intermediate-2	1.2
High	0.4

transfusion-dependent,[5] while patients with high-risk MDS (intermediate-2, and high) are considered for alloHCT.[8,9] Despite advances in alloHCT, including the use of RIC preparative regimens, the use of alloHCT remains low among older patients. For example, records from the Center for International Blood and Marrow Transplant Research (CIBMTR) show that out of a total of 3,101 alloHCTs performed in the US between 2000 and 2010 for MDS, only 232 (7.5%) were among persons aged ≥65 years (personal communication, W. Saber). HMA, including azactidine and decidabine, are recommended for the treatment of high-risk MDS patients who are not candidates for or are not willing or able to undergo alloHCT.[8,9] According to a study from the CIBMTR,[10] three-year disease-free survival for patients receiving alloHCT is approximately 40% (95% CI 36%-45%). This is better than the median time to AML progression of 18 months, and median time of AML transformation or death of 21 months observed for azacitidine in two randomized controlled trials,[11,12] however it should be noted that the cumulative incidence of transplant-related mortality at 3-years in the CIBMTR study was 37% (95% CI 32%-42%).[10] The substantial risk of morbidity (including graft versus host disease and post-alloHCT infection) and mortality associated with transplant undoubtedly tips the balance for some physicians and patients considering alloHCT, especially for elderly patients with comorbidities. A biologic assignment, non-randomized trial is currently underway in Europe comparing non-transplant therapies to alloHCT based on availability of a human leukocyte antigen (HLA) matched donor, but results are not expected until June 2017. The BMT CTN clinical study recently opened in the United States, providing the opportunity to collect clinical and ancillary economic data to address the use of alloHCT in older patients in a multi-payer system. If the results of BMT CTN 1102 demonstrate superior survival at 3-years for the alloHCT group, as hypothesized by the study investigators, it is likely that the demand for alloHCT will grow and CMS and other payers will have to weigh both the clinical and economic evidence when making coverage decisions. However, there is already evidence that suggests that the use of alloHCT in older MDS patients is increasing rapidly. For example, since 2010, the year CMS issued the Coverage with Evidence decision for alloHCT, the number of alloHCTs performed in the US among patients age ≥65 years rose nearly 3.5 fold, from 65 to 220 respectively (personal communication, W. Saber). Given that this still represents a small proportion of eligible MDS patients, it is expected

that the demand would rise even more dramatically if alloHCT was covered outside of clinical trial settings.

An analysis of the ten most costly inpatient hospital procedures published by the Agency for Health Care Research and Quality found that bone marrow transplant was the most expensive procedure ($1.3 billion 2007 USD in inpatient hospital costs), and required an equivalent number of hospital stays as the other top 9 procedures combined.[13] Additionally, the process of searching for a donor, harvesting of donor cells, and immunosuppressive conditioning to prepare the patient for alloHCT transplant is extremely resource intensive. Likewise, in the post-transplant period, patients must be closely monitored to reduce the high risk of morbidity and mortality discussed above. The total first-year direct medical care costs of alloHCT have been estimated to be between $96,000 and $204,000 2012 USD.[14] The authors of the cited review of HCT costs note that few studies take a societal approach, meaning that these cost estimates do not include direct nonmedical costs (transportation, food, lodging) or indirect nonmedical costs (lost wages and productivity). These additional costs can be especially burdensome for older MDS patients receiving alloHCT, as they may need extensive caregiver support and may be living on fixed incomes that cannot absorb the financial shock of unexpected medical expenses. Direct medical costs can be obtained retrospectively from insurance claims, and are thus often the only data available to compare the economic impact of treatment strategies, however the Public Health Service's Panel of Cost Effectiveness in Health and Medicine and the International Society for Pharmaceutical Outcomes Research Randomized Control Trials – cost-effectiveness analysis (CEA) Task Force both recommend that a societal perspective be taken to comprehensively assess the economic consequences of alternative treatments.[15,16]

BMT CTN 1102 Trial

Given this knowledge gap and as a response to the Centers for Medicare & Medicaid Services (CMS) Coverage-with-Evidence-Development (CED) for National Coverage Determination (NCD) of Stem Cell Transplantation,[17] the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) launched the BMT CTN 1102.[18] This study is a prospective biologic assignment trial to compare RIC alloHCT to non-transplant therapies based on suitable donor availability. Suitable donor is defined as either a human leukocyte antigen (HLA)-matched related donor, or an 8/8 (HLA-A, -B, -C, and -DRB1) well matched unrelated donor. If no suitable donor is identified during a 90-day interval (from enrollment), subjects will be permanently assigned to the no donor arm. The 90-day interval was chosen based on the likelihood that a donor will be found, according to the median search times reported by the National Marrow Donor Program (NMDP). Four hundred patients will be enrolled over roughly 3 years at 30 centers throughout the United States. Secondary outcomes include leukemia-free survival, quality of life, and cost-effectiveness and planned subgroup analyses will evaluate key biologic questions, such as the impact of age & response to HMA on treatment effects. Figure 1 depicts the overall study schema.

1.2   Rationale for Cost-Effectiveness Analysis

Cost-effectiveness analyses can be particularly informative when conducted alongside randomized controlled trials. In this setting, CEA can provide timely economic evidence about the relative value of alternative medical strategies with a high level of internal validity.[19] In the case of the BMT CTN 1102 trial, conducting an ancillary CEA study provides the opportunity to precisely measure a range of quality of life and expenditure endpoints to complement the clinical endpoints evaluated in the parent trial, providing a comprehensive view of the tradeoffs of managing MDS with either alloHCT or HMA and best supportive care. Findings from this

study potentially may set a new standard of care for older patients with high risk MDS who are considered candidates for alloHCT.

This study is particularly important because alloHCT is the only potentially curative treatment for MDS, but is also among the most expensive medical procedures in the United States. For example, in pilot data from 38 MDS patients undergoing alloHCT at the Medical College of Wisconsin, the average total cost per patient was $212,069 for the first two years post-transplant (range $45,619 – $528,572). (Wael Saber, Personal communication)

This study will provide important information about the comparative effectiveness of alloHCT relative to standard care with HMA or best supportive care. The outcome measures include life years, quality-adjusted life years, health plan direct medical expenditure and patient out of pocket expenditure, and productivity impact. The primary analysis will calculate the incremental cost-effectiveness ratio (ICER), a measure that reflects expenditure per QALY gained. Results will be calculated over the plausible range of willingness to pay in the United States (from $20,000 to $200,000 per QALY gained).[20-22]

Several prior studies have evaluated cost and quality of life outcomes for MDS patients treated with alloHCT[23-31] and non-transplant therapy[32-35]. However, none of the previous studies included patients as old as age 75, or long-term tracking of outcomes. As a result, the findings of this ancillary study will be an important contribution to the literature by providing outcomes for older patients (age 50-75), and tracking outcomes for up to 3 years post-enrollment.

In addition, no prior studies of alloHCT or non-transplant therapy have attempted to quantify a comprehensive range of economic outcomes that includes patient out of pocket medical expenditures and work productivity impact. . This is particularly important in the case of the treatments compared in BMT CTN 1102 because alloHCT requires substantial hospital stays and non-medical costs for patients and their families can be substantial. Although many transplant centers provide subsidized housing to families, costs associated with transportation and living away from home, plus associated work loss, may pose significant burdens for patients and families. Moreover, patients may face the possibility of exceeding lifetime insurance caps, exposing them to the full cost of care thereafter. For older patients who may be retired and living off of a fixed income, the financial burden of alloHCT may be especially pronounced.

By prospectively collecting data on costs and productivity loss of patients and their families participating in the BMT CTN 1102 clinical trial, this CEA of alloHCT versus HMA or best supportive care presents <u>a time sensitive opportunity to comprehensively determine the cost-effectiveness of these two alternative options.</u>

2.   STUDY OBJECTIVES

2.1   Objective 1

From the perspective of the payer (health insurer), to determine direct medical expenditure associated with alloHCT and HMA or best supportive care over the course of the trial.
   a.   Based on trial results, use modeling to estimate lifetime direct medical expenditures

Hypothesis 1: Direct medical expenditure will be significantly greater for patients who receive alloHCT compared to those who receive HMA or best supportive care.

2.2   Objective 2

From the patient perspective, estimate and compare the economic hardship associated with use of alloHCT and HMA or best supportive care over 18 months, by directly surveying patients..
   a. Estimate the proportion of patients/families that experience economic hardship as defined by out-of-pocket-costs, financial hardship(a composite measure of the inability to pay bills, recent income loss, need to borrow money or current debt) and loss of work productivity.

Hypothesis 2: Out-of-pocket expenditures will be significantly greater for patients who receive alloHCT compared to those who receive HMA or best supportive care.

Hypothesis 3: The likelihood of financial hardship will be higher for patients who receive alloHCT compared to those who receive HMA or best supportive care.

Hypothesis 4: Patients who receive alloHCT will experience a greater loss of work productivity compared to those who receive HMA or best supportive care

2.3   Objective 3

To estimate short-term and lifetime quality adjusted life years (QALYs) associated with alloHCT and HMA or best supportive care. Short-term QALYs will be estimated directly from the trial while lifetime QALYS will be estimated through modeling.

Hypothesis 5: Patients receiving alloHCT will have significantly more QALYs than patients receiving HMA or best supportive care.

2.4   Objective 4

Using the information from objectives 1-3, to estimate the cost-effectiveness of alloHCT compared to HMA or best supportive care from the societal and health insurer perspective.

Hypothesis 6: AlloHCT will be more cost effective than HMA or best supportive care, from both a health insurer and a societal perspective, at a cost-effectiveness threshold of $100,000US per QALY.

3.   METHODS

3.1   Study Design

This ancillary CEA assesses the relative value of RIC alloHCT versus HMA or best supportive care through the incremental cost effectiveness ratio (ICER). The ICER is equal to costs divided by quality-adjusted life years (QALY), resulting in the cost per quality-adjusted life year. Costs for this study will be measured using cost diary surveys administered to patients at 1 month, 7 months and 19 months from the date of study enrollment. A QALY is a metric that measures the duration and quality of life based on health state utility data collected from quality of life surveys administered in the parent BMT CTN 1102 study. The ICER, as a cost-effectiveness endpoint, is recommended by numerous groups, including the US Preventive Services Task Force on Cost-Effectiveness in Health and Medicine.[36]

3.2   Study Population

Patients eligible to participate in the BMT CTN 1102. A biologic assignment trial open to patients age 50 – 75 with MDS.

3.2.1   Inclusion Criteria

- Any patient who provided consent to participate in the parent study BMT CTN1102 is eligible to participate in the CEA study. In addition, patients enrolled in the CEA study must:
  - Sign the CEA research consent form
  - Complete the patient contact information form with a mailing address for the cost diary surveys
  - Have a bone marrow biopsy that indicates they are eligible for HCT

3.2.2   Exclusion Criteria

- Primary language spoken: Languages other than English

3.2.3   Enrollment Procedures

1) Eligible patients presented with the option of participating in BMT CTN 1102, will at the same time be given the option to participate in the parallel CEA. Patients will be informed that they can have a caregiver/family member/alternate contact help with completing the surveybut an alternate contact is not required to participate in the CEA study.

2) For participants providing consent to participate in BMT CTN 1102 and the CEA, the Transplant Center Study Coordinator will complete the following CEA forms with the patient within 14 days of the patient's enrollment date. The Study Coordinator will:

    a) Complete **HIPAA Authorization Form** (See Appendix F) with patient.
    b) Complete **Patient Contact Information Form/Optional Alternate Contact Information Form** (See Appendix F) with patient.
    c) Complete **CEA Consent Form** with patient (See Appendix F)

    d) Securely send, by Email or fax, items a,b and c to SRG. Email: 1102SRGTeam@nmdp.org; Fax: 612-294-4370

       Note: Transplant Center Study Coordinators will also be responsible for emailing or faxing immediate notification to SRG if a patient withdraws from the study or dies.

3) CEA Coordinating Center staff located at Fred Hutchinson Cancer Research Center will:
    a) Receive email notifications from The Emmes Corporation when a patient has enrolled to the CEA study and follow-up with transplant coordinators who have not submitted patient CEA enrollment forms.
       Obtainthe **HIPAA Authorization Form** and **CEA Consent Form** from SRG to request health insurance claims data from health insurers after completion of the study.

4) The SRG team located at CIBMTR will:

    b) Call the alternate contact/caregiver to address any questions they may have in assisting the patient in completing the survey for the CEA study and confirming contact information. Add patients and agreeing alternate contacts to system to track mailing and receipt of cost diary surveys.

3.3   Study Period

3.3.1   Coordination between BMT 1102 Clinical Centers, Survey Research Group, and CEA Coordinating Center

Following enrollment in the BMT CTN 1102 parent trial, patients will have 30 days to be enrolled in the ancillary CEA. This will involve a cooperative effort between transplant coordinators, CEA coordinating center staff at the Fred Hutchinson, and the SRG at CIBMTR.

The SRG is already conducting the Quality of Life (QoL) assessments to be used in both the clinical study and the CEA. Therefore, communication about those patients enrolled in both studies will be necessary for the SRG to administer the additional surveys ascertaining cost data for the CEA.

3.3.2   Index Date for Assessment Surveys and Study Arm Assignment

The biologic assignment design of the BMT CTN 1102 necessitates a waiting period of up to 90 days between enrollment in the trial and assignment to the non-transplant HMA or best supportive care arm of the study. This poses several methodological challenges for data collection. While the date of transplantation provides a clinically meaningful date for patients to reference when providing estimates of costs incurred, no such date occurs for individuals assigned to the non-transplant HMA or best supportive care arm. Many of these patients will enter the study having already received treatment for MDS, making the date of treatment initiation an imperfect reference date that if used only for the non-transplant arm could bias the results of the CEA by allowing more follow-up time over which costs could accrue. Bias in the opposite direction could occur if the 90-day mark is used as a reference for non-transplant patients.

To overcome potential biases by use of a natural reference date, individuals in both arms of the study will be assigned the date of enrolment into BMT CTN 1102 as the baseline reference date.

There may be a lag of up to 30 days between when a patient signs a consent form and when they are enrolled in the BMT CTN 1102 CEA ancillary study. This is due to the enrollment process in the parent study. After a patient signs their consent form for the 1102 parent study, they have up to 60 days to complete a bone marrow biopsy to determine their eligibility for HCT. Search for a donor also begins at the time a patient signs their BMT CTN 1102 study consent form. If the patient's bone marrow biopsy indicates they are not eligible for HCT, then they are not enrolled in the study, even though they have signed a consent form. If the patient's bone marrow biopsy indicates they are eligible for HCT, the patient's transplant center completes an enrollment form. The parent study's Quality of Life (QOL) survey time points are then based on that enrollment date, post-bone marrow biopsy.

The enrollment date for the CEA ancillary study will also be the date a transplant center completes a parent study enrollment form, which may be up to 30 days after signing the consent forms for both the parent and ancillary studies. To be enrolled in the BMT CTN 1102 ancillary

CEA study, patients must sign the parent study consent form, the ancillary study consent form, have a bone marrow biopsy that indicates they are eligible for HCT, and have an enrollment form completed by their transplant center. The 1-month, 7-month and 19-month CEA survey dates will be based off of the enrollment date to the 1102 parent study, and not the date a patient signs their consent form.

The biologic assignment design of the patient to the HCT or best supportive care arm in the BMT CTN 1102 study occurs naturally when a patient finds a suitable donor for HCT or if they are unable to find a suitable donor within 90 days of signing their BMT CTN 1102 study consent form. The BMT CTN 1102 CEA ancillary study will use the biologic assignment of the parent study.

Figure 1 Study schema for patients enrolled in BMT 1102
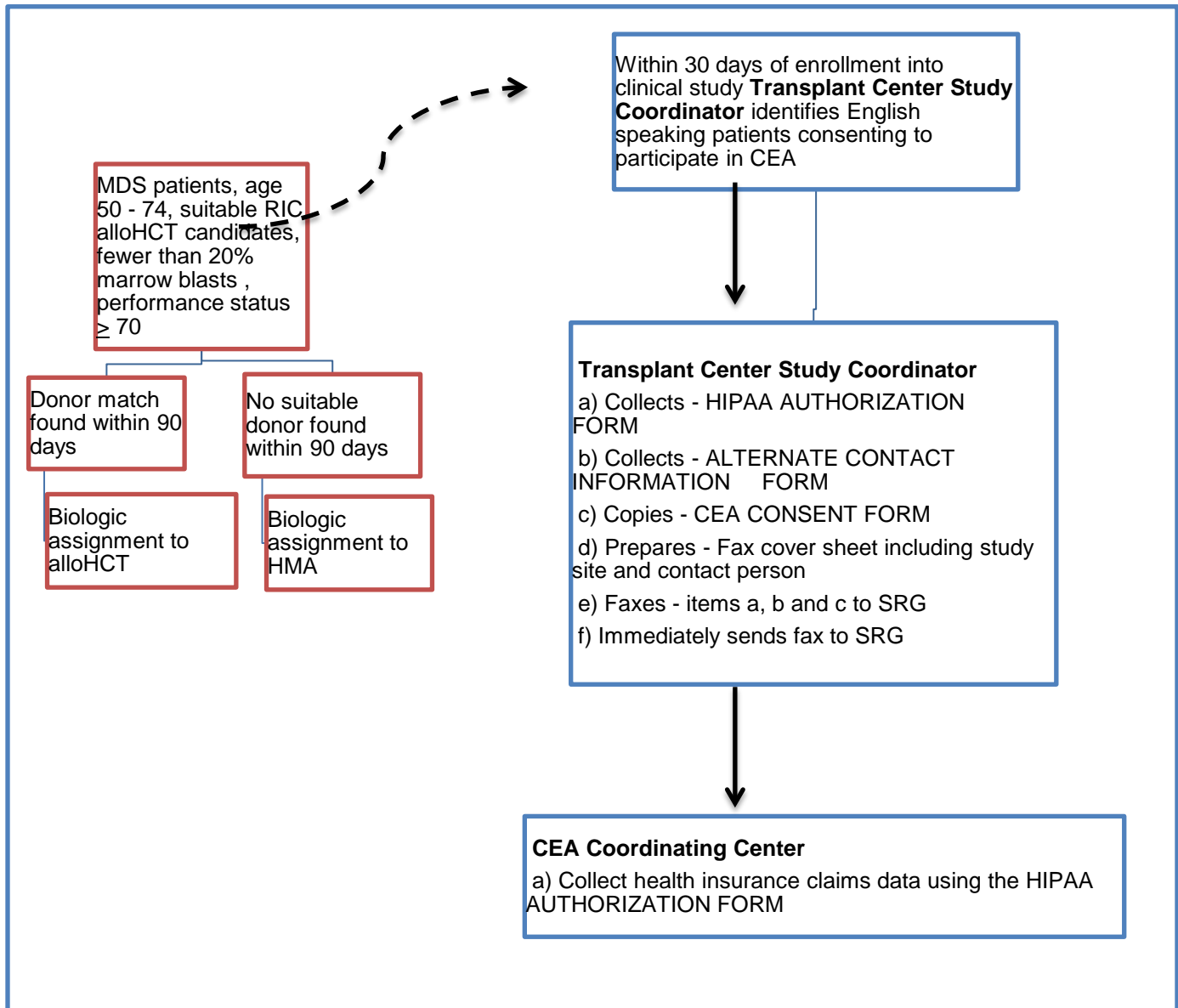
3.4   Data Sources

To comprehensively evaluate the cost-effectiveness of RIC alloHCT versus HMA or best supportive care, this study uses information from **three separate data sources**:

I.   Health insurance reimbursement records

II.   Mail-out survey

     a.   Cost diary

     b.   Work Productivity and Activity Impairment Questionnaire (WPAI)

III.   Previously collected QOL data

Cost information will be collected in four distinct areas (Table 1)**.**

Table 3 Summary of Cost Information to be Collected

Cost Category	Description	Providing Information
1. Direct medical care costs	Health insurance reimbursements	Health insurer
2. Out-of-pocket costs		
Direct medical care costs	Copays, deductibles, uncovered medical bills	Patient
Direct non-medical costs	Transportation, accommodation, child care….	Patient
3. Indirect costs	Lost productivity	Patient
4.		

3.4.1   Direct Medical Care Costs Payer: Health Insurance Reimbursements

Participants who consent to participate in BMT CTN 1102 will be given the option to participate in the parallel economic analysis. Those providing consent will be asked to provide the name(s) of their health insurer(s), the policy holder's name and date of birth, the health insurance group number(s) and policy identification number(s) (we anticipate that some patients will have multiple insurance plans).

This information will be used to request health care claims records from insurers for the period beginning 12-months prior to the date of enrollment, through 3-years following enrollment. To account for administrative delays in claims data processing, requests will be **made at least 42-months following** the date of enrollment. Claims will be requested from health insurers in batches with batch size dependent on patient accrual to the parent study and subsequent accrual into the CEA. Requests will be made regardless of outcome (i.e. for patients who remain in remission, relapse, or die).

3.4.2   Out-of-Pocket Costs

In addition to health insurance expenditure, the study will collect out of pocket expenditures directly from patients and/or the alternate contact nominated by the patient. Patients and contacts are invited to jointly participate because: there may be periods where patients are unable to provide information due to illness; patients usually have a team of people supporting them in different capacities and at different times; and to encourage discussion, recall, and reconciliation of potential expenses. These costs will include direct medical care costs for patients (e.g. copays, deductibles and uncovered medical bills) and direct non-medical patient

costs: transportation costs, travel time and distance, and accommodation costs. The survey is an adaptation of the cost diary method used by Goossens and colleagues. [37]

Patients will be mailed paper surveys by SRG and will return them to SRG at 1, 7 and 19 months post enrollment. SRG will contact patients and alternate contacts by phone to encourage returning the surveys if not received 14 days after sending.

3.4.3   Indirect costs: Work Loss Related to Illness and Treatment (Productivity Costs)

Patient time spent away from work will be estimated using the Work Productivity and Activity Impairment Questionnaire (WPAI). The WPAI measures work time missed as well as work and activity impairment due to a specific health issue.[38] The WPAI's validity has been established in a number of diseases and has proven a useful tool for measuring relative differences between treatment groups in clinical trials, including cancer, in patients with and without disease.

3.4.4   Valuing Patient Work Loss

The value of hours recorded for patient work loss will be estimated using wages from the Bureau of Labor Statistics for the sex, age, location and employment category of patients.

3.4.5   Financial Hardship

Financial hardship experienced by the patient will be captured by a set of four questions that capture the inability to pay bills, recent income loss, need to borrow money or current debt. The responses to these four questions will be combined into a composite index of financial hardship. This measure of financial hardship has been previously used and validated by Shankaran et al.[39]

3.4.6   Cost Data Collection Mechanisms

Hard copy surveys mailed out by SRG will be used to collect data on costs and work productivity. Using the cost diary method and WPAI methods described in previous sections, a SRG staff member will mail the patient a cost diary at 1 month, 7 months and 19 months from the date of study enrollment. We selected the first survey time point to be 1 month after patient enrollment in order to improve the likelihood that the patient or alternate contact will be able to collect and track their cost and time data (4).

Table 4 Cost Data Collection

Instrument	N items	Month Post-enrollment		
		1	7	19
Cost diary	10	X	X	X
Patient WPAI	7	X	X	X
Financial Hardship	4	X	X	X
TOTAL N ITEMS		21		
ANTICIPATED TIME PATIENT		15-30 min		

Given that the SRG is already contacting patients in BMT CTN 1102 to collect QoL data at specified time points, the CEA will contract with SRG to collect the additional economic data at 1 month, 7 months and 19 months follow-up. This approach is likely to improve participant

response by making SRG the single point of contact for study participants while avoiding the need for an internet connection or fluency with filling out online surveys.

3.4.7   Measuring Quality Adjusted Life Years

Quality of life and clinical data collected from the parent study will be used for the CEA study to provide an estimate for quality adjusted life years (QALYs). QALYs make up the denominator of the ICER, the cost effectiveness measure for this study.

The EQ-5D contains a five-item survey with three response levels per item measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Since there are 5 dimensions with 3 levels there are a total of 720 different health states, each with their own health utility value. The health utility value is then multiplied by the length of time spent in that health state to determine each patient's QALY. SF-36 scores will also be converted to health state utilities using the SF6D algorithm in order to calculate QALYs per patient.[40] We will estimate and compare results using the QALYs (and health utility values) estimated from both instruments since there is no single agreed upon "best" way to measure health state utilities. Measuring QALYs using these two approaches will allow us to evaluate the stability of estimates as a function of survey instrument selection.

3.5   Outcomes/Endpoints

3.5.1   Primary Endpoint

The primary end-point for the analysis will be the cost per QALY from the third party payer perspective with two time horizons: (1) within trial (at 3 years post enrollment), and (2) lifetime using simulation modeling.

3.5.2   Secondary Endpoints

The secondary end-point is the cost per quality-adjusted life year from the societal perspective, a broader measure that captures health insurer direct medical care costs and patient out-of-pocket direct medical and direct non-medical costs.[19,41] Patient productivity costs (captured as part of QALY calculations) will be reported separately.

4.   STATISTICAL CONSIDERATIONS

4.1   Analysis of Costs

4.1.1   Study Perspective and the use of Health Insurer Reimbursements

It is recommended that the comparative analysis of costs in CEAs be conducted from both a health system perspective and a broader societal perspective.[15,16] For the evaluation of the costs of alloHCT and HMA or best supportive care, the primary analysis will take the third party payer perspective where only payer direct medical expenditures are considered.

$$C_{Total} = C_{Direct\ Medical\ Expenditures}$$

Reimbursement records will be used to measure health plan expenditure for MDS care. The trial includes MDS patients that are age 50 – 75, and a substantial proportion are expected to be

enrolled in Medicare plans. All public and private insurance records will be requested and included in the primary analysis.

A secondary analysis will be to evaluate cost-effectiveness from a broader societal perspective that includes health plan expenditure, patient out of pocket expenditure, and patient productivity costs.

$$C_{Total} = C_{Direct\ Medical\ Care\ Payer} + C_{Direct\ Medical\ Care\ Patient} + C_{Direct\ Non\text{-}Medical\ Patient}$$

To avoid double counting, indirect productivity costs for patients will not be included in the ICER calculations but recorded separately (patient indirect productivity costs are captured in the QALY).

4.1.2   Direct Medical Care Costs Payer

The null hypothesis is that there is no difference between the total costs of direct medical care for patients who receive alloHCT versus HMA or best supportive care.

For the base case analysis, the mean difference in disaggregate costs and total cost between patients (i.e. the incremental cost) who receive alloHCT and hypomethylating therapy or standard or care will be analyzed. In order to estimate potential differences in cost in the two arms of the BMT CTN 1102 clinical trial, first the arithmetic mean of total per patient costs will be calculated for each arm of the trial. Differences in the arithmetic mean cost for each arm of the trial will be compared using a t-test. While in practice, the t-test is fairly robust to non-normality owing to the central limit theorem,[42] cost data are often highly skewed (e.g., small portions with very high costs), which calls into question the validity of a direct comparison of arithmetic means. Therefore, we will also evaluate differences in total costs of the two treatment strategies using non-parametric bootstrap methods[42] and the Kaplan-Meier Sample Average estimation (KMSA) technique.[43] These nonparametric techniques minimize bias due to the problems of censoring and skewed data.

Using cost histories from the patients in each study arm, the KMSA technique determines the mean cost (*M*) over the time period of interest as:

$$M = \sum_i \widehat{S}_i \widehat{C}_i$$

where S_i denotes the probability of the event occurring in the ith month and $\hat{C}_i$ is the average cost among patients who are alive at the beginning of the ith month and $\hat{S}_i$ is the estimated survival probability obtained from the Kaplan-Meier curve. Specifically, $\hat{S}_i$ is the estimated probability of being alive at the beginning of the ith month. Lin *et al.*[43] demonstrate that the KMSA estimator is unbiased and consistent as long as (i) censoring is independent in time and (ii) the time intervals for the cost analysis are sufficiently narrow. The design of the treatment trial is consistent with independent censoring and the time intervals incorporated into cost data collection provide appropriately narrow time intervals. Lin *et al.* also show that the KMSA estimator is asymptotically normal with easily estimated variances, permitting standard two-sample parametric testing.[43] For the purposes of this analysis, monthly time intervals will be used.

Finally, a regression-based KMSA model developed by Lin will be used account for baseline patient characteristics that could influence costs, to account for clustering within study centers, and to evaluate the uncertainty provided by the use of these different analytic techniques as an analytic sensitivity analysis.[37,44,45]

4.1.3   Out-of-pocket and Personal Costs

The same analytic approach described in section 4.2.2 will be used for out-of-pocket and indirect costs. Direct medical costs paid by patients will be based on patient information ascertained through the online or telephone surveys. Direct non-medical costs will be disaggregated into transportation, accommodation, telecommunication, and other costs. These costs will then be combined to calculate the total out-of-pocket costs incurred. Indirect costs for patients will be presented separately.

4.2   Analysis of Effectiveness: Quality Adjusted Life Years

Health state utilities derived from the EQ-5D. Secondary analyses will use the SF-36 (using the SF-6D algorithm)[40,46] to derive utilities. Utility scores will be combined with survival data from BMT CTN 1102, to calculate QALYs using the area under the curve method.[44] The analysis of QALYs will follow the same analytic approach used for the analysis of; using KMSA for the base case followed by mixed effects modeling. Baseline health state utilities will be included as a covariate in multivariate analysis of the difference in QALYs between alloHCT and HMA or best supportive care to account for possible differences in baseline utility between groups.[47]

4.3   Analysis of Incremental Cost Effectiveness

If objectives 1 and 3 show either treatment alternative is less costly and more effective (greater QALYs) than the other alternative, it is said to *dominate* and no numerical estimate of incremental cost-effectiveness is required. Instead the estimated reduction in cost and improvement in quality-adjusted survival, and the associated uncertainty in these estimates, will be reported. If no strategy dominates, the incremental difference in cost and/or QALYs, and the associated uncertainty in these estimates, will be reported.

The *incremental cost-effectiveness* of one alternative over another is derived using the following formula:

Incremental cost-effectiveness$_A$ = (C_A – C_B)/(E_A – E_B)

Where C_A and C_B refer to average total costs of each alternative and E_A and E_B refer to average total effectiveness for each alternative, respectively. The resulting incremental cost-effectiveness ratio (ICER) can then be used to make a judgment on the value provided by alternative A when compared to alternative B as it represents the investment required for each additional unit of effect gained.

All analyses of cost and effectiveness will be completed on an intent-to-treat basis.

4.4   Lifetime Horizon and Simulation Modeling

Mean costs and mean QALYs as estimated using data collected by objectives 1-3, will be used as input in a health economic simulation model. The model will be used to project lifetime health outcomes based on within-trial (ie. 3-year) overall survival (OS), quality of life, and medical

expenditure trends. Different parametric survival functions will be considered to extrapolate within trial results, including: Weibull, Gompertz, exponential, log-normal and generalized gamma distributions.[48] The base case analysis survival function will be selected using the Akaike Information Criterion (AIC).[49] Cox-Snell residuals will be plotted as a confirmatory test to identify the function with the best fit to the observed data.[50] The mean number of life-years for patients in each group will be estimated as the area under the OS curve.[51] QALYs will be estimated from OS by weighting with utility values obtained from the analysis of utility data. Projected utility weights for long-term survivors will be based on monthly trends in utility as observed for those who survive the year following treatment initiation or transplant. Projected utility weights for the last 6 months of life will be based on utilities for the last 6 months of life for persons who die during the year following treatment initiation or transplant. In the case where insufficient numbers of persons have died within 6 months of their survey, we will use patient's baseline utility scores as an estimate for quality of life in the last 6 months of life.

Similarly, for those who survive through the end of the study observation period, we will project costs over a lifetime horizon modeled as described above, dividing costs into two periods: continuing care and death costs. Continuing care costs will be based on monthly trends in costs observed for those who have survived the year following treatment initiation or transplant. Death costs, defined as costs of care during the last 6 months of life for persons who have died, will be based on costs of care observed for those who die during the year following treatment initiation or transplant. Costs will be modeled based on projected survival (see above).

4.4.1   Uncertainty Analysis

One-way and probabilistic uncertainty analyses will be conducted to characterize uncertainty around the base case results. In one-way uncertainty analyses, we will calculate incremental QALYs, incremental expenditure, and the incremental cost-effectiveness ratio using low and high survival, quality of life, and expenditure values derived from the 95% confidence interval bounds. This procedure demonstrates the influence of each input on incremental outcomes, and will be plotted in the form tornado diagrams. In probabilistic uncertainty analyses, we will evaluate the joint uncertainty in outcomes by sampling from the distributions all model inputs, propagating those values through the model, and obtaining the resulting distribution of incremental QALYs, incremental expenditure, and the incremental cost-effectiveness ratio. In this procedure we will assign mathematical distributions to all of the model inputs (hazard ratio=log-normal, expenditure=normal, quality of life=beta), conduct 10,000 Monte Carlo simulations, and results will be used to calculate 95% credible intervals for life years, QALYs, and expenditures.[52] Uncertainty in the primary CEA endpoint will be evaluated using cost-effectiveness acceptability curve (CEAC) plots.[53]

In the case where an incremental cost-effectiveness ratio is computed (higher costs, higher QALYs), cost-effectiveness acceptability curves will be created to characterize the level of probability that the intervention is cost-effective at different willingness-to-pay thresholds (e.g., $50,000, $100,000 per QALY).[54]

One-way sensitivity analyses will be conducted on all parameters to determine their individual impact on results with parameters varied within one standard deviation or error from their base case value.

4.5   Base Year Cost Counting and Discounting

All costs will be converted to base year costs (2014, the year 1102 began enrolling patients). The medical consumer price index[55] and the US Consumer Price Index for All Urban Consumers[56] will be used to covert direct medical costs and non-medical costs, respectively. Costs and outcomes that occur 12-months post study entry, will be discounted at a rate of 3% annually with sensitivity analyses completed with discount rates of 1% and 5%.[16]

4.6   Missing Data

Missing direct medical care costs (payer) data is not anticipated. However, missing quality of life, out-of-pocket, productivity and caregiving cost data may occur for several reasons including entire surveys being incomplete due to censoring due to death or loss to follow up or intermittent patient non-response. If the amount of missing data exceeds 10% for any particular item, we will explore the mechanism of missingness. Random effects models will be used if data is missing completely at random (MCAR) and the presence of informative missingness is assumed. Under the assumption that the data are missing at random (MAR),[57] we will impute missing data using multiple imputation.[77]

4.7   Sample Size and Power

The targeted sample size for this ancillary cost-effectiveness analysis is determined by the number of patients enrolling in the parent study, BMT CTN 1102 and by the percent of patients who do not find a matched donor within 90 days of enrollment in the parent study. Assuming that 80% of BMT CTN 1102 participants agree to enroll in the economic study, and a 10% loss to follow up over the study period, the targeted sample size is 270 (162 alloHCT, 108 non-HCT) if donor availability is 60%. If donor availability is 70%, the targeted sample size is 320 (224 alloHCT, 96 non-HCT).

The primary research question is whether costs and/or effects, measured as QALYs, differ between MDS patients age 50 – 74 years receiving either alloHCT or HMA or best supportive care. Table 3 presents the power associated with each objective and the CEA using the sample size assumptions described above. Other parameter assumptions used in these calculations include the difference in mean disease-attributable direct medical expenditure between a sample of 38 patients receiving alloHCT at the Medical College of Wisconsin ($172,532 (95% CI: $79,618-$265,446), SD=$92,914) and the mean disease-attributable direct medical expenditure of MDS patients receiving HMA presented in Wang et al.[58] Minimally clinically important difference in QALYs based on utility values provided by the EQ-5D and SF-6D (0.147, SD 0.294) were used to estimate the expected difference in effects,[59] and for ICER calculations, we used a correlation between cost and effect of 0.25.

Estimates of power for ICERs use the Incremental Net Benefit (INB) method to calculate the point estimate and confidence interval.[60] This approach is derived from the statistical test of whether the net monetary benefit is significantly different from zero by performing a sensitivity analysis of the willingness to pay (WTP) threshold. Because there is not an explicit WTP threshold in the United States, we will evaluate INB over a plausible range of WTP values ranging from $50,000 to $200,000 (Table 3).

The results of the power calculations show that regardless of the assumptions used, the difference in costs and effects between the treatments with the target sample size results in power of >0.98 for all analyses.

Table 3 Power Calculations

Scenario	Hypotheses		CEA Sample Size	Power for Costs	Power for QALYs[*]	Power for ICERs
Specific Aim 1 – Costs Direct Medical Payer (CDMP)						
H_o: $CDMP_{alloHCT} = CDMP_{HMA}$ H_a: $CDMP_{alloHCT} > CDMP_{HMA}$			(162 alloHCT, 108 HMA)	0.999		
			(224 alloHCT, 96 HMA)	0.999		
Specific Aim 2 – Costs Out-of-Pocket and Indirect (COOPI)						
H_o: $COOPI_{alloHCT} = COOPI_{HMA}$ H_a: $COOPI_{alloHCT} > COOPI_{HMA}$			(162 alloHCT, 108 HMA)	0.999		
			(224 alloHCT, 96 HMA)	0.999		
Specific Aim 3 – Effectiveness: QALYS (E)						
H_o: $E_{alloHCT} = E_{HMA}$ H_a: $E_{alloHCT} > E_{HMA}$			(162 alloHCT, 108 HMA)		0.996	
			(224 alloHCT, 96 HMA)		0.981	
1- WTP= $50,000	H_o: NB = 0		(162 alloHCT, 108 HMA)	0.999	0.996	0.999
	H_a: NB ≠ 0		(224 alloHCT, 96 HMA)	0.999	0.981	0.999
2- WTP= $100,000	H_o: NB = 0		(162 alloHCT, 108 HMA)	0.999	0.996	0.999
	H_a: NB ≠ 0		(224 alloHCT, 96 HMA)	0.999	0.981	0.999
3- WTP= $150,000	H_o: NB = 0		(162 alloHCT, 108 HMA)	0.999	0.996	0.999
	H_a: NB ≠ 0		(224 alloHCT, 96 HMA)	0.999	0.981	0.998
4- WTP=$200,000	H_o: NB = 0		(162 alloHCT, 108 HMA)	0.999	0.996	0.999
	H_a: NB ≠ 0		(224 alloHCT, 96 HMA)	0.999	0.981	0.999

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Cost-Effectiveness Research

INFORMED CONSENT

Study Title: Ancillary Cost-Effectiveness Study to BMT CTN 1102

Principal Investigator: Scott Ramsey, MD, PhD; Email: sramsey@fhcrc.org;
Tel: (206) 667-7846

Mailing Address: 1100 Fairview Ave N, MS: M3-B232; Seattle, WA 98109

Cost-Effectiveness Research (Optional)

This section of the consent form is about cost-effectiveness research that will look at how much you and your insurance pay for your treatment. The researchers want to understand how much different therapies cost. You may choose to let the researchers collect information on the cost of your treatment for this study if you want to.

You can still be a part of the main study (health evaluations by phone) even if you say 'no' to give information on the cost of your treatment.

Study purpose: The study doctors want to learn more about the costs of the two types of treatments that are being compared in the main study: 1) transplant from a well matched family donor or unrelated donor; and, 2) blood transfusion and drug therapy only (no transplant).

This research will help doctors understand the cost-effectiveness of these treatments. In particular, researchers want to know if costs are a problem for patients and their families. They also want to know how out-of-pocket financial costs (costs not covered by your

insurance) differ by treatment type and by type of insurance. This will help them understand cost barriers for patients with different treatments.

Lead study doctor: Scott Ramsey of the Fred Hutchinson Cancer Research Center in Seattle is the lead study doctor for the cost-effectiveness research. Dr. Ramsey is a medical doctor and well-known health economist who has studied costs of many different cancer treatments.

Your health insurance and out-of-pocket medical costs: If you agree to join this study, we will ask for the following information about your health insurance:

1) Type

2) Provider

3) Policy number

4) Group number

5) Policy holder's name and date of birth.

We will also want to know about your out-of-pocket costs. The out-of-pocket costs you and

your family have to cover are important in understanding the overall cost of medical care, so we want to collect this information as well. For example, we want to know how much you spend on:

1) Medical costs (for example, co-pays, prescriptions)

2) Travel and lodging

3) Cost of time away from work

Your health insurance and out-of-pocket information is called the 'study data' in this consent form.

How we will use your health insurance information: After you finish the study, we will use your insurance information to learn about the payments your health insurer made. We will calculate the cost of your medical care (both groups that are being compared, the transplant group and the no transplant group). Because treatment (either transplant or non-transplant therapies) can impact your health for many years after you join the study, we want to collect insurance payment information for the 12 months before you joined the study, and for 3 years after your treatment start date.

Privacy, confidentiality and use of information: Only the study doctors at the Fred Hutchinson Cancer Research Center (FHCRC) will have access to your health insurance information and out-of-pocket cost information (study data). The FHCRC will contract with the Survey Research Group (SRG) at the CIBMTR to collect out-of-pocket cost data, who are also administering the telephone health surveys as part of the

parent study. To maintain your confidentiality, we will not link your name to the study data. Also, all of the study doctors signed a confidentiality agreement and promised to keep electronic data protected under passwords and physical data (paper or other media such as CDs) in secure facilities (for example, on-campus locked offices and locked filing cabinets).

Collecting the study data: We will collect your health insurance information at the time of study enrollment. Out-of-pocket cost data will be collected by mail-out survey. The mail-out surveys were designed to be very user friendly, but we will help you with the cost diary over the phone if needed. We will also place phone call reminders.

We will ask you about your out-of-pocket costs only 3 times during the course of the study: at 1, 7 and 19 months after enrollment. We think each questionnaire will take between 10 and 30 minutes to complete, but this depends on how much information there is to enter.

Alternate contact: We ask that you give us the name of an alternate contact. This may be your spouse, partner, parent, adult child or sibling, or friend. You may not feel like answering the questionnaires or need help gathering cost information, so we ask that this individual help with this information

Risks to participating: The risks to participating in the cost-effectiveness study are small. A possible risk is the loss of confidentiality about your medical information, but the chance that this

information will be given to someone else is very small.

Payment and costs: You will not get paid for participating in this study. You will not be charged for taking part in this study.

Right to ask questions and/or withdraw: You do not have to be part of the cost-effectiveness research study. Your participation is voluntary. If you decide not to be part of this study, it will not affect your regular medical care or services. You can quit the study at any time.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary

of the results. You can search this Web site at any time.

For more information: Contact the Study Coordinator at the Fred Hutchinson Cancer Research Center at (844) 840-2731 or email: 1102-CEA@fredhutch.org

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call Karen Hansen, Director at the FHCRC research review board at: (206) 667-4867.

No matter what you decide to do, it will not affect your care.

Statement of Consent for Cost-Effectiveness Research Study (Optional)

The purpose of the cost effectiveness research, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to participate in the cost effectiveness research. If I decide to not participate, it will not affect my medical care in any way.

❑ I agree to be part of the cost-effectiveness research.

❑ I do not agree to be part of the cost-effectiveness research.

_____   _____

Signature   Date

(Version date 1/30/15)

FRED **HUTCHINSON**
CANCER RESEARCH **CENTER**
Institutional Review Board

HIPAA Authorization for the Use of Member Protected Health Information for Research

IR number: 9159   **Protocol number:** 1.0

Title of Research Study: *Ancillary Cost-Effectiveness Analysis to:* A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome BMT CTN 1102

The research study named above and described more fully in the informed consent form that you sign ("Research Consent") requires that the researchers have access to health insurance information about you (also called "Protected Health Information" or "PHI"). By law, your health insurance provider (the "Insurer") must protect the confidentiality of your PHI.   The researchers can obtain your PHI from the Insurer and use it for research **only if you authorize and direct the Insurer to share it with them.**.

This authorization form ("form") describes what types of PHI the researchers need and what they will do with it as part of the research study. Please read it carefully. If you agree with it, please sign your name at the bottom. You will be given a copy of this form after you have signed it.

If you sign this form, your PHI will be shared with Fred Hutchinson Cancer Research Center, its staff, and others who work with them. In this form, the term for all these people is "Researchers" and they are described more fully in the Research Consent. The Researchers will use the PHI only for the purposes described in the Research Consent and in this form.

1. The protected health information to be obtained and used by the Researchers for the Study includes:

- All health insurance information including the type of health insurance, provider, policy number, group number and the policy holder's name and date of birth. It also includes information about health care costs and health care claims information as well as reimbursements made by your health insurer(s).

- The specific protected health information that will be obtained from the Insurer and used for the Research is described below:

    - Dates and codes associated with medical service and diagnoses
    - Location of medical service
    - Provider of medical service

2. What the Researchers will do with your Protected Heath Information.

The Researchers will use your PHI only in the ways described in the Research Consent form that you sign and as described here. They may also share your PHI with certain people and groups. These may include:

- The sponsor of the Study, The National Heart, Lung and Blood Institute. The sponsor reviews the Study. Government agencies, review boards, and others who watch over the safety, effectiveness and conduct of the research

- Others, if the law requires.

By law, the Researchers are required to protect the confidentiality of your PHI. The Research Consent form you sign describes in more detail how your PHI will be protected. You may ask questions about what the Researchers will do with your information and how they will protect it. Privacy laws do not always require the receiver of your information to keep your information confidential. After your information is given to others, there is a risk that it could be shared without your permission.

You are free to refuse to allow the Researchers access to your PHI. If you refuse, you will not be able to participate in this research study but your refusal will not affect your health insurance eligibility or coverage.

3.   How long the permission will last?

The permission for the Researchers to obtain and use your protected health information will end when the Researchers complete the research study AND any review of the research study is completed.

4. Canceling your permission.

You may change your mind and take back your permission anytime. To take back your permission, please send a written request to the research study coordinator, Lisel Koepl, at Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, M/S M3-B232, Seattle, Washington 98109-1074. If you do this, you may no longer be allowed to be in the research study. The Researchers may still keep and use any Protected Health Information they already have. But they can't obtain more PHI about you for the research study unless it is required by a federal agency that reviews the research.

5. Giving permission

You give your permission for the use of your protected health information by signing this form.

Signature

I authorize and direct the Insurer   to provide access to my protected health information to the Researchers as described in this authorization form.

_____ _____

Signature of participant or participant's Legal   Date
Representative

_____ _____

Printed name of participant or participant's   Representative's relationship
Legal Representative   to participant

Primary insurance (if any):

Health Insurer: _____ Type of Insurance: _____

Policy Number: _____ Group Number: _____

Policy Holder's Name: _____Policy Holder's Date of Birth: _____

Additional insurance (if any):

Health Insurer: _____ Type of Insurance: _____

Policy Number: _____ Group Number: _____

Policy Holder's Name: _____Policy Holder's Date of Birth: _____

If more than 2 insurance providers, please add additional insurance information below:

Health Insurer:_____ Type of Insurance: _____

APPENDIX G

REFERENCES

APPENDIX G

REFERENCES

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