month post-transplant period with PTCy and similar incidence of cGVHD, 2-year non-relapse mortality, relapse, progression-free survival, and overall survival.[22]

Cord Blood Transplantation

Since the first umbilical cord blood transplant (UCBT) performed in 1988,[23] the field of UCBT has evolved significantly. Due to reduced stringency of the HLA-match requirement and faster availability of banked cryopreserved umbilical cord blood units, cord blood has served as an alternative source of hematopoietic stem cells, and contributed to increased access to HCT for patients who lack of an HLA-matched related or unrelated donor, primarily in younger patients. So far, over 750,000 cord blood units have been stored for transplantation worldwide,[24] and approximately 3,000 UCBTs have been performed each year for both hematologic malignancies and non-malignant diseases.[25]

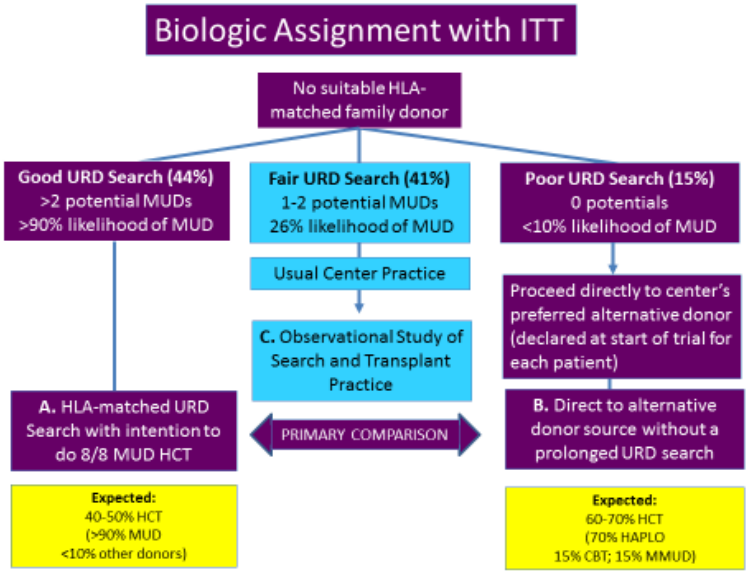
In pediatric patients with acute leukemia, Eapen et al. demonstrated a leukemia-free survival at 3 years of 60% after HLA-matched UCBT, 36% after 1 HLA-mismatched UCBT with low cell dose (<3 $X10^7$ TNCs/kg), 45% after 1 HLA-mismatched UCBT with high cell dose, and 33% after 2 HLA-mismatched UCBT.[26] The encouraging results have also been demonstrated in pediatric patients with benign diseases such as thalassemia, sickle cell anemia[27] and Fanconi anemia[23].

Although there have been no randomized prospective studies comparing outcomes of UCBT and other donor sources, results from several retrospective and prospective studies have demonstrated that UCBT is associated with lower rates of GVHD and can provide long-term survival rates comparable to HLA-matched unrelated donor transplants.[28-32] A recent meta-analysis included 9 studies of pediatric and adult patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) and showed a similar relapse rate, overall survival and progression-free survival of unrelated single-unit UCBT and unrelated donor bone marrow transplantation. However, time to neutrophil and platelet recovery was shorter after unrelated donor transplantation compared to UCBT.[32] The median age of UCBT patients included in this meta-analysis was 27.5 years.

Even though cord blood contains a high density of hematopoietic progenitor cells (HPCs) with an extensive proliferative capacity and can be cryopreserved for more than 20 years[33], the total volume of each cord blood unit infused is low, resulting in delayed hematopoietic recovery, delayed immune reconstitution and increased treatment-related mortality as it has been shown in many studies that the successful transplantation using cord blood depends primarily on number of HPCs in the cord blood unit.[26,27,34] The optimal cell dose per recipient body weight can be achieved in small children while this becomes an important limitation of using cord blood cells in adult patients. Improvements in UCBT outcomes for adult patients are due to better HLA matching, supportive care, patient selection and optimal cord blood unit selection based on nucleated cell dose. The Japanese group reported better 5-year disease-free survival of 60–70% in selected acute leukemia patients receiving myeloablative single unit UCBT, presumably because lower recipients' weight and less genetic variability in the Japanese population.[35]

To overcome the low number of HPCs in a single cord blood unit, double UCBT was developed. In a study of 23 adults with high-risk hematological malignancies undergoing double CBT, the engraftment was derived from a single cord blood unit with the median time to engraftment of 23

Although the best study design would be a randomized controlled trial among patients who do not have a suitable HLA-identical sibling donor, the number of patients required is too large and preliminary assessment suggested that this type of study is not feasible. Thus, the protocol team opted for an intention-to-treat biologic assignment design, where biologic assignment is made to matched unrelated donors vs. all other alternative donors (haploidentical family members, cord blood, mismatched adult unrelated donors) based on the donor search prognosis score.[14] The score is calculated using the patient's HLA typing and race. Recent unpublished data suggest that patients who are Very Likely to find a MUD (about 44% of patients) have a >90% chance of finding a matched unrelated donor. Patients who are Very Unlikely to find a MUD (about 15% of patients) have <10% chance of finding a matched unrelated donor (J Dehn, BeTheMatch, personal communication to provide the current distribution of search prognoses). These two patient groups, those who are Very Likely to find a MUD and those who are Very Unlikely to find a MUD, will be analyzed for the primary endpoint since the biologic assignment is not associated with disease type, disease stage and most other patient factors known to be associated with transplant outcome. Patients who are Less Likely to find a MUD (about 41% of patients) have a 26% chance of finding a matched unrelated donor. Patients who are Less Likely to find a MUD will be enrolled and their outcome tracked but they will not be included in the primary analysis because there is no consensus on whether and for how long to search for a matched unrelated donor. Donor search prognosis is correlated with race/ethnicity but not with disease or disease stage. Thus, donor search prognosis will be used to assign patients to a group that is very likely to find a matched unrelated donor and a group that is very unlikely to find a matched unrelated donor, while minimizing biases due to disease status. It is acknowledged that the groups will be unbalanced for race (13% racial/ethnic minorities in the Very Likely to find a MUD group and 37% in the Very Unlikely to find a MUD group based on 229 searches conducted in a 2 week period in 2018; personal communication J Dehn) and comparisons will be stratified on this variable.



Because of the inherent biases in alternative donor selection, we plan to collect key data that will allow us to understand and adjust as much as possible for these biases. First, we will have centers keep screening logs so that we understand why potentially eligible patients were not enrolled, for example, disease considerations, logistics, patient refusal etc. We want to enroll patients once they are considered "serious" transplant candidates but before too many have been lost to factors that could be associated with a preferred donor source. For example, if it takes too long to identify or arrange for a certain type of donor, then we want to understand how this impacts relapse and toxicity due to need for additional chemotherapy etc. We will track survival for all patients enrolled on the study, irrespective of whether or not they are transplanted and which donor source is used.

their survival is much worse since transplantation was recommended for them, and we will track the outcomes for non-transplanted patients in this study.

1.6.3. Choice of Interventional Design

What will be the impact of the study on the field given the expected rapid changes in transplant and disease management? How will evolving practice such as shifts in preference in donor selection be addressed?

If the field shifts to rapid alternative donor transplant for patients in the Very Unlikely to find a MUD group that means centers have evaluated the observational data themselves and concluded that this is the best algorithm for their patients. However, our study question is not about how to improve the outcomes in the Very Unlikely to find a MUD group, although this is anticipated to be a derivative of the study. Our study question is how does a matched unrelated donor transplant compare to use of another alternative donor, specifically haploidentical donors. The donor search prognosis score serves as a biologic assignment tool to define groups for this primary comparison.

Would the same study with prospective data collection but omitting the algorithm be sufficient to identify current practice including barriers to transplantation and result in identifying hypotheses for future testing?

The study team considered an observational study but this design would only address the barriers to transplantation, not the outcomes comparison of matched unrelated donors to other alternative donor sources.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

The study hypotheses are: (1) disease and clinical status are the major determinants of deferred transplants rather than inability to identify a donor; and (2) if donor search prognosis is used to guide the donor selection strategy, Very Unlikely and Very Likely to find a MUD patients will have less than a 10% difference in survival, adjusting for baseline clinical variables, despite having different donor sources.

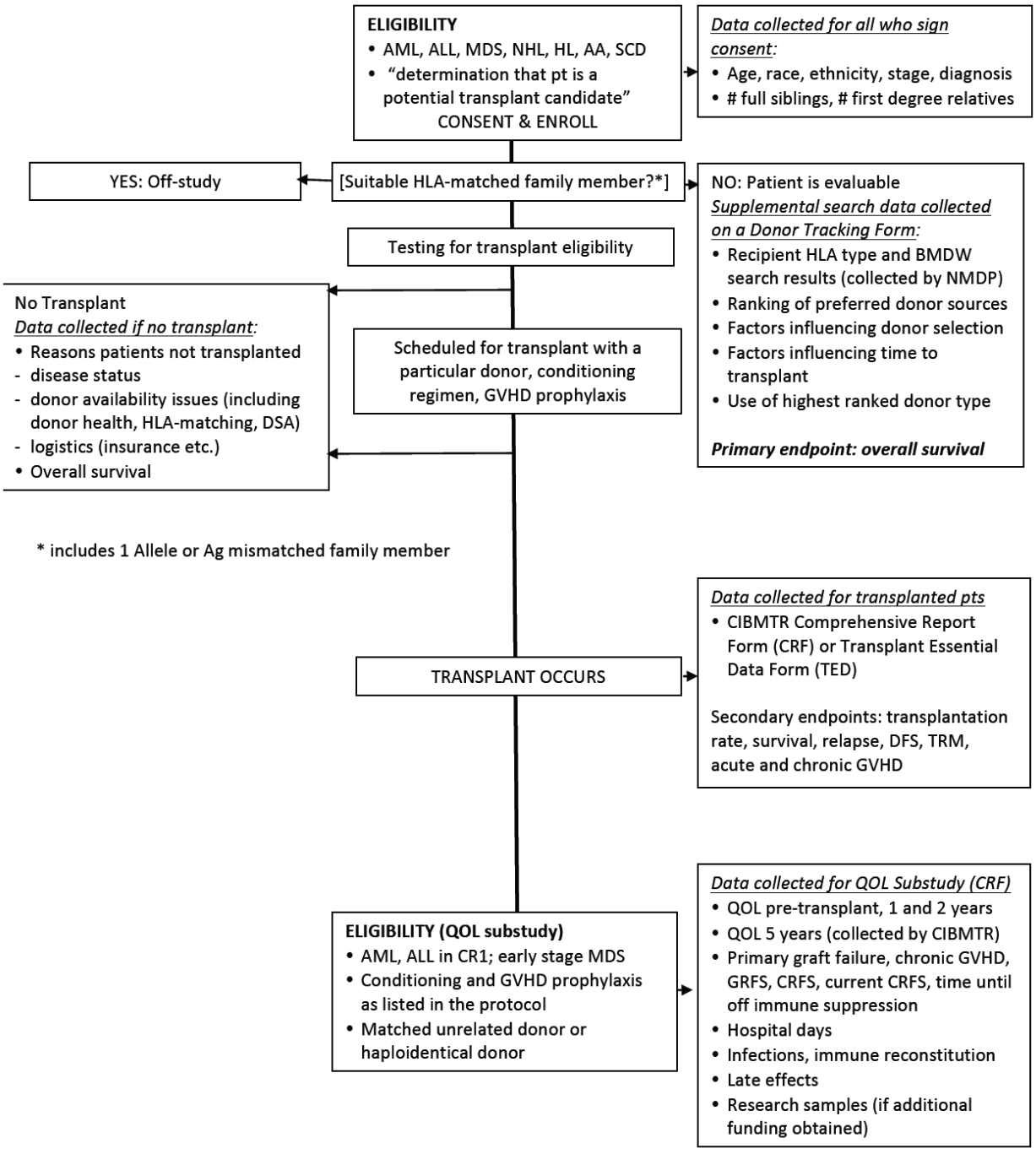
To test these hypotheses we need to enroll patients before a formal alternative donor search is launched. Patients may be enrolled as early as when initial HLA-typing is sent or at the time of initial evaluation for transplantation, preferably but not necessarily before results of the recipient HLA typing are back. Patients are not considered evaluable until they are declared to have no suitable HLA-matched or 1-antigen mismatched family member donor and the center confirms they are still transplant candidates based on available information. Enrollment is facilitated by allowing patients with any planned conditioning or GVHD prophylaxis regimen to participate and relying on standard CIBMTR forms for almost all outcomes data.

Data about the alternative donor search is collected on a Donor Search Tracking form. Data collection about the search focuses on barriers to transplantation and choices about donor type. The intention is that centers use the donor search prognosis to guide their search strategies. If a patient is Very Likely to find a MUD, a MUD is prioritized with the expectation that >90% will identify a fully matched unrelated donor. If a patient is in the Very Unlikely to find a MUD group, the center will move rapidly to the alternative donor of choice - a haploidentical family member, cord blood or mismatched unrelated donor because fewer than 10% will be able to find a fully matched unrelated donor. The eligibility criteria will ensure that at the time of enrollment the intent is to tailor the donor search according to the donor search prognosis. It is expected that >90% of patients transplanted in the Very Likely to find a MUD group will have a matched unrelated donor and the 70%, 15% and 15% of patients transplanted in the Very Unlikely to find a MUD group will have a haploidentical, mismatched unrelated donor or cord blood transplant, respectively.

Patients who do not undergo transplant will be followed long-term for survival only for at least 2 years after they are declared evaluable, through telephone contact with the patient/family, medical records review or search of administrative databases such as the social security death index.

All enrolled and evaluable Very Likely and Very Unlikely to find a MUD patients will be considered in the intention-to-treat primary analysis of survival. A Donor Search Tracking form will be designed to capture details of the alternative donor search and selection. This form also captures information about the patient's health and clinical status that are relevant to the timing of transplant. Data from the regular TED and CRF CIBMTR forms are sufficient for secondary endpoints such as occurrence of acute and chronic GVHD, relapse, disease-free survival, and treatment-related mortality. The CRFs but not the TED forms will capture primary graft failure,

NIH graded moderate-severe cGVHD, date of discontinuation of steroid and non-steroid immunosuppression, infections, number of hospital days in the first 100 days post-transplant, basic immune reconstitution data and late effects.



2.3.1. Intention-to-treat Cohort

Patient Inclusion Criteria

Patients fulfilling the inclusion criteria will be eligible for enrollment in this study. Of those who consent, only patients who lack a suitable HLA-identical or 1 allele or antigen mismatched related donors are evaluable. Patients with an HLA-identical sibling or 1 allele or antigen mismatched family member donor are evaluable as long as the center deems the family member donor as unsuitable for other reasons. Patients may co-enroll with other interventional or observational studies.

1. Patients of all ages with AML, ALL, MDS, NHL, HL, AA, or SCD are eligible.
2. Any planned conditioning regimen and GVHD prophylaxis approach is eligible.
3. Patients must be considered suitable allogeneic transplant 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 by the treating physician to judge transplant suitability.
4. Patient and physician must intend to proceed with allogeneic HCT within the next 6 months if a suitable donor is identified.
5. Center plans to follow the algorithm for alternative donor identification: (a) for subjects who are Very Likely to find a MUD, attempt to identify a matched unrelated donor; (b) for a subjects who are Very Unlikely to find a MUD, proceed expeditiously to a haploidentical, cord blood or mismatched unrelated donor.
6. Signed informed consent, and assent if applicable. Consent may be signed prior to completion of family typing but patients will only be considered evaluable upon confirmation that there is no suitable HLA-identical or 1 allele or antigen mismatched related donor available.

Patient Exclusion Criteria

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

1. Prior allogeneic HCT (prior autologous transplant is allowed)
2. Previous formal unrelated donor search

2.3.2. QOL Substudy

Patient Inclusion Criteria (QOL Substudy)

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

1. 8/8 HLA-matched unrelated donor or haploidentical family member donor

Any chronic GVHD as reported by the center will be reported.

3.3. Endpoints for the QOL Substudy

All patients on the QOL Substudy will have their transplant data collected on CRFs, which will capture all of the planned endpoints except for QOL.

3.3.1. Chronic GVHD

Moderate and severe chronic GVHD will be defined per the NIH consensus criteria.[75]

3.3.2. Time Until Off Immunosuppression for Patients Diagnosed with Chronic GVHD

Defined as the time since chronic GVHD onset until all systemic immunosuppression given for chronic GVHD treatment is discontinued. Continuation of low dose steroids for adrenal insufficiency (5 mg or less of prednisone or 0.1 mg/kg prednisone for children < 18 years old) is not considered systemic immunosuppression. Extracorporeal photopheresis and PUVA are considered systemic immunosuppression.

3.3.3. GVHD, relapse-free survival (GRFS)

Events for GRFS include grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppression, relapse or death.

3.3.4. Moderate-severe Chronic GVHD, Relapse-free Survival (CRFS) and Current CRFS

Events for CRFS include moderate-severe chronic GVHD, relapse or death. Current CRFS will also be calculated, defined as the prevalence of moderate-severe chronic GVHD requiring systemic immunosuppression for treatment of GVHD, disease-free survival, considering chronic GVHD, as a potentially reversible complication if systemic immunosuppression is stopped. Although relapse may be treated and the patient placed back in remission, relapse will not be considered a reversible state.

3.3.5. Primary Graft Failure

Primary graft failure is defined among patients surviving at least 28 days after graft infusion as failure to achieve a post-nadir absolute neutrophil count of >500 cell/μL for 3 days or donor peripheral blood T-cell chimerism of at least 5%. If T-cell chimerism is not available, testing of unsorted blood or marrow is acceptable.

3.3.6. QOL

Summary and subscales of QOL instruments will be scored according to the recommendations of the developers. The primary QOL endpoint is the global physical health scale from the PROMIS Global 10. Secondary QOL endpoints are the LSS chronic GVHD summary score and the PROMIS fatigue, pain and sleep scales. Other scales: mental health, social functioning, anxiety,

and depression, and chronic GVHD subscales will be described but are not expected to differ substantially or to have enough power to detect differences.

3.3.7. Hospital Days

Number of hospital days within the first 100 days will be collected on CRFs. The CIBMTR forms do not distinguish ICU days from regular hospitalization days. We are not able to collect departmental costs due to the differing accounting systems and rules at institutions.

3.3.8. Infections

Clinically significant viral, fungal, bacterial, and parasitic-defined infections will be reported by pathogen, site of disease, and date of onset from the CIBMTR CRF Form 2100 at 100 day, 6 months, 1 year and 2 years after transplant. If no clinically significant infections have occurred, the absence of infection will be reported. Reporting of certain specific fungal and viral infections will trigger subsequent forms in order to capture more detailed information. Please refer to the CIBMTR forms instruction manual for more details.

3.3.9. Immune Reconstitution

CIMBTR CRFs will collect data about neutrophil and lymphocytes counts, immunoglobulin subsets and T-cell/B cell numbers, if available. If additional funding is obtained, peripheral blood will be collected for immune reconstitution studies for the QOL Substudy at the following time points: pre-transplant and up to 6 times over the first two years after transplant. Thirty milliliters will be drawn at each time point for research tests. Participants in the QOL Substudy will be consented to these research blood draws at the time of enrollment, but no sampling will be performed until additional funding is obtained and the protocol is modified to reflect activation of the research blood draws.

3.3.10. Late Effects

Late effects are captured on the CIBMTR CRFs, and include selected cardiac, pulmonary, renal, metabolic, endocrine and other late complications.

identification process to understand clinical decision-making relevant to donor choice. Upon initiation of the Donor Source Tracking form, the NMDP will provide the donor search prognosis.

Key data collected include:

1. Initial preferred alternative donor source (priority ranking at enrollment): A rank list of preferred donors with "1" indicating the preferred alternative donor and descending. If a donor type would not be used, "0" should be entered. Options include: matched unrelated donor, mismatched unrelated donor, haploidentical family member donor (i.e. ≥2 allele mismatch), cord blood, or combinations of donors such as haploidentical + cord blood. For patients in the Very Likely to find a MUD group, this form will define the donor choice if a matched unrelated donor is not identified. For patients in the Very Unlikely to find a MUD group, it will identify the preferred donor among haploidentical, cord blood or mismatched unrelated donor. For the Less Likely to find a MUD group, it will capture the search algorithm planned by the center in the absence of protocol guidance.
2. Target time to transplant (# of weeks to infusion)
3. Patient weight
4. Confirmation of patient-defined race and ethnicity
5. Current patient diagnosis and disease stage, date of diagnosis
6. Date of patient and full sibling typing
7. Patient HLA typing and NMDP Recipient ID
8. Results of any special testing and dates
9. Date final donor selected
10. Reasons for delay or cancellation of transplantation.

See Study Procedure and Guidance Manual for the full list of collected variables. For patients who are never transplanted, this form will also capture survival information.

4.1.4. Donor Search and Identification

Once the patient is deemed evaluable, the transplant center transmits the high resolution HLA typing to the NMDP Immunogenetic Program who will prepare a report within 2 business days and send the information back to the center. Once the donor search prognosis information and preliminary search summary have been received and reviewed by the Center, the transplant coordinators at the transplant center should proceed with their institution's standard procedure to identify a donor including additional family member typing and/or initiation of an unrelated donor and/or cord blood search. Updates on patient and search status will be requested at least monthly after enrollment, and include any revision to the donor priority ranking and rationale for changes. Details of the final donor selection and donation schedule will be captured. Guidance on the search is provided in the Study Procedure and Guidance Manual.

4.2. Methodology and Documentation of Study Events

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

Subjects may be approached for this study from the time when they are considered to be potential allogeneic HCT candidates through when the determination that no suitable HLA-matched or 1 allele or antigen mismatched related donor is available. For centers who see patients for a transplant consult then do not see them again until a donor has been identified, consent may happen as soon as HLA-typing is sent. For centers that will see potential participants more frequently before transplant, consent may also take place once it is determined there is no suitable HLA-matched or single mismatched related donor. Eligible patients willing to participate in the study will sign an Institutional Review Board (IRB) approved consent form for this protocol. Parents or legal guardians will consent for minors, and minors will provide assent per local institutional guidelines.

If patients are determined to have a suitable HLA-matched or 1 allele or antigen mismatched related donor (i.e. $\leq$1 mismatch; 7+/8 HLA-A, B, C, DRB1) who will serve as the donor, they are not considered evaluable for this study.

4.3. Study Monitoring

4.3.1. Transplant Data

Transplant outcome data will be collected on CIBMTR forms. Whether or not a patient participates in BMT CTN 1702, centers must register pre- and post-transplant clinical data on all consecutive HCTs done at their institution through the CIBMTR, which holds the contract for the US Stem Cell Therapeutic Outcomes Database (SCTOD) charged with collecting data on US allogeneic HCTs. Registration is done using procedures and forms of the SCTOD. (Note: Federal legislation requires submission of these forms for all US alloHCT recipients.) Enrollment on BMT CTN 1702 must be indicated on the SCTOD pre-transplant registration form. Assignment to the TED or CRF track will not be affected by participation in BMT CTN 1702, unless patients are eligible for the QOL Substudy in which case all will be assigned to the CRF track. If they consent to QOL data collection, this information will be collected using CIBMTR supplemental forms.

4.3.2. Collection of QOL Data

At the time a patient is identified as participating in the QOL Substudy, the CIBMTR Survey Research Group (SRG) is notified and then adds that patient to CIBMTR's electronic Patient Reported Outcomes (ePRO) system for long-term QOL tracking.

Pre-transplant (baseline) QOL data will be collected by the center or CIBMTR electronically or on paper forms within 4 weeks of the start of conditioning. If conditioning is delayed, the QOL surveys should be repeated so they are within 4 weeks of conditioning. Electronically-collected baseline QOL surveys will be entered in the ePRO system. The center will securely email or fax baseline QOL instruments completed on paper to the SRG to enter into their ePRO system. Along with the pre-transplant QOL instruments, the center will securely email or fax a patient contact information form so that the SRG can reach the patient for 1, 2 and 5 year QOL time points.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Overview

This study is designed as a multicenter prospective study to assess outcomes of alternative donor search prioritizations and transplants, for patients with AML, ALL, MDS, NHL, HL, AA, or SCD who are considered eligible for a transplant within the next 6 months. Patients who consent are considered evaluable once the center determines no suitable HLA-matched or 1 allele or antigen mismatched related donor is available and the center confirms the patient is still transplant eligible.

The primary objective is to estimate and compare the overall survival between two arms: patients who are Very Likely to find a MUD, who will pursue a fully matched unrelated donor, versus those who are Very Unlikely to find a MUD, who will pursue a haploidentical, cord blood, or mismatched unrelated donor. Patients who are Less Likely to find a MUD will be enrolled but not analyzed for the primary endpoint because there isn't agreement on whether a matched unrelated donor should be pursued first. Additional secondary endpoints look at the cumulative incidence of receiving a transplant and reasons for not receiving a transplant, as well as post-transplant outcomes in those who receive a transplant by search prognosis arm and by type of transplant received. An additional QOL substudy will examine post-transplant outcomes of a smaller, more homogeneous subgroup with more detailed data collection on chronic GVHD, QOL, infections, and immune reconstitution.

5.1.1. Accrual

Based on historical CIBMTR data from 2016 for the diseases included in this study, there were 3133 HCTs from alternative donors, including 2013 from matched unrelated donors, 653 HCTs from haploidentical relatives, 201 from mismatched unrelated donors and 266 cord blood transplants at Core and non-Core BMT CTN centers. Assuming 50-70% of patients slated for unrelated donor transplantation actually undergo transplantation, there are potentially 4500-6000 transplant candidates per year. Assuming 15% of these patients participate in the trial, and 60% of these are in the Very Likely or Very Unlikely to find a MUD groups, we would be able to accrue between 400-540 patients per year who are eligible for the primary analysis. Based on these assumptions and accounting for variable time to open protocols at participating centers, it is estimated that approximately 3 years of accrual are necessary to enroll the targeted sample size for the primary analysis.

5.2. Sample Size and Power Calculations

Sample size requirements for this study are based on enrolling sufficient patients to have adequate power for the primary analysis, which is to compare the overall survival between patients who are Very Likely to find a MUD vs. those who are Very Unlikely to find a MUD, starting at the time of evaluability for the study when a center confirms that there is no suitable matched or 1 allele or antigen mismatched related donor. We assumed baseline survival probabilities for patients who are in the Very Likely to find a MUD group would be approximately 30% at 2 years, since

model for co-morbidities or disease risk index because this information is not available for all patients in the intention-to-treat analysis.

5.6.2. Analysis of Secondary Endpoints for Primary Analysis Population

Transplantation

Cumulative incidence of transplant, treating death prior to transplant as a competing risk, will be plotted over time for each donor search prognosis group as a descriptive summary, and will be compared between the groups using a Fine-Gray model, adjusting for the following pre-specified patient characteristics at the time of registration: age, sex, race, ethnicity, disease and disease stage. Adjusted cumulative incidence curves using the method of Xu and Zhang may also be provided to supplement the univariate estimates.[78] This analysis will be conducted as early as 6 months after the last evaluable participant is enrolled, since this analysis will not affect the primary endpoint.

Barriers to Transplantation

Barriers to transplantation will be summarized with descriptive statistics (number, frequencies) in each group, and compared between groups using chi-square tests. This analysis may be conducted as early as 6 months after the last participant is enrolled, since this analysis will not affect the primary endpoint.

5.6.3. Analysis of Secondary Endpoints for Less Likely to find a MUD Population

Cumulative incidence of transplant, Kaplan-Meier estimates of overall survival, and descriptive summaries of frequencies of barriers to transplantation will be provided both overall and by alternative donor preference group.

5.6.4. Analysis of Secondary Endpoints for Transplant Population

Overall Survival (OS)

OS will be analyzed in the transplant population, and in the patients enrolled in the QOL Substudy. OS will be summarized in each alternative donor group using the Kaplan-Meier estimate, and compared between donor search prognosis groups and by type of alternative donor transplant received using a Cox proportional hazards model adjusted for the following pre-specified patient characteristics: age, race/ethnicity, performance status, CMV serostatus, disease risk index,[79] co-morbidity index,[80,81] conditioning regimen intensity, donor age, graft type (bone marrow vs. peripheral blood), and GVHD prophylaxis regimen. A Cox model stratified on alternative donor type will be used to provide adjusted overall OS probabilities at two years for each alternative donor type, using the method of Zhang et al.[77]

Disease-free Survival

Disease-free survival will be analyzed in the malignant disease patients in the transplant population, and in the patients enrolled in the QOL substudy. Disease-free survival will not be

reported for non-malignant patients. Disease-free survival will be summarized in each alternative donor group using the Kaplan-Meier estimate, and compared between alternative donor groups using a Cox proportional hazards model adjusted for the same pre-specified patient characteristics as above. A Cox model stratified on alternative donor type will be used to provide adjusted overall disease-free survival probabilities at two years for each alternative donor type, using the method of Zhang et al.[77]

Relapse

Relapse will be analyzed in the malignant disease patients in the transplant population, and in the patients enrolled in the QOL Substudy. Relapse is not applicable to patients with non-malignant diseases. The cumulative incidence of relapse will be estimated and plotted over time for each alternative donor group, treating death as a competing event. The cause specific hazard rate for relapse will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for the same pre-specified patient characteristics as above.

Treatment-Related Mortality

Treatment-related mortality will be analyzed in the malignant disease patients in the transplant population, and in the patients enrolled in the QOL Substudy. Treatment-related mortality will not be reported for non-malignant diseases. The cumulative incidence of treatment-related mortality will be estimated and plotted over time for each alternative donor group, treating relapse as a competing event. The cause specific hazard rate for treatment-related mortality will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for same pre-specified patient characteristics as above.

Acute GVHD

Acute GVHD will be analyzed in the entire transplant population. The cumulative incidence of grade II-IV and grade III-IV acute GVHD will be estimated and plotted over time for each alternative donor group, treating death as a competing risk. The cause specific hazard rate for acute GVHD will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for the same pre-specified patient characteristics as above.

Chronic GVHD

Chronic GVHD will be analyzed in the entire transplant population. The cumulative incidence of chronic GVHD will be estimated and plotted over time for each alternative donor group, treating death as a competing risk. Relapse will not be considered a competing risk. The cause specific hazard rate for chronic GVHD will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for the same pre-specified patient characteristics as above.

5.6.5. Analysis of Secondary Endpoints for QOL Substudy participants

Chronic GVHD

The cumulative incidence of moderate-severe chronic GVHD according to the NIH consensus criteria[75,82] will be estimated and plotted over time for HLA-matched unrelated donor and haploidentical transplant groups, treating death as a competing risk. The cause specific hazard rate for cGVHD will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for the same pre-specified patient characteristics as above.

Time until off immunosuppression for patients diagnosed with acute or chronic GVHD

The cumulative incidence of stopping immunosuppression for patients diagnosed with acute or chronic GVHD will be estimated and plotted over time for HLA-matched unrelated donor and haploidentical transplant groups, treating death as a competing risk. The cause specific hazard rate for stopping immunosuppression will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for age, race/ethnicity, sex matching, graft type (bone marrow vs. peripheral blood), and GVHD prophylaxis regimen.

Chronic GVHD-free, Relapse-free Survival

Probabilities of GRFS and CRFS will be estimated and plotted over time for each alternative donor group using the Kaplan-Meier method. GRFS and CRFS will be compared between alternative donor groups using a Cox proportional hazards model adjusted for the same pre-specified patient characteristics as above for the secondary analysis of overall survival. Current CRFS will be described using simple frequencies, or by multistate model techniques if needed due to censoring.

Primary Graft Failure

The cumulative incidence of primary graft failure for patients who survive at least 28 days after transplant will be estimated and plotted over time for HLA-matched unrelated donor and haploidentical transplant groups, treating death as a competing risk. The cause specific hazard rate for graft failure will be compared between alternative donor groups using the Cox proportional hazards model, adjusted for the same pre-specified patient characteristics as above.

Quality of Life

QOL will be described and compared between alternative donor groups for the primary QOL endpoints: the PROMIS general health physical summary score, the fatigue, sleep and pain scales, and the LSS summary score. The questionnaires will be scored according to standard procedures. The self-report questionnaires will be completed prior to HCT and subsequently at 1, 2 years and 5 years, and the first analysis will be conducted at 2 years adjusting for pre-transplant scores.

Differences in QOL 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 analysis of covariance adjusted for baseline values of QOL. 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

6.2. APPENDIX B. HUMAN SUBJECTS

Subject Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates, provide them with information about the purpose of the study and obtain voluntary consent if the candidates agree to participate. The BMT CTN will provide a template of the consent form to each center. Each center will add their NMDP IRB approved boiler-plate language to the consent and submit for review by the NMDP IRB. The DCC will verify the adequacy of the consent forms prior to submission to the IRB. The NMDP IRB will provide evidence of IRB approval.

Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

Participation of Women and Minorities

Women and 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 incidence of AML, ALL, MDS, NHL, HL, AA, or SCD in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

days.[36] This approach has been studied in several diseases, which showed promising outcomes.[37,38] However, the benefit of double as opposed to single UCBT remains unclear as demonstrated from a prospective randomized study comparing single versus double UCBT in children and adolescents, which showed a similar rate of neutrophil engraftment and survival, while a higher incidence of grade III-IV aGVHD and cGVHD was observed in patients receiving double UCBT.[39]

Beside the use of double UBCT, several methods have also been pioneered to help increase numbers of HPCs and enhance engraftment after UCBT such as novel strategies of cord blood expansion[40-44] or strategies to increase cord blood HPC homing[45-47]. So far, all of these approaches appear to be safe and have faster engraftment; however, survival benefits remain unclear.

Haploidentical Transplantation with Post-transplant Cyclophosphamide

Haploidentical HCTs have been performed ever since the beginning of transplantation. However, high treatment-related mortality, initially because of aGVHD seen with T-cell replete grafts, then due to infectious complications associated with extensive T-cell depletion, has been noted. A recent development is the application of PTCy with a T-cell replete donor graft, which makes haploidentical transplantation feasible, with lower cost, low rates of GVHD and reproducible results worldwide. This has allowed a significant increase in donor availability and in the number of haploidentical transplants performed.[2]

Based on promising preclinical studies, O'Donnell and colleagues reported the first phase I clinical trial results of 13 patients who underwent haploidentical transplantation using non-myeloablative conditioning with fludarabine 30 mg/m^2 on day -6 to -2 and 2 Gy TBI on day -1 and PTCy 50 mg/kg on day +3.[48] Additional immunosuppression included MMF (day +4 to day +35) and tacrolimus. Cyclophosphamide 16.5 mg/kg on day -6 and -5 was subsequently added (Flu/Cy/TBI regimen) after the first few treated patients experienced primary graft failure. [48,49] Subsequent studies refined the prevention of GVHD by administering two doses of Cy on days +3 and +4.[49]

Since then, there has been a considerable interest in developing this approach for clinical practice. In 2011, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) jointly published results of 2 phase II studies of haploidentical and cord blood transplants. The studies were conducted in parallel in patients with high-risk hematological malignancies.[50] BMT CTN 0603 reported the results of haploidentical transplants with PTCy and a bone marrow graft. All patients were treated with reduced intensity conditioning using the Flu/Cy/TBI regimen. The patients in the haploidentical transplant trial had a low incidence of grade II-IV acute GVHD (32%) and, remarkably, there were no cases of severe (grade III-IV) aGVHD. The 1-year treatment-related mortality was also very low (7%), but the relapse rate was high (45%). The 1-year overall survival and progression-free survival were 62% and 48% in the haploidentical trial and 54% and 46% in the cord blood trial.

The MD Anderson Cancer Center group also performed two parallel phase II trials, one exploring the use of PTCy-based GVHD prophylaxis for haploidentical HCT and the other for 9/10 unrelated donor transplants, each using the same conditioning regimen (Flu/Mel/2GyTBI).[51] A total of 104 patients were treated, 60 with a haploidentical donor and 46 with a 9/10 unrelated donor transplant. Most patients received a bone marrow (BM) graft and all had the same GVHD prophylaxis with

This will fill a large unmet need for information about the patient evaluation and donor search process and the reasons that otherwise seemingly eligible patients do not receive a transplant. There are few data about these barriers (especially collected prospectively in a systematic manner across multiple centers), which may include, as noted above, disease progression and non-HCT-related complications but may also include patient reluctance, financial barriers, lack of social support and others.

The rationale for limiting the in-depth outcome analyses requiring complete clinical and patient-reported data collection to a smaller, more homogeneous subset (QOL Substudy) is to use resources wisely to focus QOL questions on a group of patients who will provide interpretable data. Patients with rare diseases, advanced disease status or unusual conditioning regimens or GVHD prophylaxis approaches may increase the background noise and/or lead to subtle confounding effects on the main outcomes comparisons. The power for this analysis is limited but it will provide important information for planning future studies that aim to improve QOL. Little additional work is required other than collecting patient-reported outcomes and assigning patients eligible for the QOL Substudy to the CIBMTR CRF track.

Given the large number of patients to be followed and understanding that data quality and burden of data collection are often inversely related, we opted to be parsimonious about endpoints. Thus, we will focus on overall survival. Secondary endpoints include relapse, disease-free survival, treatment-related mortality, aGVHD and cGVHD, all endpoints that can be derived from data routinely collect on the CIBMTR Transplant Essential Data (TED) forms, which are mandated for all US allogeneic HCT recipients. Detailed cGVHD data, number of hospital days, primary graft failure, infection/immune reconstitution and late effects data are limited to a smaller homogenous population of patients with AML or ALL in first complete remission or early stage MDS (refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, 5q- syndrome or $\leq$5% bone marrow blasts), with data collected on the CIBMTR CRFs. For example, GRFS (acute grade III-IV aGVHD and cGVHD requiring immunosuppression-free, relapse-free survival) and CRFS (moderate-severe cGVHD-free, relapse-free survival) can only be derived from the CRF forms and not TED forms, so these endpoints are not reported for the entire cohort but will only be reported for the QOL Substudy. Both GRFS and CRFS will be reported to allow comparisons with other BMT CTN studies. Because patient-reported outcomes data require specialized infrastructure and attention, QOL data will also be reported only for the QOL Substudy patients. We limited the QOL assessments to pre-transplant and 1 and 2 years after transplant in order to focus on times where we anticipate more complete collection will result in more meaningful data. Participants also consent to a 5 year QOL assessment when they sign the study consent form but this data collection will be performed separately by CIBMTR, referencing BMT CTN 1702 as the source of consent.

This protocol also outlines research blood sampling but no funding currently exists for collection. Patients in the QOL Substudy will be asked to consent for potential future research samples, and it will be made clear that this sampling is contingent on securing additional funding. If additional funding is obtained, patients will be notified and research sampling will commence. Appropriate sample volume adjustments for patient age and weight will be included. If no additional funding is secured, no research blood samples will be taken as part of this protocol. Donor blood samples

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective is:

1. Compare overall survival between Very Likely to find a matched unrelated donor search prognosis patients and Very Unlikely to find a matched unrelated donor search prognosis patients who are evaluable

2.2.2. Secondary Objectives

Secondary objectives include all patients regardless of donor search prognosis:

1. To estimate and compare the cumulative incidence of receiving a transplant according to donor search prognosis
2. To describe barriers to achieving transplantation with different donor search strategies

2.2.3. Post-Transplant Objectives:

Post-transplant objectives include all patients who are transplanted regardless of donor search prognosis:

3. To compare overall survival, relapse, disease-free survival, treatment-related mortality, and acute and chronic GVHD in patients transplanted for malignant diseases, according to the donor search prognosis and the alternative donor used.
4. To describe survival and acute and chronic GVHD in patients with acquired aplastic anemia and sickle cell disease after transplantation, according to the donor search prognosis and the alternative donor used
5. In patients with AML or ALL in first complete remission or early stage MDS (refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, 5q- syndrome or $\leq$5% bone marrow blasts) treated with a limited subset of conditioning and GVHD prophylaxis regimens and transplanted with either matched unrelated donors or haploidentical related donors (QOL Substudy), to compare QOL and describe primary graft failure, cGVHD, time until off systemic immunosuppression, aGVHD grade III-IV and cGVHD requiring immunosuppression-free, relapse-free survival (GRFS), moderate-severe cGVHD relapse-free survival (CRFS), current CRFS (still on systemic treatment for cGVHD), hospital days in the first 100 post-transplant days, infections, immune reconstitution and late effects after transplantation, according to the donor search prognosis and alternative donor used.

2.3. Patient Eligibility

Patients must meet specified eligibility criteria for entry into the intention-to-treat cohort and the QOL Substudy.

2. AML or ALL in first complete remission and early stage MDS (as defined according to CIBMTR criteria) at the time of transplantation. Early stage MDS is refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, 5q- syndrome or ≤5% bone marrow blasts
3. Conditioning regimen from the list below:
    a) Cyclophosphamide and total body irradiation +/- fludarabine
    b) Cyclophosphamide and busulfan +/- total body irradiation
    c) Fludarabine and melphalan +/- total body irradiation
    d) Fludarabine and busulfan
    e) Fludarabine and myeloablative dose total body irradiation
4. GVHD prophylaxis from the list below:
    a) Calcineurin-inhibitor and methotrexate or mycophenolate mofetil +/- antithymocyte globulin
    b) Calcineurin-inhibitor and sirolimus
    c) Post-transplant cyclophosphamide +/- others

Patient Exclusion Criteria (QOL Substudy)

Patients with the following are ineligible for inclusion in the QOL component of the QOL Substudy. They are eligible for all other QOL Substudy components.

1. For the QOL component, have not celebrated 8th birthday at the time of enrollment
2. For the QOL component, psychosocial conditions that would prevent study compliance
3. For the QOL component, inability to read English or Spanish

2.4. Donor Selection Guidelines

Once a participant is enrolled and (a) the HLA typing and race/ethnicity data are transmitted to NMDP and (b) the patient is deemed evaluable, NMDP will provide treating centers with a report detailing: the donor search prognosis, aggregate results of a preliminary search, and a qualitative estimate of the likelihood of finding a fully matched unrelated donor (see below for examples). However, specific donors will be selected by centers, according to their current methods. Guidance is provided in the BMT CTN 1702 Study Procedure and Guidance Manual. Testing for donor-specific antibodies (DSA) is highly recommended for all HLA-mismatched transplants. The Study Procedure and Guidance Manual contains guidance on interpretation of DSA and outlines methods of depleting DSA prior to transplantation.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

1. Patients may be screened for basic eligibility criteria without informed consent based on a waiver for screening. A screening log will capture all patients screened and their study disposition, e.g., enrolled, reasons they were not approached, etc.
2. The study is described to potentially eligible patients. The background, rationale and study requirements are discussed. Patients are given time to ask questions and consider whether they wish to participate. After the patient has given informed consent to participate on the study, an authorized user at the transplant center completes the BMT CTN 1702 Registration Form.
3. Once a patient is deemed evaluable by virtue of no suitable HLA-matched family donor (or 1 allele or antigen mismatched family donor if that is the center's practice), NMDP Immunogenetic Operations sends the donor search prognosis and preliminary search information to the Center. A Donor Search Tracking form is started.
4. Almost all of the post-transplant outcomes data for this study will be collected through the CIBMTR. If a participant proceeds to transplant, centers must obtain a CIBMTR Research Identification (CRID) number and enter it on the BMT CTN 1702 Segment A CIBMTR Research ID Form (see CIBMTR Data Collection below).

4.1.2. Evaluations at Enrollment

Data collected when consent is signed include the following:

1. Patient age, sex, patient-identified race and ethnicity
2. Disease and disease stage
3. Number of full siblings
4. Number of other first degree relatives
5. Date HLA typing sent, both low resolution and high resolution

4.1.3. Evaluations at Evaluability

A new form (BMT CTN Donor Source Tracking, see Study Procedure and Guidance Manual) will be started once a center determines that an alternative donor is required. The form will be updated at least monthly to provide information until conditioning for transplant starts, or the search for a donor is no longer active (survival will be captured on this form until the patient either goes to transplant, dies, or the study ends). The form will collect detailed data about the donor

The SRG will administer the 1, 2 and 5 year QOL instruments online, or on paper if requested by the patient. They will first confirm the patients' status with the transplant center because reporting of deaths may lag. They will then contact the patient via email, phone or mail to collect the QOL information online or on paper.

- 1 year +/- 2 months
- 2 years +/- 2 months
- 5 years +/- 3 months [funded and performed under a separate protocol]

At the conclusion of each QOL administration, patients will be reminded of the next date of contact. The SRG will notify the transplant center if a patient's contact information has changed or if they find through follow-up that the patient has died.

4.3.3. Locating Missing Patients

If patients cannot be located through the contact information provided, or through the transplant center, then the SRG will request the NMDP Call Back Unit to conduct a paid search for new contact information using Accurint, a government website accessible to only those with permission. Patients give their permission for the SRG to conduct this paid search when they sign the informed consent.

4.3.4. Adverse Event Reporting

Only adverse events related to the study consent process, collection of the optional research blood 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. Research Samples Pre-transplant and Post-transplant

If additional funding is obtained, peripheral blood samples (30 mL blood) will be collected from patients on the QOL Substudy pre-transplant and up to 6 times within the next 2 years after transplant. The study protocol will be modified prior to sample collection to specify the time points and additional information but participants will not have to be reconsented.

approximately half are expected to make it to transplant, and most patients who do not make it to transplant are not expected to survive past 2 years. Calculations use a log-rank test with a two-sided significance level of 5% for the primary comparison of the Very Likely vs. Very Unlikely to find a MUD groups. We account for approximately 5% exponential rate of loss to follow-up per year, and we assume 3 years of accrual, total study time of 4.5 years (or 18 months after last evaluable patient enrolled when the primary analysis is conducted), and we censor all patients at 2 years since few events are expected to occur after 2 years. We assume that the sample size ratio between MUD Very Likely and MUD Very Unlikely donor search prognosis is 2.5 to 1, based on preliminary data. The targeted total sample size of n=1022 (n=730 MUD Very Likely; n=292 MUD Very Unlikely donor search prognosis) patients would provide >85% power to detect a Hazard Ratio (HR) of 0.76, corresponding approximately to a 10% improvement in overall survival at two years for either group. Although preliminary data suggest a <5% survival difference between matched URD and haploidentical transplants (Steve Devine, personal communication), we assume that patients having haploidentical donor transplant are able to proceed to transplant earlier and thus have higher transplantation rates and better overall survival in an intention-to-treat analysis. We are using a two-sided test of the primary endpoint because we do not want to miss the possibility that matched URD recipients have better survival.

The targeted sample size for the Very Likely to find a MUD and Very Unlikely to find a MUD patients is based on the ratio of patients who are Very Likely to find a MUD to patients who are Very Unlikely to find a MUD . This number will be monitored throughout the study and the sample size may be increased or decreased depending on the ratio of Very Likely to Very Unlikely to find a MUD patients; potential increases in sample size are shown in the table below.

	Sample size ratio (MUD Very Likely DSP vs. MUD Very Unlikely DSP)								
	2.5 to 1			1.5 to 1			1 to 1		
2 yr OS (Very Likely DSP)	80% power	85% power	90% power	80% power	85% power	90% power	80% power	85% power	90% power
30%	889	**1022**	1190	745	850	995	702	802	938
40%	1001	1148	1344	835	955	1115	786	898	1052

DSP = donor search prognosis

While the targeted sample size for the power calculation is based on the primary comparison between patients who are Very Likely and patients who are Very Unlikely to find a MUD, we will also concurrently enroll patients who are Less Likely to find a MUD for analysis of secondary research questions (expected to be approximately 40% of all eligible patients, or n=710).

5.3. Interim Analysis and Stopping Guidelines

No interim analysis or stopping guidelines for efficacy or futility are planned for this study. We will review the study design assumptions, particularly the ratio of patients who are Very Likely to find a MUD vs. patients who are Very Unlikely to find a MUD and percentage proceeding to transplant, on a periodic basis, and may adjust the sample size if needed to maintain power in the event that our assumptions are incorrect. In order to ensure safety of patients who are Very

estimated using the inverse probability of censoring-weighted generalized estimating equations with independent working correlation model of Kurland and Heagerty.[83] Imputation methods may also be used.

Hospital Days

Total hospital days in the first 100 days post-transplant will be described. To account for patient death in the first 100 days, two analyses will be conducted; either normalizing the hospital days out of the number of days alive, or using the number of days alive and out of the hospital in the first 100 days. Nonparametric Mann-Whitney tests will be used to compare the median values between groups in both cases.

Infection

The number of infections and the number of patients experiencing infections will be tabulated for the two groups by type of infection and time period after transplant.

Immune Reconstitution

The distribution of the following laboratory markers will be described in the two groups: absolute neutrophil count, absolute lymphocyte count, IgG level, and absolute numbers of T-cell subsets and B cells. Research blood samples will be banked for future studies, not conducted as part of this protocol.

Late Effects

The number and types of late effects will be tabulated for each group at 1 and 2 years after transplant

6.3. APPENDIX C. LIKELIHOOD OF A MATCHED UNRELATED DONOR TRANSPLANT BY DONOR SEARCH PROGNOSIS

REANALYSIS OF THE WADSWORTH ET AL PAPER

African American, Hispanic, Asian-Pacific Islander

								Transplants							
										Donor					
Category	Total	Formal		Work-ups		Transplants		Cord		10/10		9/10		8/10 or less	
Very Likely	86	64	74%	42	49%	34	40%	2	2%	32	37%	0	0%	0	0%
Less Likely	318	211	66%	85	27%	88	28%	28	9%	22	7%	30	9%	8	3%
Very Unlikely	104	63	61%	16	15%	22	21%	14	13%	0	0%	6	6%	2	2%
Total	508	338	67%	138	27%	144	28%	44	9%	54	11%	36	7%	10	2%

Caucasian

								Transplants							
										Donor					
Category	Total	Formal		Work-ups		Transplants		Cord		10/10		9/10		8/10	
Very Likely	313	244	78%	170	54%	154	49%	7	2%	141	45%	6	2%	0	0%
Less Likely	130	88	68%	48	37%	54	42%	10	8%	26	20%	18	14%	0	0%
Very Unlikely	88	57	65%	14	16%	22	25%	13	15%	2	2%	7	8%	0	0%
Total	531	389	73%	231	44%	230	43%	30	6%	169	32%	31	6%	0	0%