BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D)

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BMT CTN PROTOCOL 1702
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PROTOCOL SYNOPSIS - BMT CTN PROTOCOL 1702

Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D)

Study Chairpersons: Stefan Ciurea, M.D. and Stephanie Lee, M.D., M.P.H.

Study Design: This is a multicenter, interventional and observational study to understand factors affecting the likelihood of transplantation in patients without a human leukocyte antigen (HLA) matched family donor and to compare outcomes associated with pursuing an HLA-identical unrelated versus other alternative donor graft sources. Alternative donors are defined as any donor other than an HLA-matched or 1 antigen-mismatched related donor. Patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), acquired aplastic anemia (AA) or sickle cell disease (SCD) are eligible. The primary comparison for the interventional study will be between two arms based on biologic assignment, analyzed on an intention-to-treat basis: **Arm 1**: Patients who are Very Likely to find a matched unrelated donor (MUD), defined as having a >90% chance of finding an 8/8 HLA-matched unrelated donor, for whom a fully matched unrelated donor will be pursued; and **Arm 2**: Patients who are Very Unlikely to find a MUD, defined as having a <10% chance of finding an 8/8 HLA-matched unrelated donor, for whom a haploidentical, cord blood, or mismatched unrelated donor transplant will be pursued. Patients with a Less Likely chance of finding a MUD, i.e., those not falling into the other two groups (a 26% chance), will be enrolled onto the observational component of the study and analyzed for all relevant endpoints but will not be included in the primary comparison.

Primary Objective: The primary objective is to estimate and compare overall survival between the two arms: patients who are Very Likely to find a MUD versus those who are Very Unlikely to find a MUD.

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 alternative donor search strategies

Post-transplant Objectives:

3. To compare survival, relapse, disease-free survival, treatment-related mortality, and acute and chronic graft-versus-host-disease (GVHD) in patients transplanted for malignant diseases, according to 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 alternative donor used

5. In patients with AML or ALL in first complete remission and early stage MDS (refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, 5q- syndrome or ≤5% bone marrow blasts) who are treated with a limited subset of conditioning and GVHD prophylaxis regimens and transplanted with either matched unrelated donors or haploidentical related donors (approximately 286 patients meeting eligibility criteria), to compare quality of life (QOL) and describe the incidence of primary graft failure, chronic GVHD, time until off systemic immunosuppression, acute grade III-IV and chronic GVHD requiring immunosuppression-free, relapse-free survival (GRFS), moderate-severe chronic GVHD relapse-free survival (CRFS), current CRFS, number of hospital days, infections, immune reconstitution and late effects after transplantation, according to the alternative donor used (**QOL Substudy**). All clinical data will be captured on Center for International Blood and Marrow Transplant Research (CIBMTR) comprehensive report forms (CRFs) while QOL data will be collected centrally.

Accrual Objective: The study will enroll 1022 patients in the MUD Very Likely plus MUD Very Unlikely search prognosis groups and approximately 710 patients in the Less Likely to find a MUD group.

Accrual Period: The estimated accrual period is 3 years.

Study Duration: Total study duration from first enrollment through last follow-up will be approximately 5 years. Adults included in the QOL substudy will be asked to consent to a final QOL assessment done at 5 years after transplantation. This 5 year QOL assessment will be separately funded and conducted through CIBMTR, referencing Protocol 1702 as the source of consent.

Eligibility Criteria: Patients of all ages with AML, ALL, MDS, NHL, HL, AA or SCD are eligible. Patients must be considered suitable allogeneic hematopoietic cell transplantation (HCT) candidates based on available medical history, physical examination, and laboratory tests. Specific testing for organ function is not required for eligibility but, if available, these tests should be used to judge transplant suitability. Centers must confirm their intention both to follow the recommended search algorithm and to perform the transplant within the next 6 months if a suitable donor is identified. Patients who consent are considered evaluable once the center determines no suitable HLA-matched or 1 antigen mismatched related donor is available (center will also confirm that the patient is still considered a transplant candidate). Patients may be enrolled on other studies.

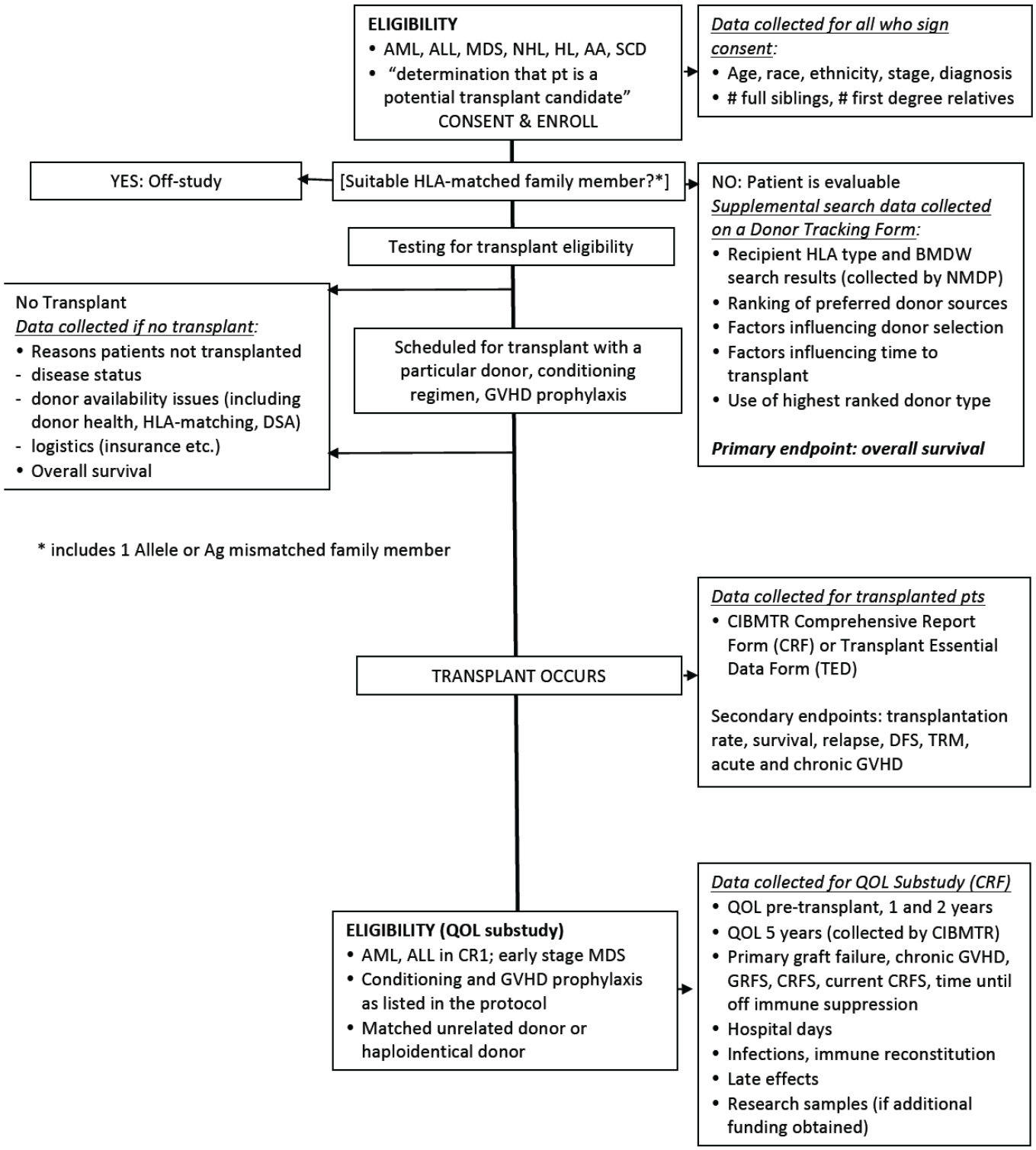
Interim Analysis: No interim analysis or stopping guidelines for efficacy or futility are planned for this study. We will review the study design assumptions, particularly the ratio of patients who are Very Likely to find a MUD vs. patients who are Very Unlikely to find a MUD and percentage proceeding 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.

Stopping Guidelines: Monitoring of a key safety endpoint of post-transplant mortality will be conducted monthly to ensure that the donor selection recommendations for the Very Unlikely to find a MUD group are not leading to significantly lower than expected post transplant outcomes. If rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are

described in the BMT CTN's Manual of Procedures. The stopping guideline serves as trigger for consultation with the DSMB for additional review.

Correlative Studies: QOL Substudy involving patients with AML or ALL in first complete remission and early stage MDS who are treated with a limited subset of conditioning and GVHD prophylaxis regimens and transplanted with either matched unrelated donors or haploidentical related donors, to compare quality of life (QOL) and describe the incidence of primary graft failure, chronic GVHD, time until off systemic immunosuppression, acute grade III-IV and chronic GVHD requiring immunosuppression-free, relapse-free survival (GRFS), moderate-severe chronic GVHD relapse-free survival (CRFS), current CRFS, number of hospital days, infections, immune reconstitution and late effects after transplantation, according to the alternative donor used. If funding for research samples is received, immune reconstitution and other testing will be performed for the Substudy population.

STUDY SCHEMA



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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Barriers to Identifying Matched Unrelated Donors

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment and is standard of care for patients with high-risk or advanced hematologic malignancies and other hematologic diseases. The use of allogeneic HCT has expanded rapidly over the past decades owing to substantial advances in transplant procedures and supportive care.[1,2] However, providing a suitable donor for all potential HCT patients in an optimal period of time remains an unmet need. Even though a fully HLA-matched related donor (MRD) is considered the first graft choice for transplantation, approximately two-thirds of patients who need a transplant do not have a MRD available; most patients must rely on alternative donor choices.[3] Historically, an HLA-matched adult unrelated donor has been accepted as the next best option. The success of unrelated donor HCT was primarily influenced by the degree of HLA matching between the donor and the recipient. High resolution matching at 8 alleles at HLA-A, -B, -C, and -DRB1 (8/8 match) is considered standard for unrelated donor transplantation,[4,5] and transplant outcomes after unrelated donor grafts approximate those of matched related donor grafts.[6-9] Hence, most transplant centers usually proceed with an unrelated donor search for all patients in need of a transplant if no matched related donor is available. However, identification of an unrelated donor may be challenging due to low donor availability for non-Caucasian populations or mixed race individuals.[10] In addition, the unrelated donor search and procurement of stem cell product usually takes longer (on average 3-4 months) than that of a matched related donor (approximately 1 month). As a result, patients may develop progressive disease[11] or become medically unfit while waiting for an unrelated donor transplant, which might have a negative impact on overall survival. With recent improvements in haploidentical donor transplant outcomes using post-transplant cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis, an increasing number of patients without an HLA-matched donor are receiving grafts from HLA-mismatched relatives. Some data suggest outcomes of haploidentical sibling donor HCTs are similar to those of HLA-identical HCTs, though numbers of evaluable patients remain small and follow-up relatively short.[12,13] Centers also continue to use cord blood and mismatched unrelated donors. It is currently unclear which is the best alternative donor source and if it is better to proceed with an alternative donor as soon as possible or wait and complete an unrelated donor search, even if it takes a longer period of time to perform transplantation.

Work by Dehn and colleagues has defined a “donor search prognosis” based on HLA allele frequencies and race/ethnicity. This score predicts the likelihood of successfully identifying a 10/10 matched unrelated donor.[14] Patients who are Very Likely to find a MUD have a >90% likelihood of finding a matched unrelated donor, while those who are Very Unlikely to find a MUD have a <10% chance. Patients who are Less Likely to find a MUD have a 26% chance of finding a matched unrelated donor. Worse search prognosis is associated with racial and ethnic minority status but not with other patient and disease biology characteristics that might influence the success of HCT. Thus, the use of donor search prognosis in this trial as a tool for biologic assignment to

matched unrelated donors vs. mismatched donors provides a mechanism to minimize bias from disease characteristics.

A recent survey (July 2018) of donor choice practices by different BMT CTN core and affiliate transplant centers revealed that the majority of centers (78%) will initially start a formal unrelated donor search in the absence of a matched related donor, while only 16% may proceed to a haploidentical donor transplant without a formal unrelated donor search. If a patient lacks a matched related or unrelated donor, 69% of the centers would likely choose a haploidentical donor, 16% a mismatched unrelated donor and 15% a cord blood donor. Eighty nine percent said they would be comfortable proceeding to transplant with a haploidentical related donor or cord blood without a formal unrelated donor search if a predictive algorithm could identify patients with a <10% chance of finding a matched unrelated donor.

1.2. Alternative Donor Graft Sources Provide Outcomes Comparable to Matched Unrelated Donors

While most centers would choose a readily available matched unrelated donor over other alternative donors for a patient lacking an HLA-identical sibling donor, in reality the reported outcomes for all alternative donor transplants appear similar (Section 6.4. Appendix D). Survival for transplanted patients is anticipated to be superior to outcomes without transplantation.

Mismatched Unrelated Donor Transplantation

Despite the availability of more than 32 million worldwide potential donors for HCT accessible through the National Marrow Donor Program registry, the probability of finding a suitable HLA-matched donor for HCT varies considerably, from 75% in Caucasians to 16-35% among other races.[10] One of the alternative options in such cases is the use of an HLA- mismatched unrelated donor; however, previous studies found an increased risk of graft-versus-host disease (GVHD) and treatment-related mortality with reduced overall survival and progression-free survival compared to HLA-matched donor transplantation.[4,8,15]

The standard pharmacological GVHD prophylaxis regimen for HLA-matched unrelated donor or -matched related donor transplantation includes a calcineurin inhibitor (commonly tacrolimus or cyclosporine) and methotrexate.[8,16] This is often intensified with *in vivo* T-cell depletion, generally with antithymocyte globulin (ATG) or alemtuzumab in mismatched unrelated donor HCT.[17,18] With this intensive regimen, the incidence of grade II–IV acute GVHD (20–35%), grade III–IV aGVHD (4–20%) and cGVHD (22–67%) in mismatched unrelated donor HCT approaches comparable levels to those seen after matched unrelated donor HCT.[17,18] However, *in vivo* T-cell depletion delays T-cell immune reconstitution[19] and poses heightened risk of bacterial and viral infections, including herpes simplex virus, cytomegalovirus (CMV), Epstein–Barr virus, and infection-related deaths,[20] as well as fatal post-transplant lymphoproliferative disorder (PTLD).[21] An alternative approach to prevention of GVHD in mismatched unrelated donor HCT is the use of post-transplant cyclophosphamide (PTCy), administered in a similar fashion as in haploidentical transplantation on days +3 and +4, along with tacrolimus and mycophenolate mofetil (MMF). A recent retrospective comparison for patients with mismatched unrelated donor HCT treated with either PTCy or conventional GVHD showed a lower incidence of grade II-IV aGVHD in the first

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

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

PTCy, tacrolimus and MMF. Engraftment with the two donor types was similar (95% and 98%). Cumulative incidences of grades II-IV aGVHD were 28% and 33%. Corresponding rates of grades III-IV acute GVHD were 3% and 13%, of cGVHD 13% and 14%, treatment-related mortality 21% and 31%, and relapse 19% and 25%. One year rates of survival and progression-free survival were 70% and 60% and 60% and 47%, respectively (Table 1).[51]

Table 1. Outcomes of two sets of parallel Phase II trials performed by MD Anderson Cancer Center and BMT CTN. The first set included a trial of haploidentical donor transplants and a trial of 9/10 unrelated donor transplants; the second set included a trial of haploidentical transplants and a trial of cord blood transplants.

	MD Anderson		**BMT CTN**	
	HAPLO with Flu/Mel/TBI (N=60)	**9/10 URD with Flu/Mel/TBI (N=46)**	**HAPLO with Flu/Cy/TBI (N=50)**	**CBT with Flu/Cy/TBI (N=50)**
Engraftment	95%	98%	96%	94%
aGVHD gr II-IV	28%	33%	32%	40%
aGVHD gr III-IV	3%	13%	0%	21%
cGVHD	13%	14%	13%	25%
TRM (1yr)	21%	31%	7%	24%
RR (1yr)	19%	25%	45%	31%
OS (1yr)	70%	60%	62%	54%
DFS (1yr)	60%	47%	48%	46%

Legend: HAPLO – haploidentical, URD – matched unrelated donor, CBT – cord blood transplant, N – number, Flu – fludarabine, Mel – melphalan, TBI – total body irradiation (2Gy), Cy – cyclophosphamide, aGVHD – acute graft versus host disease, cGVHD – chronic graft versus host disease, TRM – treatment-related mortality, RR – relapse rate, OS – overall survival, DFS – disease-free survival.

Comparative Outcomes Between Haploidentical and Matched Unrelated Donor Transplants

Multiple retrospective studies have shown similar outcomes between different alternative donor sources including haploidentical transplants and 8/8 HLA matched unrelated donor transplants.

A summary of the results from the first 7 single institution studies[52-57] comparing these two donor sources showed a median incidence of grade II-IV aGVHD of 27% (range 14%-43%) vs. 37% (range 22-63%) and cGVHD 24% (range 13%-38%) vs. 36% (22%-63%), respectively. In these studies, treatment-related mortality rates ranged from 9% at 2 years to 18% at 1 year for haploidentical donors vs. 8% to 34% at 2 years for unrelated donors, relapse rate ranged from 18% at 1 year to 40% at 2 years for haploidentical donors and from 16% at 1 year to 52% at 2 years for unrelated donors, while progression-free survival ranged from 41% at 3 years to 60% at 4 years for haploidentical and from 29% at 2 years to 52% at 2 years for unrelated donors, indicating considerable overlap but also showing wide confidence intervals as a result of the relatively small number of haploidentical transplant recipients in these studies.

In addition, several larger registry studies compared outcomes between these two donor sources (Table 2). Two of these studies were performed by CIBMTR, one in patients with AML[12] and one in patients with lymphoma.[13] These studies also showed similar results between the two groups. In the first study more than 2,000 patients were analyzed (though only 192 had a haploidentical donor) and the 3-year progression-free survival was similar for haploidentical and unrelated donor transplant patients treated with myeloablative (41% vs. 42%) and reduced intensity/non-myeloablative conditioning (35% vs. 37%), while lower incidences of acute and chronic GVHD were observed in the haploidentical transplant groups.[12] In the second study of 917 lymphoma patients, 185 had a haploidentical donor (all treated with Flu/Cy/TBI regimen), and similar results were observed: the 3-year progression-free survival for haploidentical transplants was 47% vs. 49% for unrelated donor transplants performed without ATG and 38% for unrelated donor transplants with ATG (p=0.02), while the haploidentical transplants again had significantly lower incidence of severe aGVHD (8% vs. 12% vs. 17%, p<0.01) and cGVHD (13% vs. 51% vs. 33%, p<0.001).[13] In all of these studies, the confidence intervals for the outcomes estimates were wide and differences as large as 10-15%, while clinically meaningful, could have been missed. There is need to assess these comparisons in much larger cohorts to have adequate statistical power.

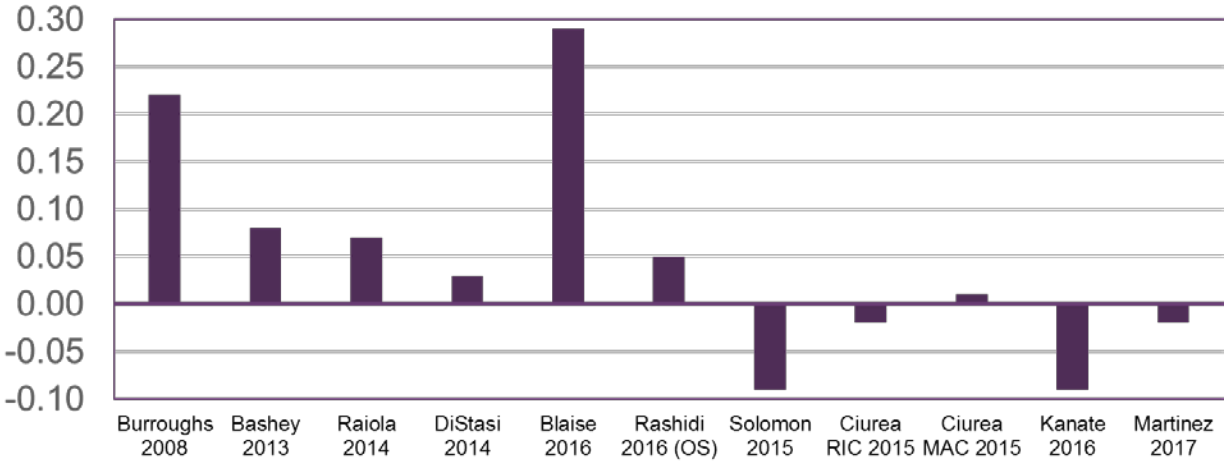
Table 2. Registry studies comparing haploidentical vs. 8/8 matched unrelated donor transplant outcomes.

Diseases	N	Gr 2-4 aGVHD	cGVHD	TRM	RR	DFS	95% CI	Reference
AML MAC RIC	HAPLO N=192 URD N=1,982	16% v 33% 19% v 28%	30% v 53% 34% v 52%	14% v 20% 9% v 23%	44% v 39% 58% v 42%	45% v 50% 46% v 44% @3 years	N/A N/A	Ciurea SO. Blood. 2016[12]
Lymph-oma	HAPLO N=185 URD w/ATG N=241 URD w/o ATG N=491	27% 40% 49%	13% 33% 51%	11% 13% 20%	36% 36% 28%	47% 38% 49% @3 years	40-55 31-45 44-54	Kanate AS. Blood. 2016[13]
Hodg-kin's lymph-oma	HAPLO N=98 URD N=273	33% v 30%	26% v 41%	17% v 21%	39% v 32%	43% v 45% @ 2 years	33-54 39-51	Martinez. JCO. 2017[58]

Legend: AML – acute myeloid leukemia, MAC – myeloablative conditioning, RIC – reduced intensity conditioning, HAPLO – haploidentical donor, MUD – matched unrelated donor, N – number, Gr – grade, aGVHD – acute graft-versus-host disease, cGVHD – chronic acute graft-versus-host disease, TRM – treatment-related mortality, RR – relapse rate, DFS – disease-free survival, OS – overall survival.

Thus, most available data support comparability of outcomes between matched unrelated donors and haploidentical donors once patients make it to transplant. The figure below shows the absolute

difference in disease-free survival probability according to donor type. Negative numbers favor matched unrelated donors over haploidentical donors; none of the differences were statistically significant.



To date, only limited data on differences in immunologic reconstitution between different alternative donor sources exists. The MD Anderson group compared immunologic reconstitution between haploidentical transplants performed with PTCy and HLA matched related and unrelated donor transplants performed with conventional GVHD prophylaxis for patients with AML/MDS. They reported similar recovery of CD3+ cells, CD3+CD4+, CD3+CD8+, CD3-CD56+ (NK cells) and CD19+ (B-cells) between these 3 groups starting at 3 months post-transplant. However, at day +30 matched related donor transplants had significantly higher CD3+ cells, CD3+CD4+, CD3+CD8+ T-cells compared with the other two donor sources.[59] Although in depth evaluation of immune reconstitution is beyond the scope of this trial, the study will examine rates of clinically significant infections and may provide an opportunity for sample collection for further, separately funded assessment of immune markers, depending on identification of additional resources beyond BMT CTN.

1.3. Quality of Life and Late Effects

Quality of life (QOL) refers to every dimension of life except for its length and includes physical abilities, symptoms, social well-being, psycho-emotional status, and spiritual/existential qualities. It reflects how well people feel, what they can accomplish, how satisfied they are with their lives, and whether their lives have meaning and purpose. HCT survivors generally report high global QOL following HCT, but many specific symptoms[60-65] and limitations on their daily activities.[66]

The purpose of the QOL component of this trial is to explore the long-term QOL implications of using an 8/8 HLA-matched unrelated donor vs. a haploidentical donor. While the trial is powered with survival as the primary endpoint, QOL will be an especially important secondary endpoint if survival is not statistically different. It is also possible that immunologic recovery, peri-transplant experiences and complications, speed of physical recovery, and expectations may influence

ultimate QOL. Since patients are already consented to BMT CTN 1702, the incremental effort of collecting QOL data on a subset of informative patients is worth the potential information gained.

It is very important that data collection is centralized, patients' response burden is minimized and QOL assessments are fully integrated into the trial to maximize the chance of complete data collection. With this goal in mind, the number of survey items will be minimized and focused on answering the research questions.

Late effects occurring more than 1 year after HCT may be related to the disease, treatment before transplant, or the transplant itself. The most common late effects are chronic GVHD and complications related to its treatment, bone density loss, hypothyroidism, diabetes, cardiovascular complications and subsequent neoplasms.[67] These late effects will be captured via the CIBMTR CRFs. No additional data collection forms are required.

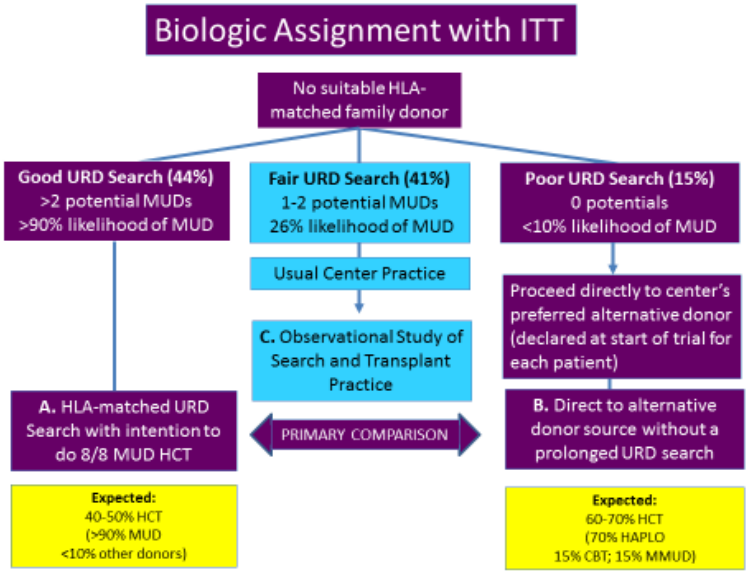
1.4. Key Research Questions

Donor availability for patients who do not have an HLA-identical related donor remains a major factor in determining the success of transplantation. Overall, this study aims to assess donor availability and outcomes of patients receiving alternative donor transplants. More specifically, the primary objectives of this study are: 1) To understand how donor search prognosis affects the likelihood and timing of undergoing transplantation; and 2) To understand survival differences between MUD Very Likely and MUD Very Unlikely prognosis search groups, where MUD Very Likely search prognosis patients are anticipated to undergo matched unrelated donor HCT after some delay to identify a donor and MUD Very Unlikely search prognosis patients will instead pursue a mismatched donor source with less delay.

1.5. Study Design Rationale

Current transplant statistics show that haploidentical donor transplant numbers are increasing in the US and internationally, while unrelated donor and cord blood numbers are stable or declining. Physicians and patients wish to know which alternative donor source is preferable in which clinical situations. Because disease progression is a major reason that transplants are not performed, both the speed of getting to transplant and the outcome of transplantation are important determinants of which donor source is preferable.[11]

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.

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

are not included in the protocol now because of the complicated donor consent issues. If additional funding is obtained to support donor research sampling, this protocol will be modified.

1.6. Potential Concerns About the Study Design

1.6.1. Concerns About Minority Imbalance

Will a higher proportion of racial/ethnic minorities in the Very Unlikely to find a MUD group be problematic in interpretation of study results or an ethical concern for the study?

Racial and ethnic minorities comprise a greater proportion of the group that is Very Unlikely to find a MUD (37% of 292, n=108) than the Very Likely to find a MUD group (13% of 730, n=95) but because of the different sizes of the groups, the absolute number of racial/ethnic minorities is comparable in the Very Likely and Very Unlikely groups. All analyses will adjust for racial/ethnic minority status to try to address other, non-HLA factors that might be confounders.

Racial/ethnic minorities in the Very Unlikely to find a MUD group have the lowest chance of finding a matched unrelated donor, so prompt use of another alternative donor is expected to benefit them most by allowing them to proceed to transplant. Further analysis of the Wadsworth et al study showed none of the 104 minority patients in the Very Unlikely to find a MUD group had a matched unrelated donor transplant, and in fact, only 21% were transplanted using a mismatched unrelated donor or cord blood (haploidentical transplants could not be tracked). Racial and ethnic minorities in the Very Likely to find a MUD group achieved a 40% transplant rate, closer to the 49% transplant rate achieved in the Caucasians in the Very Likely to find a MUD group, suggesting that failure to promptly identify a donor is contributing to the barrier to transplantation experienced by the Very Unlikely to find a MUD group. Thus, while racial/ethnic minorities comprise a higher proportion of the Very Unlikely to find a MUD group, they are still less than 40% of that group. Use of the donor search prognosis score and rapid use of an alternative donor is anticipated to benefit everyone in the Very Unlikely to find a MUD group.

1.6.2. Concerns About the Comparator Group

The study tests the hypothesis that rapid access to a transplant improves survival compared to delayed progress to transplant after a more extensive donor search to try to identify a matched unrelated donor. What is the comparator group to measure this outcome? Is the primary outcome appropriate given the inherent ethnic/racial imbalance?

Appendix C shows the outcomes of transplantation from matched unrelated donors vs. other alternative donors. Multiple other studies (Section 1.2) suggest that once patients undergo transplantation, outcomes are fairly similar between the different graft sources. However, the greatest barrier to getting to transplant in the Very Unlikely to find a MUD group is identifying a donor. Under current practice, half as many patients in the Very Unlikely to find a MUD group get to transplant with a mismatched unrelated donor or cord blood, whether racial/ethnic minorities or Caucasians, and almost no one has a matched unrelated donor transplant. We do not know what happens to those patients who do not undergo transplantation but presumably

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.

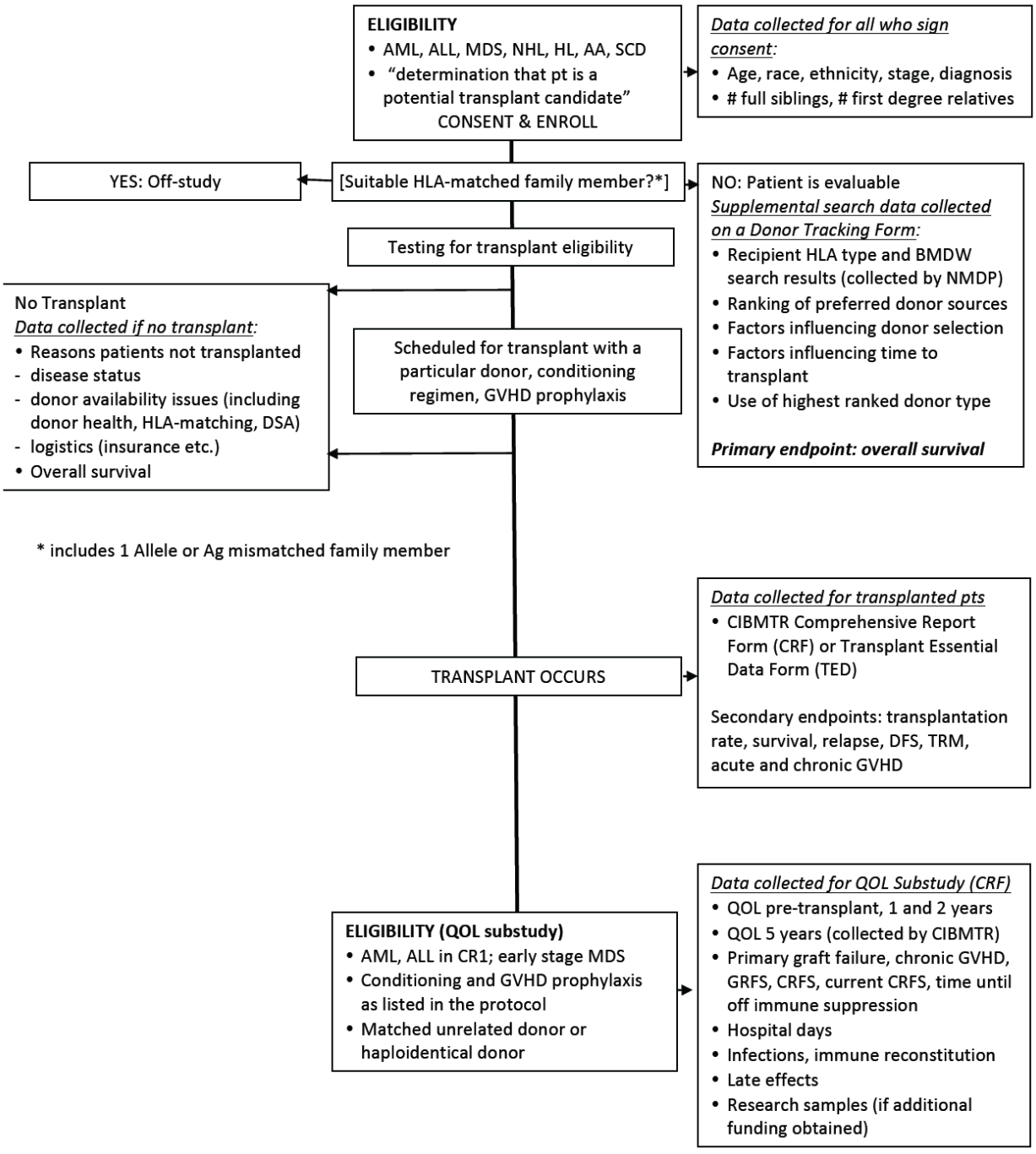
To test these hypotheses we need to enroll patients before a formal alternative donor search is launched. Patients may be enrolled as early as when initial HLA-typing is sent or at the time of initial evaluation for transplantation, preferably but not necessarily before results of the recipient HLA typing 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.



2.2. 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.

2.3.1. 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

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.

Example of a VERY LIKELY to find a MUD Search Prognosis and Preliminary Search Summary report

RID XXX-XXX-X or Patient Name
Transplant Center Name

Patient HLA:

A	B	C	DRB1	DQB1	DPB1
02:01	13:02	06:02	07:01	03:01	04:01
03:01	07:02	07:02	04:01	02:02	02:01

Patient Ethnicity: White

***Patient Search Prognosis Category:** Very Likely
*Calculated from HLA data and race/ethnicity. Does not correspond to actual donors on the registry.

NMDP Preliminary Search Results as of: 01/03/2019
Patient Weight: 64 kg

Adult Unrelated Donors
NMDP Potential List:

Match Category	Number of donors
8/8 donors > 75% likelihood of allele match	598
8/8 donors 25-75% likelihood of allele match	40
7/8 donors > 75% likelihood of allele match	17000
7/8 donors 25-75% likelihood of allele match	787

WMDA Donor Search:

Match Category	Number of donors
Likely 8/8 matched donors	101
Likely 7/8 matched donors	4508

Summary:

- Many likely 8/8 matched donor options are available on this search.

Cord Blood Units-
NMDP Potential List:

Match Category	Number of units
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) single units (TNC 2.5 x 10^7/kg and CD34+ 1.5 x 10^5/kg)	450
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) double units (TNC 1.5 x 10^7/kg and CD34+ 1.0 x 10^5/kg)	662

Summary:

- There are many 4/6 or better matched single and double units available on this search

Example of a VERY UNLIKELY to find a MUD Search Prognosis and Preliminary Search Summary report

RID XXX-XXX-X or Patient Name
Transplant Center Name

Patient HLA:

A	B	C	DRB1	DQB1	DPB1
02:01	47:01	06:02	04:05	03:02	04:01
03:01	35:01	04:01	04:03	03:02	04:01

Patient Ethnicity: White

***Patient Search Prognosis Category:** Very Unlikely
*Calculated from HLA data and race/ethnicity. Does not correspond to actual donors on the registry.

NMDP Preliminary Search Results as of: 01/03/2019
Patient Weight: 108 kg

Adult Unrelated Donors
NMDP Potential List:

Match Category	Number of donors
8/8 donors > 75% likelihood of allele match	0
8/8 donors 25-75% likelihood of allele match	0
7/8 donors > 75% likelihood of allele match	53
7/8 donors 25-75% likelihood of allele match	12

WMDA Donor Search:

Match Category	Number of donors
Likely 8/8 matched donors	0
Likely 7/8 matched donors	40

Summary:

- No likely 8/8 matched donor options are available on this search.
- There are many likely 7/8 matched donors.

Cord Blood Units-
NMDP Potential List:

Match Category	Number of units
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) single units (TNC 2.5 x 10^7/kg and CD34+ 1.5 x 10^5/kg)	1
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) double units (TNC 1.5 x 10^7/kg and CD34+ 1.0 x 10^5/kg)	8

Summary:

- There are some 4/6 or better matched single and double units available on this search

Example of a LESS LIKELY to find a MUD Search Prognosis and Preliminary Search Summary report

RID XXX-XXX-X or Patient Name
Transplant Center Name

Patient HLA:

A	B	C	DRB1	DQB1	DPB1
24:02	27:05	01:02	01:01	03:01	03:01
26:01	39:06	07:02	04:01	05:01	04:02

Patient Ethnicity: White

***Patient Search Prognosis Category:** Less Likely
*Calculated from HLA data and race/ethnicity. Does not correspond to actual donors on the registry.

NMDP Preliminary Search Results as of: 01/03/2019
Patient Weight: 137 kg

Adult Unrelated Donors
NMDP Potential List:

Match Category	Number of donors
8/8 donors > 75% likelihood of allele match	3
8/8 donors 25-75% likelihood of allele match	2
7/8 donors > 75% likelihood of allele match	171
7/8 donors 25-75% likelihood of allele match	51

WMDA Donor Search:

Match Category	Number of donors
Likely 8/8 matched donors	3
Likely 7/8 matched donors	340

Summary:

- A few likely 8/8 matched donor options are available on this search.
- There are many likely 7/8 matched donor options available on this search.

Cord Blood Units-
NMDP Potential List:

Match Category	Number of units
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) single units (TNC 2.5 x 10^7/kg and CD34+ 1.5 x 10^5/kg)	0
4/6 or better matched (HLA-A, -B antigen, -DRB1 allele) double units (TNC 1.5 x 10^7/kg and CD34+ 1.0 x 10^5/kg)	2

Summary:

- There are 2 double units available on this search

2.5. Study Treatments

Patients will be transplanted according to institutional guidelines. They may participate in other clinical trials as long as the cumulative data collection will not compromise adherence to data submission for this protocol.

2.6. Quality of Life

The following instruments will be used to assess QOL within one month before transplant (Baseline), at 1 year, 2 years and 5 years for QOL Substudy participants defined above. Only English- or Spanish-speaking trial participants aged 8 years and older will be included in the QOL studies. Patients aged 8-17 at the time of assessment will complete pediatric instruments. Proxy reports (e.g., parents, guardians) of child QOL will not be collected.

At the Baseline time point, center or CIBMTR staff will administer QOL instruments electronically or on paper. At 1 year, 2 year and 5 year time points, the CIBMTR will administer the QOL surveys electronically or on paper upon request. The number of questions may vary based on method of delivery, but each time point will take approximately 14-27 minutes for adults and 11-19 minutes for pediatric patients. The survey times vary based on method of delivery because computerized adaptive testing will be used for participants who complete the survey online which may increase the number of survey items given to provide more precise scoring with questions that are more closely aligned to a subject's functioning.

2.6.1. PROMIS Global

The PROMIS Global measure contains 10 items for adults and 9 items for pediatric patients, with two summary scores for physical and mental functioning. The median score is 50 with a standard deviation of 10. Higher scores indicate better QOL.[68,69]

2.6.2. PROMIS Domains

Eight PROMIS domains for adults and seven for pediatric patients will be used to measure detailed functioning and symptom burden for patients. For the physical and social functioning scales, higher scores indicate better functioning; for fatigue, pain, anxiety, depression, and sleep scales, higher scores indicate a higher symptom burden.[70] Scores are normalized to 50 with a standard deviation of 10, and scores greater than 0.5 times standard deviation (i.e., <45 or >55, compared to the general population) are considered clinically meaningful.

The PROMIS domains for adults are: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. The PROMIS domains for pediatric patients are: physical function mobility, anxiety, depressive symptoms, fatigue, peer relationships, pain interference, and pain intensity.

When delivered on paper, the domains will be delivered combined in a Profile form. The PROMIS 29 Profile for adult patients contains 7 subscales with 4 questions each, and a single item for pain intensity (29 total items).

When delivered electronically, the domains will be delivered as Computer Adaptive Tests (CAT), in which the questions a person answers are tailored to that person. Each response is used to further refine the questions a participant receives, and thus the participant's score, for that domain. The PROMIS CAT item banks for a domain typically involve 4-12 items. The first item administered is usually in the middle of the range of function or severity for that domain. After a participant responds, an estimated score is calculated. The PROMIS CAT algorithm then selects the best item in the item bank for refining the estimated score, and recalculates the participant's score as they continue responding. The PROMIS CAT continues to administer items until a specified level of measurement precision is reached, or the maximum number of 12 items per measure have been administered. Studies have shown that the average number of items delivered in a CAT domain is 5-8.[71]

2.6.3. Lee Chronic GVHD Symptom Scale

The Lee chronic GVHD symptom scale (LSS) is a 30 item measure with 7 domains referent to the past 7 days: skin, mouth, eye, lung, psychoemotional, vitality and nutrition.[72] Responses are captured on a five-point Likert scale ("no symptoms, or not bothered at all", "slightly bothered," "moderately bothered," "bothered quite a bit," or "extremely bothered"). Scores for each domain are converted to a 0-100 scale where higher scores indicate more bother. The LSS has distinguished between people with different severities of chronic GVHD[68] and been used in randomized clinical trials to show difference in treatment arms.[73,74] Although patients will not have chronic GVHD before transplant, we will still administer the instrument at baseline to capture any pre-existing symptoms and aid in interpreting post-transplant scores. Participants aged 12 and older will complete the LSS.

2.6.4. Occupational Functioning

Occupational functioning was measured in the NHLBI T-cell depleted trial using 6 items that assess current job status, type of work (will be captured using Hollingshead categories), number of hours of paid and unpaid work, school, importance of work and change in work goals.[60,73] Only adults will complete the occupational functioning items.

2.6.5. Sociodemographic Data

Sociodemographic data are collected from adults in the QOL Substudy on the pre-transplant survey only: education, income, marital status, and religiosity. Zip code will be available from the TED/CRFs. Contact information including email address, cell phone numbers and alternate contacts will also be collected. Only adults will complete the sociodemographic questions.

Adult instruments (aged 18 and over at time of assessment)

Instrument	Description	Number of items		Estimated Time to complete
		Paper	Electronic	
PROMIS Global	Overall evaluation of one's physical and mental health	10	10	2-3 minutes
PROMIS Physical function domain	Self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.	4	4-12	1-2 minutes
PROMIS Anxiety domain	Fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness).	4	4-12	1-2 minutes
PROMIS Depression domain	Negative mood (sadness, guilt), views of self (self- criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).	4	4-12	1-2 minutes
PROMIS Fatigue domain	Range of symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.	4	4-12	1-2 minutes
PROMIS Sleep disturbance domain	Perceptions of sleep quality, sleep depth, and restoration associated with sleep.	4	4-12	1-2 minutes
PROMIS Ability to participate in social roles and activities domain	Perceived ability to perform one's usual social roles and activities.	4	4-12	1-2 minutes
PROMIS Pain interference domain	Consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities.	4	4-12	1-2 minutes

Instrument	Description	Number of items		Estimated Time to complete
		Paper	Electronic	
PROMIS pain intensity	How much a person hurts	1	1-3	< 1 minute
Lee Chronic GVHD Symptom Scale	How much symptoms of skin, mouth, eye, lung, psychoemotional, vitality and nutrition bother the patient	30	30	2-3 minutes
Occupational Functioning	Job status, type of work, amount of work	6	6	1-2 minutes
Sociodemographic	At Baseline only. Education, income, marital status, religiosity	5	5	1-2 minutes
TOTAL		**80**	**80-138**	**14-27 minutes**

Pediatric instruments (patients 8-17 at time of assessment)

Instrument	Description	Number of items		Estimated Time to complete
		Paper	Electronic	
PROMIS Global	Overall evaluation of one's physical and mental health	9	9	2-3 minutes
PROMIS Physical function mobility domain	Activities of physical mobility such as getting out of bed or a chair to activities such as running.	4	4-12	1-2 minutes
PROMIS Anxiety domain	Fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness).	4	4-12	1-2 minutes
PROMIS depressive symptoms domain	Negative mood (sadness, guilt), views of self (self- criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).	4	4-12	1-2 minutes
PROMIS Fatigue domain	Range of symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion.	4	4-12	1-2 minutes
PROMIS Peer relationships domain	Quality of relationships with friends and other acquaintances.	4	4-12	1-2 minutes
PROMIS Pain interference domain	Consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities.	4	4-12	1-2 minutes
PROMIS pain intensity domain	How much a person hurts	1	1	< 1 minute

Instrument	Description	Number of items		Estimated Time to complete
		Paper	Electronic	
Lee Chronic GVHD Symptom Scale (age 12+)	How much symptoms of skin, mouth, eye, lung, psychoemotional, vitality and nutrition bother the patient	30	30	2-3 minutes
TOTAL		**64**	**64-112**	**11-19 minutes**

2.7. Participant Risks

The majority of the physical risks are related to the transplant itself, a treatment which the transplant center has already deemed appropriate for the participant. Patients and their doctors make treatment decisions including donor source, timing of transplant, conditioning regimen intensity and GVHD prophylaxis. The risks of transplant will be determined by the transplant care plan.

The intervention being applied in this study is a biologic assignment variable, i.e., the use of the donor search prognosis to guide the donor search strategy, is not per se being tested. Rather, it is being used to classify participants into two groups, those Very Likely and those Very Unlikely to find a MUD, for comparison. A center is not allowed to enroll a patient in the trial until they attest that the protocol's donor search algorithm that uses the donor search prognosis is appropriate for the patient. The primary risk of participation in the study is the possibility that the donor search algorithm suggested by the donor search prognosis will be misleading for individual patients, i.e., a Very Likely to find a MUD patient may not find a matched unrelated donor, or conversely, a Very Unlikely to find a MUD patient may be able to identify a matched unrelated donor. Centers should use clinical judgment in these cases to deviate from the intended donor source based on the participant's best interest. For children, the risks of this protocol would be the same as for adults.

No sensitive psychosocial or medical data will be collected from medical records. The risks of the QOL Substudy are anticipated to be minimal. Completion of patient-reported outcomes is unlikely to cause distress, as these surveys have been administered to thousands of patients without complaint and they do not ask sensitive questions. Collection of research blood samples in the QOL Substudy is contingent on securing additional funding. If this aspect of the protocol is activated, additional risks to participants in the QOL Substudy include bruising and fainting. The small amount of blood taken is not expected to affect blood counts.

CHAPTER 3

3. ENDPOINTS

3.1. Primary Endpoint

The primary endpoint for this study is survival from the time the center declares that no suitable matched family member is available and the patient is considered evaluable. Survival is analyzed as time to event with survivors censored at last follow up or 2 years, whichever is earlier.

3.2. Secondary and Post-transplant Endpoints

3.2.1. Transplantation Rate

Receipt of a transplant is defined as starting conditioning, whether or not the stem cell graft is infused.

3.2.2. Barriers to Transplantation

Reasons for delay or cancellation of the transplant, as collected on the donor tracking form, will be summarized by search prognosis category and reported descriptively.

3.2.3. Relapse

Relapse criteria for the different malignant diseases will be according to the CIBMTR data dictionary.

3.2.4. Disease-free Survival

Disease-free survival is defined as the time from the date of graft infusion to the date of recurrent disease or death from any cause, whichever comes first in patients with malignant disease. Observation is censored at the date of last follow-up for patients known to be alive without malignancy.

3.2.5. Treatment-related Mortality

Treatment-related mortality is defined as death without prior relapse in patients with malignant disease. Relapse is considered a competing risk.

3.2.6. Acute GVHD

Grade II-IV and III-IV acute GVHD will be reported. Acute GVHD grade will be calculated from the center-reported organ scores using current CIBMTR approaches.

3.2.7. Chronic GVHD

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.

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

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. $\geq$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.

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.

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

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

Unlikely to find a MUD who are biologically assigned to prioritize an alternative donor for transplant to improve likelihood of transplant, we will monitor a key safety endpoint of overall mortality within 100 days post transplant in the Very Unlikely to find a MUD group. Details of this safety monitoring are below.

5.3.1. Guidelines for Safety Monitoring

Monitoring of a key safety endpoint of post transplant mortality will be conducted monthly to ensure that the donor selection recommendations for the Very Unlikely to find a MUD group are not leading to significantly lower than expected post transplant outcomes. If rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guideline serves as trigger for consultation with the DSMB for additional review.

The key safety endpoint for this study is mortality post transplant. The rate of mortality will be monitored up to 100 days post-transplant, and only Very Unlikely to find a MUD patients who are transplanted will be included in this monitoring rule, which is designed to minimize the likelihood risk that patients are exposed to a risk of early mortality that is higher than would be expected with match unrelated donor transplantation. Monitoring will be applied to two separate cohorts, defined by malignant vs. non-malignant disease. Monitoring will be performed monthly beginning when at least 3 patients are evaluable for the monitoring rule (died or been followed for at least 100 days post transplant), until enrollment is closed. At least three deaths must be observed, along with crossing of a stopping boundary as described below, in order to trigger referral to the DSMB for further review. The expected probability of 100 day mortality is <=15% for malignant disease and <=10% for nonmalignant disease, based on CIBMTR data for HLA-identical unrelated donor transplantation. Each month, the null hypothesis that the 100-day mortality rate is less than or equal to a specified probability (10% for nonmalignant disease, 15% for malignant disease) is tested. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for monitoring, as described in greater detail below and in Appendix E.

This sequential testing procedure conserves type I error at 5% across all of the monthly examinations separately for both malignant and nonmalignant disease cohorts. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study (e.g. in months or years, x axis) is plotted against the total number of endpoints (e.g., patients experiencing death, y axis). 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 100-day mortality. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment is closed.

This procedure assumes a censored exponential distribution for the time until death during the first 100 days, and censors follow-up time after 100 days. Only deaths that occur on or before the patient has been followed for 100 days are counted. Total time on study is computed as time from transplant to death, or to 100 days, whichever comes first, summed for all patients on study.

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 $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRTs:

- Malignant disease: A SPRT contrasting 15% versus 25% 100-day rate of mortality results in decision boundaries with a common slope of 0.067 and an upper intercept of 4.372, with nominal type I and II errors of 7% and 15%, respectively.
- Non-malignant disease: A SPRT contrasting 10% versus 30% 100-day rate of mortality results in decision boundaries with a common slope of 0.063 and an upper intercept of 1.938, with nominal type I and II errors of 8% and 15%, respectively.

The actual operating characteristics of the truncated tests, shown in Table 5.3a and 5.3b for the malignant and non-malignant cohorts respectively, were determined in a simulation study that assumed uniform accrual of 292 Very Unlikely to find a MUD individuals (approximately 260 malignant and 32 nonmalignant) over a three-year time period, and exponential time to failure after transplant. Deviations from these expected distributions of malignant vs. nonmalignant sample sizes may lead to small changes in the rejection probabilities and other operating characteristics.

TABLE 5.3a: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Day 100 MORTALITY (MALIGNANT COHORT)

True 100-Day Rate	15%	20%	25%
Probability Reject Null	0.053	0.523	0.963
Mean Month Stopped	37.9	27.5	13.7
Mean # Endpoints in 100 Days	37.6	36.3	21.9
Mean # Patients Enrolled	251.2	187.1	98.3

For example, the testing procedure for the malignant cohort rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day mortality rate is 15%, and 96% of the time when the rate is 25%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.04$. When the true 100-day mortality rate is 25%, on average, the DSMB will be consulted 14 months after opening, when 22 events have been observed in 98 patients.

TABLE 5.3b: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Day 100 MORTALITY (NON-MALIGNANT COHORT)

True 100-Day Rate	10%	20%	30%
Probability Reject Null	0.049	0.428	0.853
Mean Month Stopped	38.1	30.4	19.6
Mean # Endpoints in 100 Days	3.1	5.0	4.9
Mean # Patients Enrolled	31.1	25.5	17.3

For example, the testing procedure for the non-malignant cohort rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day mortality rate is 10%, and 85% of the time when the rate is 30%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.15$. When the true 100-day mortality rate is 30%, on average, the DSMB will be consulted 20 months after opening, when 5 events have been observed in 17 patients.

5.4. Analysis Populations

Primary Analysis Population: The primary analysis population will include all patients registered who meet study eligibility, do not have a suitable matched or 1 allele or antigen mismatched family donor, and who are Very Likely to find a MUD or are Very Unlikely to find a MUD. Outcomes will be analyzed according to the donor search prognosis, regardless of the alternative donor prioritized, as an Intention-to-Treat analysis. Outcomes will be measured from the time the patient is deemed evaluable by virtue of needing to pursue alternative donors.

Less Likely to find a MUD group: Patients who are registered and meet study eligibility but have a donor search prognosis of Less Likely to find a MUD will not be included in the primary analysis population, but rather will be analyzed separately in a descriptive analysis, both overall and according to the specified alternative donor preference. Outcomes will be measured from the time the patient is deemed evaluable.

Transplant population: Several secondary analyses will be done on the subset of patients in all three search prognosis groups who receive a transplant. Here patients will be analyzed according to both their initial search prognosis score and by the type of alternative donor transplant received, and outcomes will be measured from the time of transplant. Outcomes will be measured from the start of transplant.

QOL Substudy population: A substudy will be conducted on a homogeneous group of AML and ALL patients who are transplanted in first complete remission and early stage MDS patients, in order to collect more detailed post-transplant outcome data. Based on the eligibility for the QOL Substudy and transplant activity in 2016, we anticipate having 286 patients across the 3 search prognostic groups. This estimate is based on an enrollment of 1732 evaluable patients, 50% of whom are transplanted and 33% of those meet the eligibility criteria for the Substudy. Patients will be analyzed according to the type of alternative donor transplant received (matched unrelated donor vs. haploidentical), and outcomes will be measured from the time of transplant. These

analyses will be exploratory in nature, and hypothesis-generating for future studies. Although these are primarily exploratory analyses, we calculated the detectable mean difference with 85% power in the physical subscale of the PROMIS global health measure to be 5.1. This assumes that 90% of the 286 patients would have baseline QOL, 60% would be alive at 2 years, and 70% of those would have complete 2 year QOL data, for an evaluable sample size of n=108. It is based on a two-sample t-test with two-sided significance level of 5%, standard deviation of 8, and a sample size ratio of 2.5 to 1.

5.5. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for each of the analysis populations. Characteristics to be examined for the primary analysis population and Less Likely to find a MUD group are: age, race/ethnicity, socioeconomic status as determined by zip code, disease (including known high risk cytogenetics or molecular markers), disease stage and duration, performance score, number of siblings, preferred alternative donor, and transplant center. Characteristics to be examined for the transplant population also include disease risk index, donor type, graft source (peripheral blood vs. bone marrow vs. cord blood), donor age and gender, CMV matching, co-morbidity index, time to transplant, preferred alternative donor identified, preferred alternative donor available, transplant center. Characteristics of interest for the QOL Substudy include: all of the variables listed above plus baseline QOL, and self-reported socioeconomic status.

5.6. General Analysis Considerations

As this is a biologic assignment study where there may be potential biases in donor search prognosis groups or alternative donor transplant groups being compared, all analysis will include summary univariate measures as well as multivariate analyses whenever feasible with sufficient numbers to adjust for confounding. Proportional hazards assumption will be assessed for all Cox models using graphical methods or time-dependent covariates. Interactions between patient characteristics and donor search prognosis group or alternative donor transplant group will also be investigated but will be considered exploratory.

5.6.1. Analysis of the Primary Endpoints

The primary endpoint of the trial is overall survival from the time of evaluability determination in the primary analysis population, analyzed according to the donor search prognosis group (Very Likely vs. Very Unlikely to find a MUD), in an intent-to-treat fashion. The primary null hypothesis of the study is that there is no difference in overall survival between the Very Likely and Very Unlikely to find a MUD groups. Because of the potential bias resulting from this biologic assignment mechanism (using donor search prognosis as a surrogate for prioritization of alternative donor types),[76] the comparisons of overall survival between groups will be done using a Cox proportional hazards model adjusted for the following pre-specified patient characteristics: age, sex, race, ethnicity, disease, and disease stage, if applicable. A Cox model stratified on alternative donor type will be used to provide adjusted overall survival probabilities at two years for each alternative donor type, using the method of Zhang et al.[77] It is not possible to adjust this

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

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. APPENDICES

6.1. APPENDIX A. LIST OF ABBREVIATIONS

AA – Acquired Aplastic Anemia
aGVHD – Acute Graft versus Host Disease
ALL – Acute Lymphoblastic Leukemia
AML – Acute Myeloid Leukemia
ATG – Antithymocyte Globulin
BMT CTN – Blood and Marrow Transplant Clinical Trials Network
CAT – Computer Adaptive Tests
cGVHD – Chronic Graft versus Host Disease
CIBMTR – Center for International Blood and Marrow Transplant Research
CMV – Cytomegalovirus
CRF – Comprehensive Report Form
CRFS – Moderate-Severe Chronic GVHD Relapse-free Survival
CRID – CIMBTR Research Identification
Cy – Cyclophosphamide
DCC – Data and Coordinating Center
DSA – Donor-Specific Antibodies
DSP – Donor Search Prognosis
ePRO – Electronic Patient Reported Outcomes
Flu – Fludarabine
GRFS – Acute Grade III-IV and Chronic GVHD Requiring Immunosuppression-free, Relapse-free Survival
GVHD – Graft versus Host Disease
HCT – Hematopoietic Cell Transplantation
HL – Hodgkin Lymphoma
HLA – Human Leucocyte Antigen
HPC – Hematopoietic Progenitor Cell
HR – Hazard Ratio
ICU – Intensive Care Unit
IRB – Institutional Review Board
LSS – Lee Chronic GVHD Symptom Scale
MDS – Myelodysplastic Syndromes
MMF – Mycophenolate Mofetil
MRD – Matched Related Donor
NHL – Non-Hodgkin Lymphoma
NHLBI – National Heart, Lung, and Blood Institute
NK – Natural Killer
NMDP – National Marrow Donor Program
PROMIS – Patient-Reported Outcomes Measurement Information System
PTCy – Post Transplant Cyclophosphamide
PTLD – Post-Transplant Lymphoproliferative Disorder
PUVA – Psoralen and Ultraviolet A
QOL – Quality of Life
SCD – Sickle Cell Disease
SCTOD – US Stem Cell Therapeutic Outcomes Database
SRG – CIBMTR Survey Research Group
TBI – Total body irradiation
TED – Transplant Essential Data
UCBT – Umbilical Cord Blood Transplant

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.

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%

Unknown

								Transplants							
										Donor					
Category	Total	Formal		Work-ups		Transplants		Cord		10/10		9/10		8/10	
Very Likely	47	27	57%	18	38%	15	32%	2	4%	13	28%	0	0%	0	0%
Less Likely	54	38	70%	21	39%	22	41%	7	13%	4	7%	9	17%	2	4%
Very Unlikely	79	51	65%	18	23%	21	27%	7	9%	9	11%	3	4%	2	3%
Total	180	116	64%	55	31%	58	32%	16	9%	26	14%	12	7%	4	2%

Total

								Transplants							
										Donor					
Category	Total	Formal		Work-ups		Transplants		Cord		10/10		9/10		8/10	
Very Likely	446	335	75%	230	52%	203	46%	11	2%	186	42%	6	1%	0	0%
Less Likely	502	337	67%	154	31%	164	33%	45	9%	52	10%	57	11%	10	2%
Very Unlikely	271	171	63%	48	18%	65	24%	34	13%	11	4%	16	6%	4	1%
Total	1219	843	69%	432	35%	432	35%	90	7%	249	20%	79	6%	14	1%

6.4. APPENDIX D. CURRENT 1 YEAR AND 100 DAY SURVIVAL FOR VARIOUS PATIENT AND DONOR GROUPS BASED ON 2012-2015 CIBMTR DATA

Table 1. OS at 1 year for all diseases for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	6782	72 (71-73)	10596	69 (68-70)	1918	61 (59-63)	708	68 (65-72)	1555	63 (61-66)
Black/African American	855	79 (77-82)	351	71 (66-76)	351	58 (53-63)	296	75 (70-80)	456	55 (51-60)
Non-black Hispanic	1122	76 (74-79)	731	74 (71-77)	427	65 (60-70)	133	61 (52-70)	524	64 (61-69)
Asian/Pacific Islander	531	75 (71-79)	341	70 (66-76)	155	67 (59-75)	71	59 (47-71)	207	66 (60-73)
Missing race	565	77 (74-81)	226	76 (70-82)	129	67 (59-76)	82	71 (60-81)	174	65 (58-72)
Total	9855	74 (73-75)	12245	69 (69-70)	2980	62 (60-64)	1290	69 (66-71)	2916	63 (61-64)

Table 2. OS at 1 year for malignant diseases[a] for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	6055	71 (70-72)	9586	68 (67-69)	1701	59 (57-62)	621	69 (66-73)	1312	61 (58-63)
Black/African American	509	71 (67-75)	246	67 (61-73)	268	53 (47-60)	228	72 (66-78)	349	51 (45-56)
Non-black Hispanic	963	71 (71-77)	608	72 (68-76)	344	64 (59-69)	121	59 (49-68)	413	61 (56-66)
Asian/Pacific Islander	442	72 (68-76)	272	68 (63-74)	126	66 (57-75)	61	57 (44-71)	171	64 (56-71)
Missing race	453	74 (70-78)	166	75 (68-82)	126	63 (53-73)	61	67 (54-79)	124	57 (48-66)
Total	8422	71 (71-73)	10878	68 (67-69)	2538	60 (58-62)	1094	68 (65-71)	2369	59 (57-61)

[a]Excludes multiple myeloma and solid tumor

Table 3. OS at 1 year for non-malignant diseases for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	507	89 (87-92)	771	84 (81-86)	169	80 (74-86)	43	65 (50-81)	232	78 (73-84)
Black/African American	313	95 (92-97)	98	82 (73-90)	75	75 (64-85)	54	89 (80-98)	102	72 (62-81)
Non-black Hispanic	125	94 (89-98)	113	84 (77-91)	75	73 (63-84)	9	89 (63-100)	108	80 (72-88)
Asian/Pacific Islander	74	97 (93-100)	64	81 (71-92)	27	74 (56-92)	7	71 (31-100)	35	83 (69-97)
Missing race	102	94 (89-99)	55	80 (69-91)	29	86 (72-100)	15	87 (66-100)	47	87 (77-98)
Total	1121	92 (91-94)	1101	83 (81-85)	375	78 (73-82)	128	80 (72-87)	524	78 (75-82)

Table 4. OS at 1 year for Severe Aplastic Anemia for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	239	92 (88-96)	278	85 (81-89)	57	79 (67-90)	17	65 (39-90)	10	50 (14-86)
Black/African American	40	90 (79-100)	12	83 (58-100)	20	65 (42-88)	10	70 (37-100)	14	79 (54-100)
Non-black Hispanic	64	92 (85-100)	43	91 (81-100)	24	67 (46-88)	1	100 (50-100)	12	83 (58-100)
Asian/Pacific Islander	34	100 (99-100)	17	76 (53-100)	7	71 (31-100)	2	100 (75-100)	6	100 (92-100)
Missing race	43	93 (84-100)	10	100 (95-100)	10	70 (37-100)	8	75 (39-100)	3	100 (83-100)
Total	420	93 (90-95)	360	86 (82-89)	118	73 (64-81)	38	71 (55-87)	45	78 (65-91)

Table 5. OS at 1 year for sickle cell anemia for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	11	100 (95-100)	1	100 (50-100)	0		1	100 (50-100)	0	
Black/African American	240	96 (94-99)	61	80 (70-91)	21	81 (62-100)	37	97 (91-100)	24	83 (66-100)
Non-black Hispanic	14	100 (96-100)	1	100 (50-100)	4	75 (20-100)	0		0	
Asian/Pacific Islander	3	100 (83-100)	0		0		0		0	
Missing race	18	94 (81-100)	4	100 (88-100)	1	100 (50-100)	0		2	100 (75-100)
Total	286	97 (94-99)	67	82 (72-92)	26	81 (64-98)	38	97 (91-100)	26	85 (69-100)

Table 6. OS at 100 days for all diseases for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	6782	92 (91-93)	10596	89 (89-90)	1918	85 (83-87)	708	90 (88-93)	1555	85 (83-87)
Black/African American	855	94 (93-96)	351	86 (83-90)	351	83 (79-88)	296	89 (85-93)	456	80 (77-84)
Non-black Hispanic	1122	95 (93-96)	731	91 (89-93)	427	88 (85-91)	133	89 (84-95)	524	84 (81-87)
Asian/Pacific Islander	531	93 (91-96)	341	88 (85-92)	155	88 (82-93)	71	73 (62-84)	207	86 (82-91)
Missing race	565	93 (90-95)	226	91 (87-95)	129	87 (81-93)	82	95 (90-100)	174	85 (79-91)
Total	9855	93 (92-93)	12245	89 (89-90)	2980	85 (84-87)	1290	89 (87-91)	2916	84 (83-85)

Table 7. OS at 100 days for malignant diseases[a] for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	6055	92 (91-92)	9586	89 (89-90)	1701	84 (82-86)	621	91 (89-93)	1312	84 (82-86)
Black/African American	509	92 (90-95)	246	84 (79-89)	268	81 (76-86)	228	89 (84-93)	349	79 (75-83)
Non-black Hispanic	963	94 (93-96)	608	90 (88-93)	344	88 (85-92)	121	88 (82-95)	413	83 (79-87)
Asian/Pacific Islander	442	92 (89-95)	272	88 (84-92)	126	74 (82-94)	61	74 (62-86)	171	87 (81-92)
Missing race	453	92 (90-95)	166	92 (88-97)	99	95 (78-93)	63	95 (89-100)	124	80 (72-87)
Total	8422	92 (92-93)	10878	89 (89-90)	2538	90 (83-86)	1094	90 (88-91)	2369	83 (81-84)

[a]Excludes multiple myeloma and solid tumor

Table 8. OS at 100 days for non-malignant diseases for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	507	95 (93-97)	771	92 (90-94)	169	92 (88-97)	43	81 (69-94)	232	91 (88-95)
Black/African American	313	97 (96-99)	98	92 (86-98)	75	92 (85-99)	54	93 (85-100)	102	83 (76-91)
Non-black Hispanic	125	97 (93-100)	113	93 (88-98)	75	89 (82-97)	9	100 (94-100)	108	87 (80-94)
Asian/Pacific Islander	74	100 (99-100)	64	89 (81-97)	27	85 (70-100)	7	71 (31-100)	35	89 (77-100)
Missing race	102	96 (92-100)	55	87 (78-97)	29	90 (77-100)	15	93 (77-100)	47	98 (93-100)
Total	1121	96 (95-98)	1101	92 (90-93)	375	91 (88-94)	128	88 (82-94)	524	89 (87-92)

Table 9. OS at 100 days for Severe Aplastic Anemia for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	239	97 (94-99)	278	93 (90-96)	57	93 (85-100)	17	82 (61-100)	10	90 (66-100)
Black/African American	40	95 (87-100)	12	83 (58-100)	20	85 (67-100)	10	80 (50-100)	14	86 (64-100)
Non-black Hispanic	64	94 (87-100)	43	93 (84-100)	24	79 (61-97)	1	100 (50-100)	12	92 (72-100)
Asian/Pacific Islander	34	100 (99-100)	17	82 (61-100)	7	100 (93-100)	2	100 (75-100)	6	100 (92-100)
Missing race	43	95 (88-100)	10	100 (95-100)	10	70 (37-100)	8	88 (58-100)	3	100 (83-100)
Total	420	96 (94-98)	360	92 (89-95)	118	87 (81-94)	38	84 (71-97)	45	91 (82-100)

Table 10. OS at 100 days for sickle cell anemia for first allogeneic transplants in 2012-2015

	HLA-id sib		**MUD**		**Mismatched UD**		**2+ Locus Mismatched Related Donor**		**Unrelated Umbilical Cord Blood**	
	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)
White	11	100 (95-100)	1	100 (50-100)	0		1	100 (50-100)	0	
Black/African American	240	98 (97-100)	61	95 (89-100)	21	95 (84-100)	37	100 (99-100)	24	96 (86-100)
Non-black Hispanic	14	100 (96-100)	1	100 (50-100)	4	100 (88-100)	0		0	
Asian/Pacific Islander	3	100 (83-100)	0		0		0		0	
Missing race	18	100 (97-100)	4	100 (88-100)	1	100 (50-100)	0		2	100 (75-100)
Total	286	99 (97-100)	67	96 (90-100)	26	96 (87-100)	38	100 (99-100)	26	96 (87-100)

6.5. APPENDIX E. DERIVATION OF A SQUENTIAL TEST STATISTIC FOR CENSORED EXPOENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0:\theta=\theta_o$ versus $H_1:\theta=\theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1)/f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B<1<A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta=\theta_0$, and of accepting H_0 when $\theta=\theta_1$, respectively, and the expected sample size $E(N\mid\theta_j)\equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0)\le\alpha$ and $\Pr_1(\text{reject } H_0)\le\beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2,...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1(>\theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A=(1-\beta)/\alpha$ and $B=\beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1)=(A^{h(\theta)}-1)/(A^{h(\theta)}-B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int(f(x;\theta_1)/f(x,\theta_2))^{h(\theta)}f(x;\theta)dx=1$.

The formula $E(N;\theta)=[[(1-O(\theta)]\log A+O(\theta)\log B]/E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N)\approx[E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Censored Exponential Survival Times

Suppose that we wish to construct a sequential test for the composite null hypothesis that the rate of overall mortality at an early time point t is less than or equal to p_0 versus the alternative hypothesis that it is greater than or equal to p_0. Let us assume that the survival times, $T_1, T_2, ..., T_n$, are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. Although an exponential model may not fit well for overall mortality, it usually provides a reasonable model over a short time frame for modeling toxicity, so in all discussion below we assume that exponential survival times are censored at time point t. In the exponential parameterization, a t-day survival rate of p_0 translates into a mean survival of μ_0=-t/ln(1-p_0) (rate parameter θ_0 = -ln(1-p_0)/t). .

The SPRT is derived with reference to a simple null and alternative hypothesis for the rate parameter, in this case, $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$. The log-likelihood ratio for the exponential in the presence of censoring is $\log \prod_i^n f(x_i;\theta_1) - \log \prod_i^n f(x_i,\theta_0) = d(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, where d is the number of events. The SPRT can be represented graphically when plotting the number of deaths (d) on the y axis against the total time on study $\sum_i^n T_i$ on the x axis. The continuation region in terms of d is bounded by two parallel lines given by

$$\left[\frac{\log(B)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i < d < \left[\frac{\log(A)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i$$

with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0)$, and intercepts $\log A/(\ln\theta_1 - \ln\theta_0)$ and $\log B/(\ln\theta_1 - \ln\theta_0)$, for the upper and lower bounds, respectively. For monitoring purposes, at an interim analysis calendar time point s, suppose that d(s) events have occurred and that the total time on study is $\sum_i^n T_i(s)$.The cumulative number of events d(s) is plotted on the y axis against the total time on study, $\sum_i^n T_i(s)$. When this graph crosses the upper boundary, the null hypothesis is rejected. In practice, monitoring will be scheduled monthly after the start of enrollment to the study.

A truncated version of the SPRT can be obtained by specifying a maximum sample size. We truncate the SPRT by declaring that if the test has failed to terminate after the maximum sample size, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at the maximum sample size is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity. The operating characteristics of this proposed truncated SPRT for censored exponential data can be estimated by simulation.

6.6. APPENDIX F. REFERENCES

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