BLOOD AND MARROW
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CLINICAL TRIALS NETWORK

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity(RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow (Haplo) for Patients with Hematologic Malignancies

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BMT CTN PROTOCOL 1101
VERSION 8.0

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PROTOCOL SYNOPSIS – BMT CTN 1101

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow (haplo-BM) for Patients with Hematologic Malignancies

Principal Investigators: Ephraim Fuchs, M.D., Paul O'Donnell, M.D., Ph.D., Claudio Brunstein, M.D.

Study Design: This study is a multi-center, Phase III, randomized trial of reduced intensity conditioning followed by transplantation of two unrelated cord blood units with calcineurin inhibitor and mycophenolate mofetil (MMF) for GVHD prophylaxis versus HLA-haploidentical related bone marrow with posttransplant cyclophosphamide, calcineurin inhibitor, and MMF for GVHD prophylaxis in patients with:

1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, dendritic cell leukemias, natural killer cell malignancies or Burkitt's lymphoma in remission.
2) Lymphoma, including marginal zone lymphoma, follicular lymphoma, or chemotherapy-sensitive large-cell, Hodgkin or mantle cell lymphoma, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma.

Primary Objective: The primary objective is to compare progression-free-survival at 2 years post-randomization between patients who receive unrelated double cord blood unit transplantation versus HLA-haploidentical related bone marrow transplantation.

Secondary Objectives: Patients enrolled in this study will also be followed for the following endpoints: neutrophil recovery, graft failure, platelet recovery, donor cell engraftment, acute graft-versus-host-disease (GVHD) and chronic GVHD, overall survival, treatment-related mortality, infections, hospital admission and length of stay, health related quality of life, relapse/progression, and cost effectiveness (see companion 1101 study document for ancillary cost effectiveness protocol).

Accrual Objective: The target sample size is 410 patients.

Accrual Period: The target accrual period is 4 years.

Eligibility Criteria: Patients $\geq$ 18 and $\leq$ 70 years of age with a diagnosis of a hematologic malignancy with two partially HLA-matched UCB

units, each with a minimum of 1.5 x 10^7/kg pre-cryopreserved total nucleated cell dose (for non-red blood cell depleted units, the minimum cryopreserved total nucleated cell dose of each unit must be at least 2.0 x 10^7/kg), and a partially HLA-mismatched related donor.

Adequate organ function defined as: 1) left ventricular ejection fraction ≥ 40%; 2) DLCO, FEV_1, FVC > 50% predicted; 3) total bilirubin ≤ 2.5 mg/dL except for patients with Gilbert's syndrome or hemolysis, and ALT, AST, and alkaline phosphatase all < 5 x upper limit of normal (ULN); 4) serum creatinine within normal range, or if serum creatinine outside normal range, must have measured or estimated creatinine clearance > 40 mL/min/1.73m^2; 5) Karnofsky performance score ≥ 70; and 6) if applicable, > 6 months since a previous autologous transplant.

Treatment Description: Eligible patients will be randomized to dUCB or haplo-BM transplantation:

The preparative regimen for haplo-BM transplantation will consist of:

- Fludarabine 30 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide (Cy) 14.5 mg/kg IV Days –6, –5
- Total body irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of infusion of non-T-cell depleted bone marrow

The GVHD prophylaxis regimen for haplo-BM transplantation will consist of:

- Cy 50 mg/kg IV Days 3, 4
- Tacrolimus (IV or po) beginning Day 5 with dose adjusted to maintain a trough level of 5-15 ng/mL. Cyclosporine (trough level of 200-400 ng/mL) may be substituted for tacrolimus if the patient is intolerant of tacrolimus or per institutional practice.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID, maximum dose 1 g po TID beginning Day 5 until Day 35

Supportive care for haplo-BM transplantation includes:

- Filgrastim (G-CSF) 5 mcg/kg/day beginning Day 5 until ANC ≥1500/mm^3 for 3 consecutive measurements on at least two different days

The preparative regimen for dUCB transplantation will consist of:

- Fludarabine 40 mg/m^2 IV Days –6, –5, –4, –3, –2
- Cyclophosphamide 50 mg/kg IV Day –6
- Total Body Irradiation (TBI)
  - 200 cGy Day –1 for patients who have received cytotoxic

chemotherapy within the last 3 months or an autologous transplant within 24 months of enrollment
- 300 cGY Day -1 for patients who have not received cytotoxic chemotherapy within 3 months of enrollment or an autologous transplant within 24 months of enrollment
- Day 0 will be the day of the double UCB transplant

The GVHD prophylaxis regimen for dUCB transplantation will consist of:

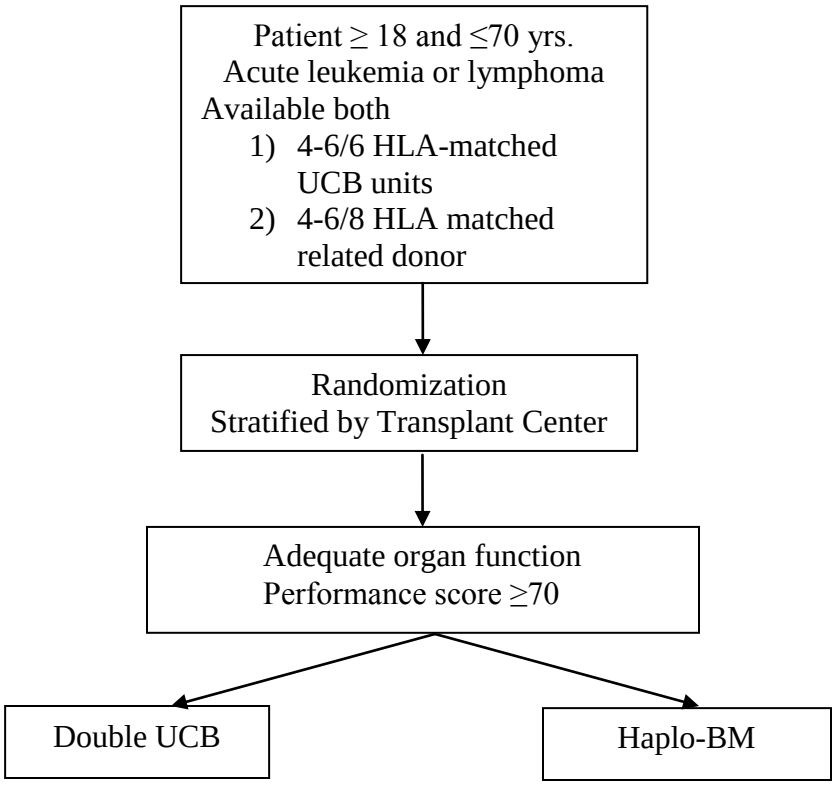
- Cyclosporine beginning Day –3 with dose adjusted to maintain a trough level of 200-400 ng/mL. Tacrolimus (trough level of 5-15 ng/mL) may be substituted for cyclosporine if the patient is intolerant of cyclosporine or per institutional practice.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID, maximum dose 1 g po TID beginning Day-3 until Day 35.

Supportive care for dUCB transplantation includes:

- Filgrastim (G-CSF) 5 mcg/kg/day beginning Day 1 until ANC $\geq$1500/mm^3 for 3 consecutive measurements on at least two different days

Study Duration: Patients will be followed for three years after transplantation.

TREATMENT SCHEMA



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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Reduced intensity conditioning (RIC) blood or marrow transplantation (BMT) has allowed older and less clinically fit patients to receive potentially curative treatment with allogeneic BMT for high risk or advanced hematological malignancies.[1, 2, 3, 4, 5] Patients lacking an HLA-matched sibling may receive a graft from a suitably HLA-matched unrelated donor. However, up to a third of patients will not have an HLA-matched sibling or a suitably matched adult unrelated donor (i.e., no more than a mismatch at a single locus). Even when a suitably matched unrelated donor is identified, data from the National Marrow Donor Program (NMDP) indicate that a median of four months is required to complete searches that result in transplantation; thus, some number of patients succumb to their disease while awaiting identification and evaluation of a suitably matched adult unrelated donor.[6]

Single or dual center studies have shown that partially HLA-mismatched related bone marrow (haplo-BM) and unrelated double umbilical cord blood (dUCB) are valuable sources of donor cells for RIC BMT, thus extending this treatment modality to patients who lack other donors.[7, 8, 9, 10, 11, 12] In order to study the reproducibility, and thus, the wider applicability of these two alternative donor strategies, The Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) conducted two parallel multicenter prospective phase II clinical trials. These two studies evaluated the safety and efficacy of related haplo-BM (BMT CTN 0603) and dUCB (BMT CTN 0604) transplantation after RIC. Eligibility criteria for the two trials were the same and included patients up to 70 years with: poor-risk acute leukemia or Burkitt lymphoma in remission, Hodgkin lymphoma, mantle cell lymphoma, or aggressive non-Hodgkin lymphoma in sensitive relapse, or multiply relapsed marginal zone or follicular lymphoma. The target accrual of 50 patients per trial was achieved in just 20 months (16 months faster than expected). The primary objective was to determine overall survival (OS) 180 days after BMT, with examination of: neutrophil and platelet recovery, graft failure, acute GVHD, chronic GVHD, incidence of

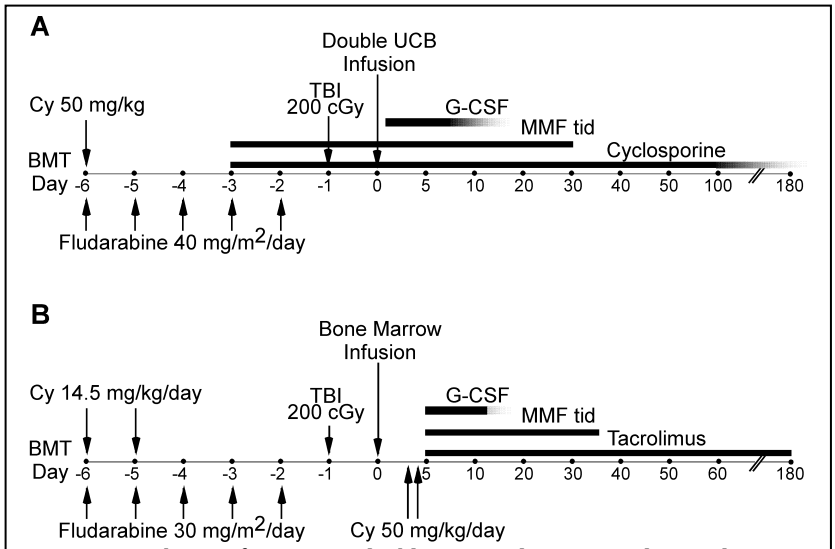

Figure 1. Schemas for non-myeloablative conditioning and transplantation of either double unrelated umbilical cord blood (A) or HLA-haploidentical related donor bone marrow (B).

infection, treatment-related mortality (TRM), time to relapse/progression, and current progression-free survival (PFS).

Figure 1 shows the schemata for reduced intensity conditioning (RIC) and transplantation of either dUCB or haplo-BM grafts. Recipients of dUCB grafts were conditioned with fludarabine (Flu) 40 mg/m^2/day intravenously (IV) from Days -6 to -2 (total dose of 200 mg/m^2), cyclophosphamide (Cy) 50mg/kg IV on Day -6, and 2 Gy total body irradiation (TBI) in a single fraction on Day -1 (Figure 1A). Graft-versus-host disease (GVHD) prophylaxis included mycophenolate mofetil (MMF) and cyclosporine A (CsA), with tacrolimus as an acceptable substitution for CsA. Filgrastim 5 mcg/kg/day was initiated on Day 1 and continued until the absolute neutrophil count (ANC) was ≥2,000/μL for 3 consecutive days.

Table 1. Patient and disease characteristics

	Cord	Haplo
Number of patients	50	50
Age (yrs)		
Median	58	48
Range	16 – 69	7 – 70
Weight (kg)		
Median	79	78
Range	46 – 119	21 – 184
Performance Status		
= 90	40 (80%)	38 (76%)
< 90	10 (20%)	12 (24%)
Primary Disease		
Acute Lymphoblastic Leukemia	6 (12%)	6 (12%)
Acute Myelogeneous Leukemia	29 (58%)	22 (44%)
Biphenotypic/ Undifferentiated Leukemia	1 (2%)	3 (6%)
Burkitt's Lymphoma	1 (2%)	0
Hodgkins Lymphoma	5 (10%)	7 (14%)
Large Cell Lymphoma	3 (6%)	8 (16%)
Marginal Zone B-cell Lymphoma	1 (2%)	1 (2%)
Follicular Non-Hodgkins Lymphoma	4 (8%)	3 (6%)
Disease Stage		
Acute Leukemia		
First Complete Remission	23 (64%)	15 (48%)
Second Complete Remission	10 (28%)	12 (39%)
Third or Subsequent Complete Remission	3 (8%)	4 (13%)
Lymphomas		
Complete Remission	5 (36%)	7 (37%)
Partial Response	8 (57%)	12 (63%)
Resistant	1 (7%)	0
Number of Prior Chemotherapy Regimens (Lymphoma Patients)		
Two	1 (7%)	4 (21%)
Three	5 (36%)	6 (32%)
More Than Three	8 (57%)	9 (47%)
Prior Autologous Transplantation		
Yes	6 (12%)	11 (22%)

Recipients of haplo-BM were conditioned with Flu 30 mg/m^2/day IV daily from Days -6 to -2 (total dose of 150 mg/m^2), Cy 14.5 mg/kg IV on Day -6 and -5, and 2 Gy TBI in a single fraction on Day -1 (Figure 1B). GVHD prophylaxis consisted of Cy 50 mg/kg IV on Days 3 and 4 followed by MMF and tacrolimus beginning on Day 5, with CsA as an acceptable substitution for tacrolimus. Filgrastim 5 mcg/kg/day was initiated on post-transplantation Day 5 and continued until the ANC was ≥ 1000/μL for three consecutive days.

Patient and graft characteristics

Characteristics of the patients enrolled in the two trials are summarized in Table 1 (BMT CTN 0603 and 0604). Fifty-four patients were registered on the dUCB trial but 4 of these patients were not treated according to protocol and excluded from the analysis; one withdrew consent, and three had disease relapsed/progression. Accrual occurred between January 2009 and March 2010. Among recipients of dUCB transplantation the median combined nucleated cell dose at the time of cryopreservation was 5.0 x 10^7/kg and at infusion, 4.2 X 10^7/kg. Donor-recipient HLA disparity was assigned based on the more highly mismatched of the two dUCB units; 33 donor-recipient pairs were categorized as 4/6 matches, 14 pairs as 5/6, and 3 pairs as 6/6 HLA-matched. Matching criteria used intermediate resolution typing at HLA-A and B with

high resolution typing at HLA-DRB1. Cord blood units for 35 donor-recipient pairs (70%) were mismatched to each other at two HLA loci.

Fifty-five patients were registered on the haplo-BM trial, but five were not treated according to the protocol and excluded from the analysis; one withdrew consent, two were found to have disease relapsed/progression, and two were not eligible for the protocol. Accrual occurred between December 2008 and May 2010. Seventeen donors were siblings of the recipient, 15 were parents and 18 were children. More than three quarters of the HLA-haploidentical related donors were mismatched for four or more HLA loci using high-resolution typing (HLA-A, -B, -C, -DRB1, and –DQB1) in both the graft-versus-host and host-versus-graft directions (not shown).

Hematopoietic Recovery and Chimerism

After dUCB transplantation, the cumulative incidence of neutrophil recovery ≥500/μL at Day 56 was 94% (95%CI, 87-100%) with a median time to recovery of 15 days (range, 4-47). The cumulative incidence of platelet recovery, ≥ 20,000/μL at Day 100 was 82% (95%CI, 71-93%) with a median time to recovery of 38 days (range, 3-87). The corresponding probability for platelets ≥ 50,000/μL was 59% (95%CI, 44-73%) with a median time to recovery of 43 days (range, 29-323). There were five cases of primary graft failure and one secondary graft failure. Three graft failure patients died at Days 23, 28, and 193 (after second dUCB transplant). Two patients had autologous reconstitution and died of relapse at Day 99 and 117. The patient with secondary graft failure was determined to have lost chimerism at Day 183, had leukemia relapse at Day 330, and died at Day 347. Median donor chimerism in marrow or peripheral blood was 92% (range, 0-100%) on Day 28 and 100% (range, 25-100%) on Day 56 after transplantation (not shown). In BMT CTN 0604, we only enrolled patients who had received immune suppressive chemotherapy within 3 months of enrollment. Earlier pilot data suggested that for patients who had not received chemotherapy within 4 months of a planned dUCB transplant with a regimen of similar intensity as described in BMT CTN 0604, graft failure rates were as high as 35% (University of Minnesota, unpublished data).

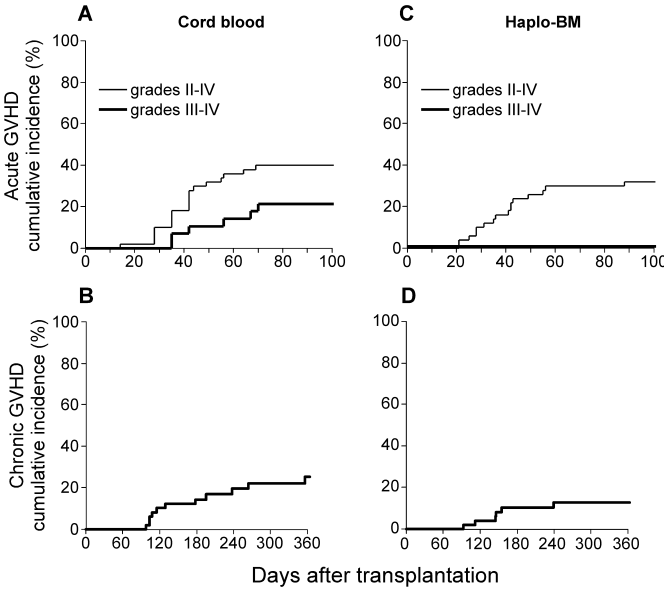

Figure 2. Acute (A,C) or chronic (B,D) graft-versus-host disease after RIC and transplantation of dUCB (A,B) or Haplo-marrow (C,D)

Recent data from the Fred Hutchinson Cancer Research Center (FHCRC) demonstrated that 300 cGy, instead of 200 cGy, is able to overcome this engraftment barrier with no obvious adverse effect on other outcomes.[13,14]

After haplo-BM the cumulative incidence of neutrophil recovery ≥500/μL at Day 56 was 96% (95%CI, 90-100%) with a median time to recovery of 16 days (range, 12-83). The cumulative incidence of platelet recovery ≥ 20,000/μL at Day 100 was 98% (95%CI, 93-100%) with a median time to recovery of 24 days (range, 1-92). The corresponding probability for platelets ≥ 50,000/μL was 76% (95%CI, 64-88%) with a median time to recovery of 26 days (range, 1-126). There was one case of primary graft failure. This patient did not receive a second transplant and died on Day 67. Median donor chimerism in marrow or peripheral blood was 100% (range 72-100%) on Day 28 and 100% (range 0-100%) on Day 56 after transplantation (not shown).

Graft-versus-host disease

After dUCB transplantation, the cumulative incidences of grade II-IV and III-IV acute GVHD at Day +100 were 40% (95% CI, 26-54%) and 21% (95% CI, 6-37%), respectively (Figure 2A). The cumulative incidence of chronic GVHD at 1 year was 25% (95% CI, 12-39%; Figure 2B).

After haplo-BM transplantation, the cumulative incidence of grade II-IV acute GVHD at Day +100 were 32% (95% CI, 19-45%; Figure 2C). There were no reported cases of grade III-IV acute GVHD. The cumulative incidence of chronic GVHD at 1 year was 13% (95% CI, 3-23%; Figure 2D).

Treatment-Related-Mortality, Relapse, and Survival

After dUCB transplantation, the median follow-up of surviving patients was 365 days (range, 56-411 days). The 1-year cumulative incidence of TRM was 24% (95% CI, 11-36%) and of relapse/progression was 31% (95% CI, 17-44%; Figure 3A). Twenty-one patients (42%) have died: 10 from relapse, 4 from acute or chronic GVHD, 3 from graft failure, 1 from infection, and 3 from other causes. Six-month survival, which was the primary endpoint, was 74% (95% CI, 59-84%). The 1-year probability of progression-free survival was 46% (95% CI, 31-60%) and overall survival 54% (95% CI, 38-67%; Figure 4B).

After haplo-BM, the median follow-up of surviving patients was 357 days (range 103-441). The 1-year cumulative incidence of TRM was 7% (95% CI, 0-15%) and of relapse/progression was 45% (95% CI, 30-61%; Figure 4C). Sixteen patients have died: 13 from relapse, 2 from infection, and 1 from graft failure. Six-month survival, which was the primary endpoint, was 84% (95%CI, 70-92%). The 1-year probability of progression-free survival was 48% (95% CI, 32-62%) and overall survival 62% (95% CI, 44-76%; Figure 4D).

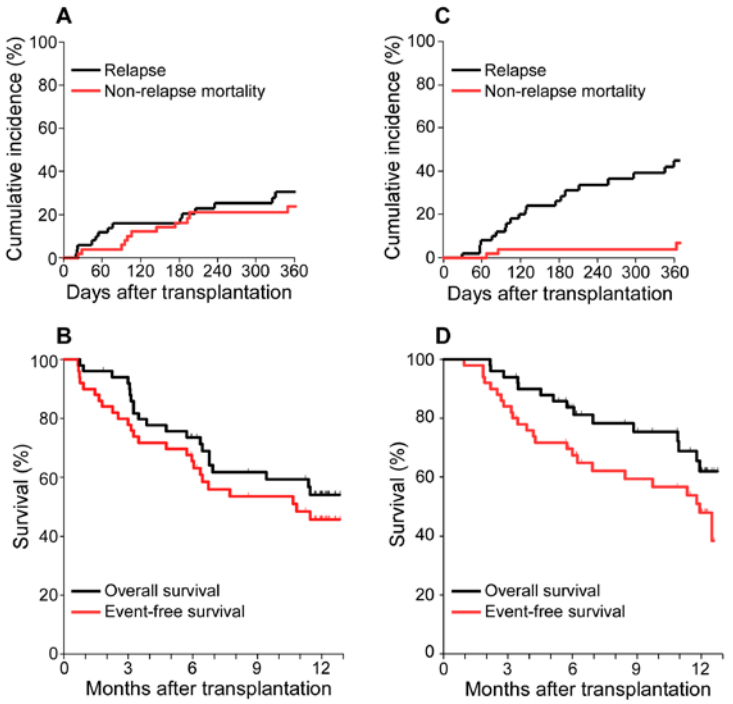

Figure 3. Relapse, NRM (A,C), overall survival, and event-free survival (B,D) after RIC and transplantation of dUCB (A,B) or Haplo-marrow (C,D).

These early results of the RIC followed by haploidentical related (0603) or double UCB (0604) transplantation in multicenter Phase II trials are quite encouraging. Importantly, in this cooperative group setting (17 different centers entered patients on the haploidentical trial and 16 on the UCB trial), both of these alternative donor approaches produced early results similar to that reported with unrelated donor, and even HLA-matched sibling, BMT1. These data demonstrate not only the efficacy of both of these approaches, but also that both can be safely exported from the single center setting. Both haplo-BM and dUCB grafts can be obtained rapidly for >90% of patients lacking an HLA-matched donor. The BMT CTN dUCB results (0604) are quite similar to those reported for a single institution trial in a similar group of patients.9 The BMT CTN haplo-BM results (0603) may even be a little better than those initially reported by Johns Hopkins and Fred Hutchinson,[12] probably because of inclusion of somewhat better-risk patients in the BMT CTN trial. When comparing 0603 and 0604, engraftment, especially of platelets, appeared slower with UCB. There also appeared to be a higher rate of TRM in the BMT CTN UCB trial (0604). Recently, we updated the results of the phase II trials. The 3-year probabilities of progression-free survival after haplo-identical related (0603) and double UCB (0604) were 35% (95% CI 21%-48%) and 36% (95% CI 23%-49%).[15] Consistent with our earlier observation, the pattern of treatment failure varied by donor source. For recipients of haploidentical related transplantation, relapse was the predominant cause of treatment failure and for recipients of double UCB transplantation, TRM was the predominant cause of treatment failure. Recent data also suggest that delayed immune recovery leading to increased serious infections may be an issue with UCB transplantation in older adults; because of thymic dysfunction, immune reconstitution after BMT in older patients appears to primarily arise from memory lymphocytes whose numbers are very low in UCB units.[16, 17, 18] However, the numbers of patients in the two BMT CTN trials are relatively small, assignment was not randomized, and longer follow-ups are needed. Moreover, some concern has been raised about the durability of remissions, especially in myeloid malignancies, after RIC haploidentical BMT. Thus, carefully controlled clinical trials are required to determine the best graft source for adult patients requiring alternative donor BMT.

Accordingly, this protocol describes a Phase III, randomized, open label, multicenter, prospective, comparative trial of double UCB versus related haplo-BMT transplantation after

RIC in patients with hematologic malignancies. Confirming the safety and efficacy of UCB and/or haploidentical related BMT would allow access to BMT for essentially all patients in need. Moreover, a successful MUD search takes a median of 3-4 months,[19] a time-frame that is too long for many patients with aggressive diseases. UCB, and haploidentical related donors, can usually be identified as quickly as HLA-matched sibling donors, again allowing many patients whose disease currently will not remain quiescent long enough for a MUD search, the option of BMT.

The central hypothesis of this trial is that progression-free survival (PFS) at two years after RIC haplo-BM transplantation is similar to the PFS after RIC dUCB transplantation. Accordingly, the primary endpoint of the trial will be two year PFS, with secondary endpoints of TRM, progression/relapse, overall survival, hematopoietic recovery, acute and chronic GVHD, infections, hospital admissions, and health-related quality of life (HQL).

Extended Family Members as Haploidentical Donors

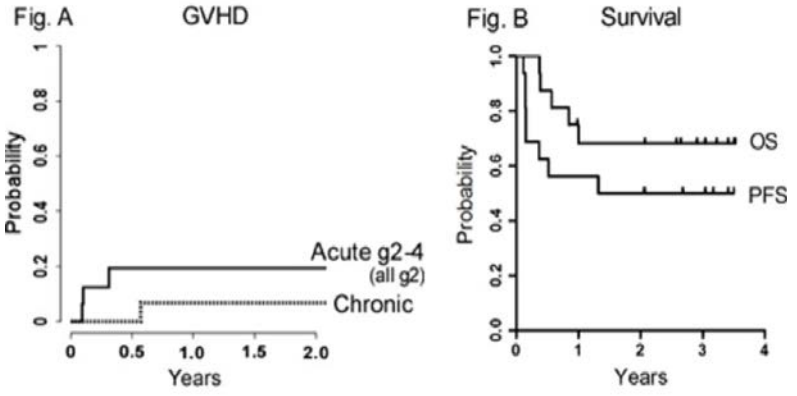

Figure 4. Data from HLA-mismatched unrelated donors showing low incidences of acute or chronic GVHD (A), and non-relapse mortality (B).

Preliminary data (Fuchs E, et al., unpublished) in which 10 patients with high-risk hematologic malignancies received HLA-haploidentical transplants from extended family donors (aunt, uncle, niece, nephew, cousin, grandchild) showed no negative impact on transplant outcomes compared to results using first degree family donors. Use of extended family members as potential donors when a suitable first degree relative is unavailable or unsuitable is supported by another Johns Hopkins study which used the 1101 haploidentical transplantation protocol for recipients of grafts from 20 heavily HLA-mismatched unrelated donors (Kasamon Y, et al. presented at ASH 2015 and submitted for publication) where genetic heterogeneity would be expected to be much greater between donor and recipient than in transplants using family donors. In this study, there was a median of 2 HLA mismatches and included three 7/10 matches, one 6/10 match and one 5/10 match. Full CD3 chimerism was 93% at day 60 and there was no grade 3 acute GVHD. The cumulative incidences of grade 2 acute GVHD and any chronic GVHD were 19% and 7%, respectively. Data from both extended family donors and HLA-mismatched unrelated donors showed high rates of engraftment and acceptably low incidences of acute or chronic GVHD and non-relapse mortality.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a Phase III randomized, open label, multicenter trial to compare PFS at 2 years post-randomization between patients who receive RIC followed by a dUCB transplant versus a related haplo-BM transplant for hematologic malignancy.

2.1.1. Hypotheses and Specific Objectives

2.1.1.1. Hypotheses

Primary Hypothesis: Two year PFS is similar after related haplo-BM donor transplantation or after dUCB transplantation.

Secondary Hypotheses: TRM is significantly lower but relapse is significantly higher after haplo-BM versus dUCB transplantation.

2.1.1.2. Study Objectives

The primary objective is to compare PFS at 2 years post-randomization between patients who receive a dUCB transplant with patients who receive a related haplo-BM transplant. Secondary objectives include comparing neutrophil recovery, primary and secondary graft failure, platelet recovery, donor cell engraftment, acute GVHD, chronic GVHD, overall survival, TRM, relapse/progression, hospital admission and length of stay, health-related quality of life, and cost-effectiveness.

2.2. Eligibility Criteria for Enrollment and Randomization

2.2.1. Patient Inclusion Criteria

Patients will be enrolled regardless of gender. Patients fulfilling the following criteria are eligible for enrollment:

1. Age: Subjects ≥ 18 and ≤ 70 years old
2. Patients must have available both:
    a. One or more potential related mismatched donors (biologic parent (s) or siblings (full or half), children or other extended family members). At least low resolution DNA based typing at HLA-A, -B and –DRB1 is required pre-randomization for potential haplo-identical donors other than biological parents and children.

b. At least two potential umbilical cord blood units identified.

i. Each unit must have a minimum of 1.5 x 10^7/kg pre-cryopreserved total nucleated cell dose. For non-red blood cell depleted units, the minimum pre-cryopreserved total nucleated cell dose of each unit must be at least 2.0 x 10^7/kg.

ii. Units must be HLA matched at a minimum of 4/6 to the recipient at HLA-A, HLA-B (at low resolution using DNA based typing) and HLA-DRB1 (at high resolution using DNA based typing). Confirmatory typing is not required for randomization.

3. Acute Leukemias (includes T lymphoblastic lymphoma):

a. Acute Lymphoblastic Leukemia (ALL) in first complete remission (CR1) (see remission definition in Chapter 3) that is NOT considered favorable-risk as defined by the presence of at least one of the following:

i. Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), other MLL rearrangements,

ii. White blood cell counts of greater than 30,000/mcL (B-ALL) or greater than 100,000/mcL (T-ALL) at diagnosis,

iii. Recipient age older than 30 years at diagnosis,

iv. Time to CR greater than 4 weeks

b. Acute Myelogeneous Leukemia (AML) in first complete remission (CR1) (see remission definition in Chapter 3) that is NOT considered as favorable-risk.

i. Favorable risk is defined as having one of the followingt(8,21) without CKIT mutation

ii. inv(16) without CKIT mutation or t(16;16)

iii. FLT3 ITD and TKD mutations without concurrent mutations in NPM1 or core binding factors (inv(16) and t(8:21)).

iv. Normal karyotype with double mutated CEBPA

v. APL in first molecular remission at end of consolidation

Please consult with the protocol chairs for patients meeting one of the above criteria but with additional features that may be considered high risk.

c. Acute Leukemias in 2nd or subsequent CR (see remission definition in Chapter 3).

d. Biphenotypic/Undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR

4. Burkitt's lymphoma: second or subsequent CR.

5. High risk lymphomas in first CR, including, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma.
6. Chemotherapy-sensitive (at least stable disease; see response criteria in Chapter 3) lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are **INELIGIBLE** for an autologous transplant. Patients with CLL are not eligible regardless of disease status.
7. Performance status: Karnofsky score ≥ 70%.

2.2.2. Patient Exclusion Criteria

Patients fulfilling the following criteria are ineligible for registration onto this study:

1. Patients with suitably matched related or unrelated donor, as defined per institutional practice.

   An unrelated donor search is not required for a patient to be eligible for this protocol, or a search and donor mobilization may be abandoned, if the clinical situation dictates an urgent transplant. Clinical urgency is defined as 6-8 weeks from referral to transplant or a low-likelihood of finding a matched, unrelated donor.
2. Recipients of prior autologous hematopoietic stem cell transplantation are ineligible if disease recurrence occurred < 6 months from their autologous hematopoietic stem cell transplant.
3. Current uncontrolled bacterial, viral or fungal infection (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).
4. Prior allogeneic hematopoietic stem cell transplant.
5. Patients with history of primary idiopathic myelofibrosis or any severe marrow fibrosis.
6. Planned use of prophylactic donor lymphocyte infusion (DLI) therapy.
7. Anti-donor HLA antibodies. Positive anti-donor HLA antibody is defined as a positive crossmatch test of any titer (by complement-dependent cytotoxicity or flow cytometric testing) or the presence of anti-donor HLA antibody to the high expression loci HLA-A, -B, -C, or –DRB1 with mean fluorescence intensity >1000 by solid phase immunoassay.
8. Fertile men or women unwilling to use 2 effective forms of birth control or abstinence.

2.3. Additional Patient Eligibility Criteria for Conditioning

2.3.1. Patients with Adequate Physical Function as Measured by

a. Cardiac: Left ventricular ejection fraction at rest must be ≥ 40%, or shortening fraction > 25%.

b. Hepatic:

   i. Bilirubin ≤ 2.5 mg/dL, except for patients with Gilbert's syndrome or hemolysis;

   ii. ALT, AST, and Alkaline Phosphatase < 5 x ULN.

c. Renal: Serum creatinine within normal range, or if serum creatinine outside normal range, then renal function (measured or estimated creatinine clearance or GFR) > 40 mL/min/1.73m^2.

d. Pulmonary: DLCO (corrected for hemoglobin), FEV_1, and FVC > 50% predicted.

2.3.2. Additional Patient Inclusion Criteria for Patients Assigned to Haploidentical BM Arm

Patients must be HLA typed at high resolution using DNA based typing at the following HLA-loci: HLA-A, -B, -C and DRB1 and have available:

A related haploidentical BM donor with 2, 3, or 4 HLA-mismatches. A unidirectional mismatch in either the graft versus host or host versus graft direction is considered a mismatch. The donor and recipient must be HLA identical for at least one antigen (using high resolution DNA based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1. Fulfillment of this criterion shall be considered sufficient evidence that the donor and recipient share one HLA haplotype, and typing of additional family members is not required. See Section 2.4 for donor selection criteria.

2.3.3. Additional Patient Inclusion Criteria for Patients Assigned to Double Umbilical Cord Blood Arm

1. Patients must have available two UCB units fulfilling the following criteria:
   a. Each unit must have a minimum of 1.5 x 10^7/kg pre-cryopreserved total nucleated cell dose. For non-red blood cell depleted units, the minimum pre-cryopreserved total nucleated cell dose of each unit must be at least 2.0 x 10^7/kg.
   b. Units must be HLA matched at a minimum of 4/6 to the recipient at HLA-A, HLA-B (at low resolution using DNA based typing), and HLA-DRB1 (at high resolution using DNA based typing).
   c. See Section 2.5 for graft selection criteria.
2. Patients must have received at least one cycle of the cytotoxic chemotherapy regimens (or regimen of similar intensity) listed in Appendix D within 3 months of enrollment (measured from the start date of chemotherapy) **OR** have had an autologous transplant within 24 months of enrollment **OR** receive 300 cGy as part of the preparative regimen.

2.3.4. Additional Patient Exclusion Criteria

Patients fulfilling the following criteria are ineligible to proceed to transplant:

1. Pregnancy or breast-feeding.
2. Evidence of HIV infection or known HIV positive serology.

2.4. Donor Selection for Haploidentical-BM

2.4.1. Donor Inclusion Criteria

1. Donors must be HLA-haploidentical relatives of the patient. Eligible donors include biological parents, siblings (full or half), children or extended family members.
2. For donors < 18 years, the maximum recipient weight (idealbody weight in kg) should not exceed 1.25 times the donor weight (actual body weight in kg).

2.4.2. Donor Prioritization Schema

In the event that two or more eligible donors are identified, the following order of priority is suggested but NOT mandated:

1. For cytomegalovirus (CMV) seronegative recipients, a CMV seronegative donor
2. Red blood cell compatibility
    a. RBC cross-match compatible
    b. Minor ABO incompatibility
    c. Major ABO incompatibility

2.5. Graft Selection for Double Umbilical Cord Units

1. Unit selection is based on pre-cryopreserved total nucleated cell dose & HLA-A, -B, and -DRB1. See Section 2.2.1 for HLA typing criteria.
2. After attaining the minimum total nucleated cell dose threshold of 1.5×10^7/kg (or 2.0×10^7/kg for units that were not red cell-depleted), it is recommended HLA-match take priority for unit selection. However, within the best available HLA match grade (e.g. 5/6), units with the largest total nucleated cell dose per kg recipient body weight should be chosen.
3. It is recommended two mismatches at a single HLA-locus be avoided if possible.
4. Matching the two units is recommended but NOT mandated. The recommendation is that units be HLA matched at a minimum of 4/6 to each other but not necessarily at the same HLA-loci as with the recipient.

For additional guidance on graft or donor selection, please contact the study chairs or protocol officer via the EMMES protocol coordinator.

2.6.Treatment Plans

Dose Adjustment Formulas

Estimated creatinine clearance determined by the Cockcroft Formula:

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{ideal body weight (IBW) (kg)}}{P_{Cr} \times 72} \times 0.85 \text{ (for female)}$$

Ideal Body Weight (IBW) Formulas:

Males IBW = 50 kg + 2.3 kg/2.5 cm over 1.52 meters

Females IBW = 45.5 kg + 2.3 kg/2.5 cm over 1.52 meters

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.6.1. Treatment Plan for Patients Randomized to Haplo-BM

All patients randomized to the haplo-BM arm will receive preparative therapy as shown in Table 2.6.1.

TABLE 2.6.1 - HAPLO PREPARATIVE REGIMEN

Day –6, -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 14.5 mg/kg IV over 1-2 hours*
Day –4→ -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes
Day –1	TBI 200 cGy
Day 0	Non-T-cell depleted bone marrow
Days 3, 4	Cyclophopshamide 50 mg/kg IV Mesna 40 mg/kg IV*
Day 5	Begin tacrolimus (or cyclosporine), mycophenolate mofetil, and G-CSF

*Uroprophylaxis may be altered per institutional preference (see below)

2.6.1.1. Fludarabine

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2 for a total dose of 150 mg/m^2. Fludarabine will be dosed according to the recipient's actual body weight. For patients who have an estimated or measured creatinine clearance < 70 mL/min/1.73 m^2, or either prior CNS disease, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Fludarabine must be administered before cyclophosphamide on Days -6 and -5.

2.6.1.2. Pre-transplantation cyclophosphamide

Hydration prior to cyclophosphamide may be given according to institutional standards. A **recommended** approach is as follows: Patients are instructed to increase fluids overnight before cyclophosphamide administration. Hydration with normal saline at 3 mL/kg/hr IV will be started 2 hours prior to cyclophosphamide, then the rate will be reduced to 2 mL/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 mL/kg/hr for 8 hours post-cyclophosphamide.

Mesna may be administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. A suggested approach is as follows: divided doses IV 30 min pre- and at 3, 6, and 8 hours post-Cy. The total daily dose of mesna must be ≥ 80% of the total daily dose of Cy.

Cyclophosphamide 14.5 mg/kg/day will be administered as a 1-2 hour intravenous infusion on Days –6 and –5. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see above for formulas). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW) and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW. Uroprotection can be administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation Cy, but is not required.

2.6.1.3. Total body irradiation (TBI)

200 cGy TBI will be administered in a single fraction on Day –1. Radiation sources and dose rates will be defined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources. Graft may be infused on the same day as TBI administration as long as there is 4-6 hours between administration of TBI and infusion of bone marrow.

2.6.1.4. Transplantation of haplo-BM

On Day 0, patients will receive unprocessed marrow unless there is a major ABO incompatibility, in which case red blood cells will be depleted from the donor marrow using institutional practices. Institutional practices will determine if there will be processing for minor

ABO incompatibilities. Donor bone marrow will be harvested with a target yield of 4 x 10^8 nucleated cells/kg recipient IBW, and a recommended minimum yield of 2.5 x 10^8 nucleated cells/kg of recipient IBW. We recommend taking no more than 10 mL per aspirate. In addition to calculating the total nucleated cell dose /kg, a sample of the product to be infused will be sent for flow cytometry to determine the content of $CD34^+$cells. The use of cryopreserved marrow is not permitted.

2.6.1.5. Post-transplantation cyclophosphamide

Hydration and uroprotection may be given according to institutional standards. See Section 2.6.1.2 for a recommended strategy.

Cyclophosphamide 50mg/kg will be given as an IV infusion over 1-2 hours (depending on volume) on Days 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW) and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW.

2.6.1.6. Immunosuppressive therapy

Corticosteroids may not be used as an anti-emetic agent and should not be administered until 24 hours after the completion of post-transplantation cyclophosphamide, unless used for adrenal support or during a medical emergency (e.g. treatment of anaphylaxis).

2.6.1.7. Tacrolimus

Tacrolimus will be given at a dose of 1 mg IV qd or 1 mg PO bid, and then will be changed to a PO dosing schedule once a therapeutic level is achieved or as per institutional standards. Tacrolimus prophylaxis will begin on Day 5 post-transplant. Serum levels of tacrolimus will be measured around Day 7 and then should be checked weekly thereafter and the dose adjusted accordingly to maintain a trough level of 5-15 ng/mL. Tacrolimus will be discontinued after the last dose around Day 180, or may be continued if active GVHD is present.

Cyclosporine (trough level of 200-400 ng/mL) may be substituted for tacrolimus if the patient is intolerant of tacrolimus or per institutional practice (see Section 2.6.2.4).

2.6.1.8. Mycophenolate mofetil (MMF)

MMF will be given at a dose of 15 mg/kg PO or IV TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID). MMF prophylaxis will begin on Day 5 post-transplant and will be discontinued after the last dose on Day 35, or may be continued if active GVHD is present.

2.6.1.9. Growth factor support

G-CSF will be given beginning on Day 5 at a dose of 5 mcg/kg/day (rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is ≥ 1,500/mm^3 for three consecutive measurements on two different days. G-CSF may be restarted to maintain ANC > 1,000/mm^3. G-CSF may be given by IV or subcutaneously.

2.6.2. Treatment Plan Selection for Patients Randomized to dUCB

All patients who are randomized to the double umbilical cord blood transplant arm and who have received cytotoxic chemotherapy within 3 months of enrollment or an auto HSCT within 24 months of enrollment (see Appendix D) will receive preparative therapy as shown in Table 2.6.2.

TABLE 2.6.2a - dUCB PREPARATIVE REGIMEN FOR PATIENTS WHO HAVE RECEIVED CYTOTOXIC CHEMOTHERAPY WITHIN 3 MONTHS OF ENROLLMENT OR AUTO HSCT WITHIN 24 MONTHS OF ENROLLMENT

Day –6	Fludarabine 40 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 50 mg/kg IV over 2 hours
Day –5→ -2	Fludarabine 40 mg/m^2 IV over 30-60 minutes
Day –3	Begin cyclosporine (or tacrolimus) and MMF
Day –1	TBI 200 cGY
Day 0	UCB Transplant
Day 1	Begin G-CSF

All patients who are randomized to the double umbilical cord blood transplant arm and who have **NOT** received cytotoxic chemotherapy within 3 months of enrollment or an auto HSCT within 24 months of enrollment (see appendix D) will receive preparative therapy as shown in Table 2.6.2b.

TABLE 2.6.2b - dUCB PREPARATIVE REGIMEN FOR PATIENTS WHO HAVE <u>NOT</u> RECEIVED CYTOTOXIC CHEMOTHERAPY[1] WITHIN 3 MONTHS OF ENROLLMENT OR AUTO HSCT WITHIN 24 MONTHS OF ENROLLMENT

Day –6	Fludarabine 40 mg/m^2 IV over 30-60 minutes, then Cyclophosphamide 50 mg/kg IV over 2 hours
Day –5→ -2	Fludarabine 40 mg/m^2 IV over 30-60 minutes
Day –3	Begin cyclosporine (or tacrolimus) and MMF
Day –1	TBI 300 cGY
Day 0	UCB Transplant
Day 1	Begin G-CSF

[1]See Appendix D for list of approved cytotoxic chemotherapy regimens

2.6.2.1. Fludarabine

Fludarabine 40 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days -6 through -2 for a total dose of 200 mg/m^2. Fludarabine will be dosed according to the recipient's actual body weight. For patients who have a estimated or measured creatinine clearance < 70 mL/min/1.73 m^2, or prior CNS disease, or prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Fludarabine must be administered before cyclophosphamide on Day -6.

2.6.2.2. Cyclophosphamide

Hydration prior to cyclophosphamide may be given according to institutional standards. A **recommended** approach is as follows: Patients are instructed to increase fluids overnight before Cy administration. Hydration with normal saline at 3 mL/kg/hr IV will be started 2 hours prior to Cy, then the rate will be reduced to 2 mL/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 mL/kg/hr for 8 hours post-cyclophosphamide.

Mesna may be administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. A suggested approach is as follows: divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide. The total daily dose of mesna must be ≥ 80% of the total daily dose of cyclophosphamide.

Cyclophosphamide 50mg/kg x 1 day to be administered on Day -6. Cyclophosphamide will be dosed according to the recipient's ideal body weight (IBW), unless the patient weighs more than 125% of IBW, in which case the drug will be dosed according to the adjusted IBW (AIBW; see Section 2.6). If the recipient's actual body weight (ABW) is less than the ideal body weight (IBW) and in the best interest of the recipient, the cyclophosphamide dosing can be based on the ABW.

2.6.2.3. Total body irradiation (TBI)

200 cGy TBI will be administered in a single fraction on Day –1 for patients who have received cytotoxic chemotherapy within 3 months of enrollment or an auto HSCT within 24 months of enrollment. 300 cGY TBI will be administered in a single fraction on Day –1 for patients who have NOT received cytotoxic chemotherapy within 3 months of enrollment or an auto HSCT within 24 months of enrollment. Radiation sources and dose rates will also be defined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources. Graft may be infused on the same day as TBI administration as long as there is 4-6 hours between administration of TBI and infusion of the umbilical cord blood units.

2.6.2.4. Cyclosporine A

Cyclosporine will be administered IV beginning on Day –3 and doses will be adjusted to maintain a trough level of 200-400 ng/mL by HPLC or 250-500 ng/mL by TDX method (or 100-250 ng/mL by Tandem MS or equivalent level for other CSA testing methods) or within therapeutic level per institutional standard testing. Dose adjustments will be made on the basis of toxicity or low cyclosporine levels (trough level of < 200 ng/mL). Once the patient can tolerate oral medications and has a normal gastro-intestinal transit time, cyclosporine will be converted to an oral form at 2-3x the current IV dose. Cyclosporine dosing will be monitored and altered as clinically appropriate. Patients will receive cyclosporine until Day +100. In the absence of GVHD, the dose will be tapered 10% per week beginning on Day 101, to be discontinued approximately Day 180-200.

Tacrolimus (trough level of 5-15 ng/mL) may be substituted for cyclosporine if the patient is intolerant of cyclosporine or per institutional practice (see Section 2.6.1.7).

2.6.2.5. Mycophenolate mofetil (MMF)

MMF will be given at a dose of 15 mg/kg PO or IV TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID) beginning on the morning of Day -3. MMF prophylaxis will be discontinued after the last dose on Day 35, or may be continued if active GVHD is present.

2.6.2.6. UCB infusion

Following the administration of the preparative therapy, all subjects randomized to the UCB arm will undergo UCB transplantation. Under **NO** circumstances should the cord blood units be irradiated. No in-line leukocyte filter should be used and no medications or fluids should be given piggyback through the catheter lumen that is being used for the cord blood unit infusion. The graft **MUST** be infused through a central line. Vital signs should be monitored before beginning the infusion and periodically during administration. The two units for dUCB transplantation are infused one after the other with an interval between unit infusion **no longer than 6h**. It is recommended a minimum interval of 30 min between the infusion of the two units in order to observe and manage any acute infusional toxicity related to the infusion of the first unit. The order of infusion of the units will follow institutional practice. Infusion should be initiated as soon as possible after thaw.

The cord blood should be thawed, diluted with or without wash per validated institutional or supplying cord blood bank procedures with the exception that bedside thawing and direct infusion is not allowed. Bedside thaws are not allowed because of the inability to rescue the product if there is loss of integrity of the UCB bag on thaw at the bedside and because of the instability of the cells in 10% DMSO post-thaw. Contingency plans for UCB units which cannot be infused due for example loss of integrity of the bag with contamination or poor viability, will follow institutional policies.

All transplant centers/cellular therapy laboratories must be familiar with thawing of cord blood units. They must have validated procedures and maintain competency in the thaw process. The cord blood unit must be thawed in a qualified laboratory by trained personnel. Generally the cryopreserved unit is removed from the protective cassette, placed in a zippered plastic bag (e.g. Ziplock™ or equivalent) and thawed rapidly in a 37°C waterbath. The zippered plastic bag allows for recovery of cells if the cryopreservation bag cracks or leaks during the thawing process, a rare but possible event. Once the contents of the bag reach a slushy consistency, the cells can be diluted in dextran/albumin, a hypertonic solution that buffers against the intracellular hypertonicity created by DMSO. Cell suspensions can subsequently be washed to remove DMSO, free hemoglobin and other cellular debris allowing for resuspension in a volume appropriate for the size of the patient to be transplanted.

Based on the NMDP Cord Blood Advisory Board Group the following recommendations are relevant, particularly for larger volume units (e.g. RBC replete or "whole blood" untis) which have been, on rare occasion, associated with transient cardiomyopathy (Takotsubo syndrome). These recommendations are not intended to supersede manufacturer's instructions or preclude the use or development of validated thawing and infusion procedures.

1. If a product is washed, after unit is spun and supernatant is removed, resuspend in a minimum of 50 mL of reconstitution solution.
2. Filter the product with standard 170 - 260 micron blood filter.
3. Thaw units independently, with preference toward thawing the second unit after the first unit was infused successfully.
4. Infuse unit independently. Should a reaction occur, appropriately manage the reaction before the second unit is thawed for infusion.
5. Time from initiation of thaw to completion of infusion should be minimized. Preferably this should be less than 2 hours, but data show stem cell integrity is maintained for longer periods.
6. Infusion rate should not exceed 250 mL/h or 5 mL/min. The order of infusion of the units will follow institutional practice.

Benadryl, epinephrine, and hydrocortisone should be available for emergency use if necessary. Oxygen with nasal prongs for standby use should be present in the room.

2.6.2.7. Growth factor support

G-CSF will be given beginning on Day 1 at a dose of 5 mcg/kg/day (rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is $\geq$ 1,500/mm^3 for three consecutive measurements on two different days. G-CSF may be restarted to maintain ANC > 1,000/mm^3. G-CSF may be given by IV or subcutaneously.

2.7. Additional Supportive Care

2.7.1. Post Transplant Maintenance Therapy

Plans for the use of post transplant maintenance therapy must be disclosed prior to randomization, and must be used irrespective of the outcome of the randomization.

2.7.2. Infection Prophylaxis

Patients will receive infection prophylaxis and nutritional support according to institutional guidelines. Infection prophylaxis should include, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to reduce the risk of bacterial, herpes simplex, CMV, HHV-6, EBV, Pneumocystis jiroveci, and fungal infections.

2.7.3. Transfusion Support

Transfusion thresholds for blood product support will be according to standard institutional guidelines. All blood products will be irradiated.

2.7.4. Indwelling Central Venous Catheter

Placement of a double or triple lumen central venous catheter will be required for the transplantation procedure and administration of IV medications and transfusion of blood products. This catheter may be removed and replaced as clinically indicated. However, the graft **MUST** be infused through a central line.

2.7.5. Pre-infusion Medication and Hydration Regimen

The pre-medication and hydration regimen prior to blood products transfusion and transplantation will be given following institutional guidelines.

2.7.6. Anti-Ovulatory Treatment

Females of childbearing potential should be started on an anti-ovulatory agent prior to the initiation of the preparative regimen per institutional practice.

2.7.7. Management of Slow Engraftment and Graft Failure

Slow engraftment or graft failure shall be managed according to institutional practices, and may include the administration of colony stimulating factors and prophylactic antibiotics.

2.8.Risks and Toxicities

Cyclophosphamide:

Cyclophosphamide side effects include: nausea/vomiting, cardiomyopathy, skin rash, mucositis, stomatitis, sterility, diarrhea, hemorrhagic cystitis, fluid weight gain/edema, alopecia, and hemolytic/anemia.

Fludarabine:

a. Neurotoxicity: Agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy or weakness have been reported. Severe neurologic effects, including blindness, coma, and death are seen in 36% of patients treated with doses approximately four times greater than recommended; severe CNS toxicity is rarely seen with doses in the recommended range for nontransplant therapy of hematologic malignancies. Effect of chronic use on the CNS is unknown, although patients have received recommended doses for up to 15 courses. The dose used in this study is approximately 1.5 times the usual one-course dose given in non-transplant settings. Doses and schedules such as those used in this study have been used in adult and pediatric patients and increased neurotoxicity has not been observed.

b. Anemia: Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported after one or more cycles of therapy in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission; no mechanisms for development of this complication have been identified. Corticosteroids may or may not be effective in controlling these episodes. The majority of patients re-challenged developed a recurrence of the hemolytic process.

c. Cardiovascular: Deep venous thrombosis, phlebitis, transient ischemic attack, and aneurysm (1%) are reported.

d. Fever: 60% of patients develop fever.

e. Skin Rash: 15% of patients develop a skin rash, which may be pruritic.

f. Digestive: Gastrointestinal side effects include: nausea/vomiting (36%), diarrhea (15%), stomatitis (9%), anorexia (7%), GI bleeding and esophagitis (3%), mucositis (2%), liver failure, abnormal liver function test, constipation, dysphagia (1%), and mouth sores.

g. Some other effects are: Chills (11%), peripheral edema (8%), myalgia (4%), osteoporosis (2%), pancytopenia, arthralgia (1%), dysuria (4%), urinary tract infection and hematuria (2%); renal failure, abnormal renal function test, and proteinuria (1%); and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

Total Body Irradiation:

TBI can cause: nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema, hyperpigmentation, fever, mucositis, and alopecia.

Late effects include: possible growth retardation, vertebral deformities, cataracts, probable increased risk of secondary malignant neoplasms, sterility, nephropathy, interstitial pneumonitis and veno-occlusive disease.

Mycophenolate Mofetil:

Side effects include: pancytopenia, nausea, vomiting, diarrhea, hypertension, headache, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, and leg cramps/bone pain.

Tacrolimus and Cyclosporine-A:

Side effects include: reversible renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, and neurologic toxicity.

2.9. Health-Related Quality of Life Assessments

2.9.1. Instruments

FACT-BMT: The Functional Assessment of Cancer Therapy – Bone Marrow Transplant subscale version 4.0 instrument is a 37 item scale comprised of a general core questionnaire, the FACT-G, that evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Trial Outcome Index, comprised of the physical well being scale, the functional well being scale and the BMT specific items, will be used as the outcome measure in summarizing the FACT-BMT data. The FACT-BMT takes 6 minutes to complete, and is being used to collect HQL data in BMT CTN 0201, 0801 and 0901.

MOS SF-36: The Medical Outcomes Study Short Form 36 is a 36 item general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data. These summary scores are derived by multiplying the z-score for each scale by its respective physical or mental factor score coefficient and summing the products. Resulting scores are then transformed into T-scores (mean=50; standard deviation=10). The SF-36 takes 6 minutes to complete, and is being used to collect HQL data in BMT CTN protocols 0801 and 0901.

Global HQL: Four standard questions will assess patient self-assessed Karnofsky performance status, overall health and overall quality of life, (excellent, very good, good, fair, poor) and a

rating scale for overall quality of life (where 0 equals death and 100 equals perfect quality of life). In addition, the presence and severity of chronic GVHD will be assessed (mild, moderate, severe). These questions take 1 minute to complete and are being collected for BMT CTN protocols 0201, 0801, and 0901.

Occupational Functioning: Occupational functioning will be measured 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. The same scale has been used in NHLBI-sponsored HCT studies and BMT CTN protocol 0201 and 0901.

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

2.9.2. Administration

The self report questionnaires will be completed prior to transplantation and subsequently at 12 months, and 24 months from randomization or until death. Only patients able to read and speak in English or Spanish are eligible to participate in the HQL component of this trial. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. The method of survey completion, the date, and the language will be recorded in the database. Surveys may not be completed by surrogates.

TABLE: 2.9 REQUIRED PATIENT-REPORTED OUTCOMES DATA COLLECTION

Instrument	N items	Pre-transplant	12 mos	24 mos
Socio-demographics	8	X		
Global quality of life	4	X	X	X
FACT-BMT	37	X	X	X
MOS SF-36	36	X	X	X
Occupational functioning	6	X	X	X
EQ-5D	5	X	X	X
Alternative contacts	2	X	X	X
TOTAL N ITEMS		98	92	92
ANTICIPATED TIME		30 min	30 min	30 min

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is PFS at 2-years from the date of randomization. PFS is defined as the time interval from date of randomization and time to relapse/progression, to death or to last follow-up.

3.2. Secondary Endpoints

3.2.1. Neutrophil Recovery

Neutrophil recovery is defined as achieving an ANC $\geq$ 500/mm^3 for three consecutive measurements on three different days. The first of the three days will be designated the day of neutrophil recovery. The only competing event for neutrophil recovery is death without neutrophil recovery.

3.2.2. Primary Graft Failure

Primary graft failure is defined as < 5% donor chimerism on all measurements up to and including Day 56.

3.2.3. Secondary Graft Failure

Secondary graft failure is defined as initial whole blood or marrow donor chimerism $\geq$ 5% declining to < 5% on subsequent measurements.

3.2.4. Platelet Recovery

Platelet recovery is defined by two different metrics as the first day of a sustained platelet count > 20,000/mm^3 or > 50,000/mm^3 with no platelet transfusions in the preceding seven days. The first day of the sustained platelet count will be designated the day of platelet engraftment.

3.2.5. Donor Cell Engraftment

Donor cell engraftment is defined as donor chimerism $\geq$ 5% on Day $\geq$ 56 after transplantation. Chimerism may be evaluated in whole blood or blood cell fractions, including CD3 and CD33 or CD15 fractions). The actual measurement dates may be within +/- 7 days of the above recommended time points.

3.2.6. Acute GVHD

The cumulative incidences of grade II – IV and III – IV acute GVHD will be determined. Acute GVHD will be graded according to the BMT CTN MOP. The time to onset of acute grades II-IV GVHD and grades III-IV GVHD will be recorded, as well as the maximum grade achieved.

3.2.7. Chronic GVHD

The cumulative incidence of cGVHD will be determined. Data will be collected directly from providers and chart review according to the recommendations of the NIH Consensus Conference. Eight organs will be scored on a 0-3 scale to reflect degree of chronic GVHD involvement. Liver function and pulmonary function results will also be recorded. These data will allow calculation of the NIH global severity scores of mild, moderate, and severe chronic GVHD, which has been associated with transplant related mortality and overall survival.[20]

3.2.8. Overall Survival

Overall survival is defined as the time interval between date of randomization and death from any cause or for surviving patients, to last follow-up. The time interval between date of transplant and death from any cause or for surviving patients, to last follow-up will also be analyzed.

3.2.9. Treatment-Related Mortality (TRM)

The cumulative incidence of TRM will be estimated at Days 100, 180, and at 1 and 2 years after transplantation. An event for this endpoint is death without evidence of disease progression or recurrence.

3.2.10. Infections

All Grade 2 and 3 infections will be reported according to the BMT CTN MOP. Grade 1 CMV infections through Day 56 will also be reported.

3.2.11. Hospital Admission and Length of Stay

The total number of hospital admissions within the first six months after transplantation, indication for admission, and length of stay per hospital admission will be captured.

3.2.12. Health-Related Quality of Life (HQL)

The instruments will be scored according to the recommendations of the developers. See Section 2.9.1 for detailed descriptions of the instruments. The FACT-BMT instrument will be summarized by the Trial Outcome Index, comprised of the physical, functional and BMT-specific items. The MOS SF-36 will be summarized by the Physical Component Summary (PCS) and Mental Component Summary (MCS). The EQ-5D utility score will be calculated.

HQL will be described and compared between the two treatment arms over time. The self report questionnaires will be completed prior to transplantation and subsequently at 12 and 24 months from randomization or until death. Only patients able to read and speak in English or Spanish are eligible to participate in the HQL component of this trial.

3.2.13. Relapse, Residual Disease and Disease Progression

Relapse of Malignancy – Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of acute leukemia consistent with pre-transplant features, or radiologic evidence (including the recurrence of fluoro-deoxyglucose [FDG]-avid lesions on PET scan) of progressive lymphoma. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Minimal Residual Disease – Minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot, or Western blot, or polymerase chain reaction (PCR), or other techniques, in absence of morphological or cytogenetic evidence of disease in blood or marrow. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease alone will not be sufficient to meet the definition of relapse in the context of this trial. However, minimal residual disease that progresses (see above) will be considered as relapse and the date of relapse will be the date of detection of minimal residual disease that prompted an intervention by the treating physician. Data on tapering immunosuppression, administering chemotherapy or biological agents to in response to detection of minimal residual disease will be captured in the case report forms.

Acute Leukemia – Relapse will be diagnosed when there is:

1. The reappearance of leukemia blast cells in the peripheral blood; or,
2. > 5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration); or,
3. The appearance of new dysplastic changes within the bone marrow; or,
4. The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid; or,
5. The reappearance of cytogenetic abnormalities present prior to transplantation.

Lymphoma – Relapse will be diagnosed when there is:

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the sum of the product diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

   Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<.1.5 cm in its long axis by CT).

   Institution of any therapy to treat persistent, progressive or relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse/progression regardless of whether the criteria described above are met.

TABLE 3.2 RESPONSE CRITERIA FOR LYMPHOMA

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

From Cheson, B.D. et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 5:579-586, 2007.

Response Criteria for Acute Leukemia

Remission is defined as < 5% blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in a bone marrow with > 20% cellularity, peripheral blood counts showing ANC >1000/μl, including patients in CRp.

Response Criteria for Lymphoma

Response criteria for lymphoma are described in Table 3.2.

3.2.14. Cost-effectiveness Analysis

The primary endpoint for the CEA is the cost per QALY from the societal perspective with two time horizons: (1) within trial, and (2) lifetime using economic modeling.

The secondary endpoints for the CEA include costs from a narrower third party payer perspective and a separate analysis of the value of informal caregiving.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1. Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

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

1. An authorized user at the transplant center enters the patient demographics and HLA typing results of the recipient, haplo donor, and both CBUs into Segment 0 in AdvantageEDC. HLA match scores will be calculated to confirm eligibility prior to randomization. Further review by the DCC will be triggered if the institutional match score disagrees with the calculated match score. The DCC review must be completed prior to proceeding to Segment A. The eligibility screening includes a question confirming that the patient (or legal guardian) signed the informed consent.

2. Upon successful completion of the Segment 0 HLA forms, an authorized user at the transplant center will enter the remainder of the eligibility criteria required prior to randomization on the Segment A enrollment form. In addition, the transplant center must commit to using or not using post transplant maintenance therapy, irrespective of the treatment assignment.

3. If the patient is eligible, the patient will be randomized to the dUCB or Haploidentical transplant arm and the treatment assignment will be displayed along with the generated patient number. Patients should be registered as close as possible to the initiation of the conditioning regimen.

4. A visit schedule based on treatment start date is displayed for printing and is referred to as ‘Segment A Follow-up.’

4.2. Study Monitoring and Data Submission

4.2.1. Follow-up Schedule

The follow-up schedule for scheduled study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User’s Guide.

TABLE 4.2.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day Post-Transplant
1 week	7 ± 3 days
2 week	14 ± 3 days
3 week	21 ± 3 days
4 week	28 ± 3 days
5 week	35 ± 3 days
6 week	42 ± 3 days
7 week	49 ± 3 days
8 week	56 ± 3 days
9 week	63 ± 3 days
10 week	70 ± 3 days
11 week	77 ± 3 days
12 week	84 ± 3 days
13 week	91 ± 3 days
6 month	180 ± 45 days
12 month	365 ± 45 days
24 month	730 ± 60 days
36 month	1095 ± 60 days

4.2.2. Criteria for Forms Submission

4.2.2.1. Electronic Case Report Forms (eCRFs)

All data for patients are recorded in the electronic Case Report Forms (eCRF) exclusively designed for the study. The Principal Investigator at each of the participating center's is responsible for complete, accurate and timely reporting of data.

Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC (the electronic data entry system) within the specified time will be considered delinquent and addressed with the delinquent center. When data are unavailable because a measure has not been taken, a test not performed or data are unknown, a form or field exception is requested by the center. A form will continue to show as "missing" either until the form is entered into the AdvantageEDC system and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Corrections in the eCRF are to be conducted only by authorized personnel and may require authorization prior to implantation of corrections. However, all earlier entires are retrievable despite corrections. All corrections are recorded automatically concerning date, time point and person. Plausibility and completeness of the eCRF are verified by personnel at the Data Coordinaring Center.

At all times, the Principal Investigators at the participating centers have full responsibility for ensuring accuracy and authenticity of all clinical and laboratory data entered on the eCRFs.

Reporting Patient Deaths: Recipient death information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment of BMT CTN #1101 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post-transplant Comprehensive Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day 90 post-transplant for GVHD. After Day 90 patients will be assessed at each follow-up visit (Day 180, 365, and 730) for the presence of GVHD.

4.2.2.2. Access to Data

Participating sites and their Principal Investigators must agree to allow trial-related on-site monitoring, including audits and regulatory inspections by BMT CTN DCC personnel such that the DCC has direct access to source data/documents as required.

4.2.2.3. Record Retention

Responsibilities of the Sponsor: As required by law, all study documents must be stored by the sponsor for at least 10 years after the clinical trial was finished or stopped.

Responsibilities of the Principal Investigator: The Investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms, copies of all CRFs, source documents, detailed records of treatment disposition and other trial-related documents. The trial-related records should be retained by the Investigator for at least 10 years or as specified by contract, whichever is longer.

4.2.3. Study Monitoring

Monitoring and audits will be performed during the clinical study to ensure that the study meets the quality criteria.

The investigator agrees that the monitor will visit the study center in appropriate intervals. During these visits, the monitor will check the quality of the data recording and ensure that the study center adheres to the timeframe as set in the study protocol. The investigators agree to provide any relevant information and documentation whenever requested by the monitor. This includes access to all original study documents and source data including access to electronic source documents if necessary. Source data are checked and compared with entries in the data base. The participant has given consent to this procedure by signing the patient information and written informed consent form.

The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the study participants.

Following a monitoring visit, the Monitor will provide a report to the sponsor and the site, which will summarize the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The Principal Investigator at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

Details of monitoring activities will be included in the Site Monitoring Plan.

4.2.4. Adverse Events

4.2.4.1. Adverse Event Reporting

Adverse event reporting will be conducted according to the BMT CTN's manual of operating proceedures (MOP).

Unexpected AE Reporting: Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event.

The principal investigator is responsible for submitting follow-up reports to the DCC for all Grade 3-5 Unexpected AEs regarding the patient's subsequent course until the Unexpected AE has resolved or until the patient's condition stabilizes (in the case of persistent impairment), or the patient dies.

Expected AE Reporting: Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals as defined on the Form Submission Schedule. All fatal (Grade 5) expected adverse events will be reported in an expedited manner to the DCC. Most protocol-specific life-threatening or disabling (Grade 4) and other non-fatal expected adverse events will be reported on study forms submitted on a defined forms submission schedule. Grade 4 adverse events not collected on study forms should be reported in an expedited manner.

4.2.4.2.Adverse Event Monitoring

Unexpected Adverse Events: Unexpected adverse events will be reported via a web-based adverse event (AE) system. The Adverse Event Coordinator will review daily all submitted unexpected adverse events and forward the information to the Medical Monitor for review.

All unexpected adverse events will be reviewed by the Medical Monitor within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, transplant centers will have 4 business days to respond to the request for additional information.

The Medical Monitor has medical expertise relevant to the study protocol and may request the participant's treatment assignment when reviewing the adverse event. A designated person at the DCC is responsible for notifying the Project Officer (National Heart Lung and Blood Insttiute [NHLBI]) immediately of all Grade 3-5 unexpected adverse events and of any concerns regarding the frequency or type of adverse event(s) on a study or study treatment arm. The NHLBI Project Officer (or designee) is responsible for reviewing the adverse event materials to determine if the materials are complete. If there are any concerns regarding the type or frequency of the event, the NHLBI Project Officer will request that the Data Saftey Monitoring Board (DSMB) Executive Secretary notify the DSMB Chair. The DSMB Chair will review the adverse event materials, determine if the information is complete, determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study. Full documentation of the procedures will be available at the DCC.

The Medical Monitor will review cumulative unexpected grades 3-5 SAEs on a quarterly basis (data will be reported in a blinded fashion). The Medical Monitor may seek additional guidance from one of the DCC Principal Investigators, based on the expertise required, for their assessments as long as the DCC Principal Investigator's institution is not participating in the protocol under consideration, and the DCC Principal Investigator is not considered to be otherwise in conflict by the NHLBI or by the Steering Committee. If there any concerns regarding safety, the NHLBI Program Directors will be notified immediately. The Medical Monitor will provide a written summary of the safety concern.

The DCC will prepare semi-annual summary reports of all unexpected adverse events for the NHLBI Project Officer and DSMB Chair. Semi-annual reports will be made available on a secure website and the NHLBI Project Officer and DSMB Chair will be notified by e-mail when the materials are posted.

Expected Adverse Events: The DCC will prepare semi-annual summary reports of all Grade 5 expected adverse events for the NHLBI Project Officer and the DSMB Chair. Semi-annual reports will be made available on a secure website and the NHLBI Project Officer and DSMB Chair will be notified by e-mail when the materials are posted. Grade 3-5 expected adverse events defined in the interim analysis plan will be reported as defined in the protocol. Any concern regarding the type or frequency of a Grade 3-5 expected adverse event will be reported to the NHLBI Project Officer who will determine if referral to the DSMB is warranted. If required, data materials will be provided by the DCC. The DSMB Executive Secretary will

arrange for review by the DSMB Chair. The Chair will determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study. The DCC will ensure that any additional reporting requirements defined by the NHLBI Project Officer, DSMB Chair and other oversight groups are identified and implemented. The DCC in collaboration with the NHLBI Project Officer will determine the exact content of these summary reports and the reporting schedule.

The Protocol Coordinator and Medical Monitor will review the adverse events monitored for stopping guidelines at least monthly.

Additionally, the Protocol Coordinator and Medical Monitor will review events reported on the protocol-specific toxicity form, the GVHD forms and the infection forms on a regular basis (at least semi-annually) to assess whether there are safety concerns that should be referred to the DSMB. The Medical Monitor may seek additional guidance from one of the physicians at the DCC in these assessments as long as this physician's institution is not participating in the protocol under consideration.

TABLE 4.2.4.1 REPORTING UNEXPECTED ADVERSE EVENTS ON A BMT CTN PHASE II OR III STUDY

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENTS
5 - Fatal 4 - Life-threatening or Disabling	All attributions	Submit unexpected adverse event form to the DCC within 24 hours of the event. For Grade 5, also submit study death form to the DCC. Submit a summary of the adverse event to the DCC within 4 working days. For Grade 5, the summary should include potential contributing causes of death. Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/treatment, resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse event.
3 – Severe	All attributions Definite Probable Possible	Submit unexpected adverse event form to the DCC within 3 working days of the adverse event. Submit a summary of the adverse event to DCC within 4 working days Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/treatment, resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse

	Unlikely Unrelated	event. Multiple recurrences of the same adverse event should be reported separately. Information reported for the adverse event must include: name of adverse event, date of first onset, peak severity, and relationship to the study drug/device/treatment. Multiple recurrences of the same adverse event should be reported together. *Note: Any adverse event prompting a change in the administration of study drug/device/treatment must include resolution date, actions taken with respect to administration of study drug/device/treatment, and other treatment for the adverse event.*

TABLE 4.2.4.2 REPORTING EXPECTED ADVERSE EVENTS ON BMT CTN PHASE II OR III STUDIES

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENT
5 – Fatal	All attributions	Submit study death form to the DCC within 24 hours of death. Submit death summaries and/or autopsy reports of the expected adverse event to DCC quarterly or as requested. The summaries should include potential contributing causes of death.
4 – Life-threatening or disabling	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date. If the event is not captured on a study from, report using the AE system in an expedited manner. *Note: Selected Grade 3-5 events will be tracked and regularly monitored by the DCC and DSMB as specified in protocol-specific monitoring plans.*
3 – Severe	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date.

4.2.4.3. Adverse Event Definitions

Adverse Event - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of definite, probable, possible, unlikely, or unrelated).

Life-Threatening Adverse Event - Any adverse event that places the participant, in view of the investigator, at immediate risk of death from the reaction.

Serious Adverse Event (SAE) - Any adverse event that results in any of the following outcomes: death, a life threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected Adverse Event - Any adverse event, the specificity or severity of which is NOT listed in the study protocol, product inserts or informed consent document.

Attribution - The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

Definite — The adverse event is ***clearly related*** to the study drug/device/procedure/ treatment(s).

Probable — The adverse event is ***likely related*** to the study drug/device/procedure/ treatment.

For BMT CTN studies: the adverse event is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship.

Possible — The adverse event ***may be related*** to the study drug/device/procedure/ treatment(s).

For BMT CTN studies: the adverse event could be attributed to the subject's underlying medical condition or other concomitant therapy, but the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/treatment administration lead the investigator to believe that there could be a causal relationship.

Unlikely — The adverse event is ***doubtfully related*** to the study drug/device/ procedure/treatment(s).

Unrelated The adverse event is ***clearly NOT related*** to the study drug/device/procedure/ treatment(s).

For BMT CTN studies: the adverse event is most plausibly explained by the subject's underlying medical condition or other concomitant therapy, or the adverse event has no plausible biological relationship to study drug/device/ treatment.

Common Terminology Criteria Adverse Events (CTCAE) – a descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term. Exhibits 6-1-1 and 6-1-2 provide reporting requirements for BMT-related complex/multi-component events. A copy of the current CTCAE guidelines is located at http://ctep.cancer.gov/reporting/.

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

4.2.5. Patient Assessments

Table 4.2.2 summarizes patient clinical assessments over the course of the study.

4.2.5.1. Pre-transplant evaluations

The following observations must be completed ≤ 30 days prior to patient enrollment:

1. History, physical examination, height and weight.
2. Karnofsky performance status.
3. CBC with differential and platelet count and blood chemistries to include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, and chloride.
4. If not already performed, HLA typing of the recipient: At least low resolution DNA based typing at HLA-A and -B, high resolution at HLA-DRB1 (see Section 2.2.1)
5. If not already performed, HLA typing (DNA-based low or high resolution acceptable) of at least one potential HLA-haploidentical first-degree relative (not required if potential haplo-donor is a biological parent or child).
6. Leukemia patients: Bone marrow aspirates for pathology and cytogenetics and/or biopsy.
7. Serum sample for anti-donor HLA antibodies.
8. Lymphomas: CT scans or Whole Body PET/CT.

9. Declaration of post transplant maintenance therapy, if intended, and independent of the randomization assignment.

The following observations are considered standard evaluations for transplant eligibility and must be determined ≤ 30 days prior to enrollment, OR ≤ 56 days prior to the initiation of conditioning therapy.

1. For patients randomized to the double umbilical cord blood arm, confirmatory HLA typing (see Section 2.3.3), if not already performed.
2. For patients randomized to the HLA haplo-identical bone marrow arm, high resolution DNA-based typing (see Section 2.3.2) of the recipient and donor, if not already performed.
3. CMV antibody test, hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab, HepC Ab), herpes simplex, syphilis, HIV and HTLV1 I/II antibody, and varicella zoster virus.
4. EKG.
5. Left ventricular ejection fraction or shortening fraction.
6. DLCO, FEV1, and FVC.
7. Chest imaging (Chest X-Ray or Chest CT).
8. Peripheral blood for pre-transplant chimerism, to establish a reference profile of host hematopoiesis.
9. HQL questionnaires.
10. Confidential Health Insurance Form and Caregivers Contact Information Form for the Cost Effectiveness Ancillary study.

The following tests **must be completed ≤ 30 days prior to the initiation of conditioning therapy**.

1. Recipient blood sample for future research.
2. Donor blood (from all Haplo-BM donors) and bone marrow (from donors ≥ 18 only) samples for future research. Donor samples to be collected on Day 0.
3. CBC with differential, and blood chemistries to include: serum creatinine, bilirubin, AST, and ALT.
4. β-HCG serum pregnancy test for females of childbearing potential.
5. Leukemia patients: bone marrow aspirate and/or biopsy for pathology. THIS TEST DOES NOT NEED TO BE REPEATED IF THE PRE-ENROLLMENT BONE MARROW WAS OBTAINED ≤ 30 DAYS PRIOR TO INITIATION OF CONDITIONING.

4.2.5.2. Post-transplant evaluations

The following evaluations are considered standard evaluations for transplant recipients:

1. Physical exam to assess GVHD and other morbidity weekly until Day 90 post-transplant, then at Days 180, 365, and 730 post-transplant. GVHD evaluation and grading to be in keeping with the BMT CTN MOP.
2. Karnofsky performance status on Days 56, 180, 365, and 730.
3. CBC at least three times a week from Day 0 until ANC > 500 mm^3 for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until Day 56, then at Days 180, 365, and 730 post-transplant.
4. Creatinine, bilirubin, alkaline phosphatase, ALT, AST, LDH, sodium, magnesium, potassium, and chloride, twice a week until Day 28 (or four weeks) and then weekly until Day 56, and then at Days 180, 365, and 730.
5. Peripheral blood on Days 28 and 56 for post-transplant chimerism assay. Chimerism to be measured by standard molecular testing. FISH may only be used with haplo sex mis-matched transplants. T cell chimerism is recommended. Peripheral blood for chimerism assay recommended on Day 180 if donor chimerism is less than 95% on Day 56. For the dUCB arm, the chimerism of individual cord blood units should be reported separately.
6. dUCB Arm: Bone marrow aspirate and biopsy with chimerism studies is required at Day 21 if WBC < 500. If there is zero donor chimerism on Day 21, repeat on Day 28. At Day 28, if the the marrow is < 5% cellular and or there is zero donor chimerism, consider management of graft failure per institutional guidelines.
7. Haplo-BM Arm: if ANC is less than 500 on Day 28, a bone marrow aspirate and biopsy with chimerism studies is required. If zero donor chimerism is present at this time, consider management of graft failure per institutional guidelines.
8. Toxicity assessments at Days 28, 56, 180, 365, and 730.
9. Disease status evaluation
    a. Leukemia Patients: Disease status evaluation with at minimum CBC with differential is required at Day 730. Abnormal counts should be followed up with bone marrow biopsy or aspirate.
    b. Lymphoma Patients – CT scans or Whole Body CT/PET scan on Day 730, per NCCN guidelines.
10. Weekly CMV monitoring through Day 56.
11. HQL questionnaires to be completed by the patient at Days 365, and 730.
12. Blood samples for future research on Days 28, 56, 180, and 365.

TABLE 4.2.2: SUMMARY OF ASSESSMENTS

Study Assessments/ Testing	Baseline	Days after Transplantation																
		7	14	21	28	35	42	49	56	63	70	77	84	91	180	365	730	1095[12]
History, physical exam, height and weight	X																	
Karnofsky performance status	X								X						X	X	X	
HLA Typing	X																	
CBC[1] differential, platelet count, and blood chemistries[2]	X	X	X	X	X	X	X	X	X						X	X	X	
Infectious disease titers[3]	X																	
CMV monitoring		X	X	X	X	X	X	X	X									
EKG and LVEF or shortening fraction	X																	
DLCO, FEV1 and FEV	X																	
Bone marrow aspirate for pathology and cytogenetics and/or biopsy	X*			X[4]	X[4]													
CT scans or Whole Body CT/PET[5]	X[5]																X[5]	
Chest x-ray or chest CT	X																	
ß-HCG serum pregnancy test (females only)	X																	
GVHD assessments[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Toxicity assessments					X				X						X	X	X	
Chimerism[7]	X				X				X						X[7]			
Anti-HLA antibody crossmatch test	X																	
Blood samples for future research[8]	X[8]				X				X						X	X		
Haplo donor blood and bone marrow sample for future research[9]	X[9]																	
Health-Related Quality of Life Assessments[10]	X															X	X	
Confidential Health Insurance Form and Contact Information Form[11]	X																	
Comprehensive CIBMTR Forms														X	X	X	X	X

Notes:

[1] CBC performed at least three times a week from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28. CBC performed weekly after Day 28 until Day 56.

[2] Blood chemistries should include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, and chloride. Blood chemistries performed twice weekly until Day 28. Blood chemistries performed weekly after Day 28 until Day 56.

[3] Infectious disease titers include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.

[*] Baseline for leukemia patients only.

[4] For dUCB arm bone marrow biopsy and aspirates to pathology required at Day 21 if WBC < 500. For both dUCB arm and Haplo-BM arm Day 28 only to be done if slow neutrophil recovery to evaluate for graft failure.

[5] LYMPHOMA PATIENTS ONLY: CT scans or Whole Body CT/PET at Baseline and Day730.
[6] GVHD assessments performed weekly until Day 90 post-transplant, and then at Day 180, 365, and 730.
[7] Chimerism to be measured by standard molecular testing of a peripheral whole blood sample. FISH may only be used with haplo sex mis-matched transplants T cell chimerism is recommended. Peripheral blood for chimerism assay recommended on Day 180 if donor chimerism is less than 95% on Day 56. For the cord blood arm, chimerism of individual cord blood units should be reported separately.
[8] Baseline blood samples for future research include samples from recipient and haplo donor. See appendix C for details.
[9] Bone marrow sample for future research from Haplo-BM donors ≥18 only. See appendix C for details.
[10] See Section 2.9 for detailed description of HQL assessments.
[11] See companion study document for detailed description of Cost Effectiveness Ancillary study and Confidential Health Insurance and Contact Information forms.
[12] Day 1095 data to be obtained from the CIBMTR.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The study is designed as a Phase III, randomized, multicenter prospective comparative study of transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow (Haplo) using non-myeloablative conditioning for patients with hematologic malignancies. The target enrollment is 410 patients, 205 for each arm.

5.1.1. Accrual

It is estimated that four years of accrual will be necessary to enroll the targeted sample size.

5.1.2. Randomization

Patients will be randomized at a ratio of 1:1 between the treatment arms using permuted blocks of random sizes. Randomization will be stratified by center.

5.1.3. Primary Endpoint

The primary endpoint is the probability of PFS at 2 years post randomization. The primary analysis will be performed using the intent-to-treat principle so that all randomized patients will be included in the analysis. Death or progression will be considered failures for this endpoint.

5.1.4. Primary Hypothesis

The primary null hypothesis of the study is that there is no difference between the 2 year PFS probabilities for dUCB vs. haplo-BM.

$$H_{o:} \quad p_{dUCB} = p_{Haplo}$$

$$H_{a:} \quad p_{dUCB} \neq p_{Haplo}$$

5.2. Sample Size and Power Considerations

The primary analysis will be done using a group sequential comparison of the 2 year PFS probabilities using the difference in Kaplan-Meier estimates[21]; sequential monitoring is described further in Section 5.3. A pointwise comparison of PFS at 2 years is proposed for the primary analysis rather than a log-rank test because of the potential for crossing hazards. Phase II data indicated potentially lower TRM and higher relapse rates for the haplo-BM arm, and differential timing between these two types of events would lead to nonproportional hazards. The logrank test would have poor power to detect a difference between these two groups if the hazards cross. The time point of 2 years was chosen based on CIBMTR data which indicated

most events after UCB and haploidentical transplantation occur by 2 years. The final patient enrolled will be followed up for a minimum of 3 years, so that the targeted total study duration is 7 years (4 years accrual + 3 years follow-up on the last patient).

The targeted sample size is 410 patients, 205 per treatment arm. The baseline PFS at 2 years is assumed to be approximately 35-40% based on CIBMTR data on RIC transplantation using unrelated adult donors. We allow for 5% censoring due to loss to follow-up by 2 years in addition to administrative censoring. In addition, we anticipate up to 5% of patients will be randomized but do not make it to the assigned transplant, and for power calculations we assume that these patients will all progress or die within 6 months. The targeted sample size of 205 patients per group is sufficient to maintain type I error of 5% across all planned interim analyses (see below) while providing 80% statistical power for a two-sided test to detect a 15% increase in the PFS probability at 2 years. Note that the targeted 15% increase in PFS is the effect attributable to the transplant type itself. This translates to a slightly lower 14.25% increase in PFS in the Intention-to-Treat (ITT) populations after accounting for the 5% of patients who are randomized but do not make it to transplant. We will monitor the proportion of patients who are randomized but do not receive a transplant, and if the proportion is higher than the anticipated 5%, we will re-evaluate the sample size to account for the resulting decrease in treatment effect for the ITT populations. Details of this power calculation are found in the section on interim analyses for efficacy and futility.

5.3. Interim Analysis and Stopping Guidelines

Interim analysis for efficacy and futility will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately one year intervals. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review and are not formal "stopping rules" that would mandate automatic closure of study enrollment. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis.

5.3.1. Interim Analysis for Efficacy and Futility

Analyses will be performed as described below for the primary endpoint. At the time of each interim analysis (tentatively planned at approximately 3, 4, 5, and 6 years), a two-sided test using the difference in Kaplan-Meier estimates of the PFS at 2 years will be conducted. These test statistics have independent increments as described in Gu et al.[21] All patients randomized prior to the time of the interim analyses will be used to compute the Kaplan-Meier estimate of PFS at 2 years. If the test statistic exceeds the critical value for efficacy, the DSMB will discuss the continuation of the trial.

In order to preserve the overall Type I error rate at 5%, the critical value for the test statistic will be inflated above 1.96, the value that would be used if no repeated testing were used. Equivalently, the nominal p-value at which an observed difference is declared significant will be reduced below 0.05. The actual critical values and nominal p-values will be computed using statistical methods for group sequential testing with O'Brien Fleming type boundaries.

To permit necessary flexibility in scheduling interim analyses, the critical values will be recomputed to correspond to the actual available statistical information using the "use-function" approach of Lan and DeMets. The error spending function $\alpha(t)=\min(\alpha,\alpha t^3)$ will be used to approximate the O-Brien-Fleming boundary with unequally spaced looks.[22] Information is defined as the reciprocal of the variance of the difference in Kaplan-Meier estimates between the two treatments. The final information at the end of the study reduces to the reciprocal of the variance of the difference in two binomial proportions, assuming no censoring prior to 2 years, computed as 450.55. Then the information fraction t is the ratio of the information at an interim analysis to the final information at the end of the study.

Interim analyses for futility will start when accrual is complete, so that these analyses do not impact power for secondary endpoints. The main benefit of these interim analyses for futility is potentially shortening of the time until the study conclusions regarding two year survival are reached, since they allow for stopping prior to the completion of the two year follow-up for the last patient enrolled. The stopping rule for futility will be triggered when the conditional power to reject the null hypothesis at the observed effect size is less than 10%.

Phase II data on dUCB and haplo transplants as well as longer-term CIBMTR data on unrelated adult donor transplants with RIC indicate PFS probabilities at 6 months, 1 year, and 2 years of 65%, 47%, and 35%. We also assume that 5% of patients will be randomized but not make it to the assigned transplant, and that all of these patients will progress or die by 6 months, so that the anticipated PFS curves in the ITT population are 62%, 45%, and 33%. We also target a difference in 2 year PFS due to transplant type of 15%, which translates to a 14.25% difference in PFS at 2 years in the ITT population.

Table 5.3.1a shows the information accumulated, the critical values for efficacy and futility, and the nominal significance levels for tests conducted at interim analyses at 3, 4, 5, and 6 years from the start of the study. The information calculations assume uniform accrual of patients over 4 years with 2 years of follow-up on the final patient enrolled. The information fraction at each interim analysis comes from the reciprocal of the variance of the Kaplan-Meier estimate, which is approximated using a piecewise constant hazard function assuming PFS probabilities as described above. Interim analyses for futility are planned to start at 4 years when accrual is completed.

Table 5.3.1b shows the cumulative probability of stopping for efficacy or futility at each interim analysis from a simulation study under various scenarios, including two null hypothesis scenarios (PFS at two years of 35% in each treated group or 40% in each treated group) and under various alternative hypotheses (improvements in 2 year PFS of 10%, 15%, or 20% over baseline PFS of either 35% or 40%, corresponding to improvements in ITT population of 9.5%, 14.25%, or 19%). Simulations used 10000 Monte Carlo samples, and generated baseline survival curves from the piecewise constant hazard model as described previously. A proportional hazards model was used with hazard ratio chosen to induce the targeted increase in PFS in the ITT population for each scenario. However, note that the proportional hazards model used in the simulation has minimum impact on the operating characteristics because all analyses are based on the pointwise comparison of the 2 year PFS probabilities. In addition to administrative censoring induced by the accrual distribution and end of study time, the

simulations also accounted for additional drop out using independent exponential censoring with 5% probability of censoring by 2 years. The results indicate that there is > 50% power to detect a 15% improvement in 2 year PFS by the interim analysis at 4 years and 80% power to detect the same improvement by the final analysis. When there is no difference in two year survival there is a 76% chance of stopping for futility by the interim analysis at 4 years.

TABLE 5.3.1a CRITICAL VALUES AT EACH INTERIM ANALYSIS

Calendar time since study start (years)	Information Fraction	Critical Value for Efficacy	Nominal Type I Error	Critical value for Futility
3	0.48	3.0103	0.0013	-
4	0.74	2.4534	0.0071	1.2057
5	0.94	2.1092	0.0175	1.6881
6 (Final)	1.00	2.0551	0.0199	2.0551

TABLE 5.3.1b CUMULATIVE PROBABILITIES OF STOPPING FOR EITHER EFFICACY OR FUTILITY BY EACH INTERIM ANALYSIS UNDER VARIOUS NULL AND ALTERNATIVE SCENARIOS, FROM A SIMULATION STUDY WITH 10,000 REPLICATES

			Cumulative probability of stopping and reaching conclusion by interim analysis at x years			
2 year PFS in treated pop (ITT pop)	Diff in treated pop (ITT pop)	Conclusion	x=3	4	5	6 (Power)
35%,35% (33.2%,33.2%)	0% (0%)	Efficacy	0.004	0.019	0.044	0.051
		Futility		0.765	0.914	
40%,40% (38%,38%)	0% (0%)	Efficacy	0.003	0.017	0.041	0.048
		Futility	-	0.767	0.911	
35%,45% (33.2%,43.7%)	10% (9.5%)	Efficacy	0.056	0.232	0.430	0.479
		Futility	-	0.300	0.442	
40%,50% (38%,47.5%)	10% (9.5%)	Efficacy	0.058	0.239	0.431	0.472
		Futility	-	0.300	0.438	
35%,50% (33.2%,47.5%)	15% (14.25%)	Efficacy	0.171	0.534	0.765	0.802
		Futility	-	0.098	0.151	
40%,55% (38%,52.2%)	15% (14.25%)	Efficacy	0.188	0.551	0.770	0.802
		Futility	-	0.087	0.142	
35%,55% (33.2%,52.2%)	20% (19%)	Efficacy	0.390	0.823	0.952	0.967
		Futility	-	0.014	0.023	
40%,60% (38%,57%)	20% (19%)	Efficacy	0.432	0.838	0.953	0.964
		Futility	-	0.011	0.021	

5.3.2. Guidelines for Safety Monitoring

Monitoring of TRM, a key safety endpoint will be conducted monthly, and 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 guidelines serve as a trigger for consultation with the DSMB for additional review. The key safety endpoint to be monitored is the cumulative incidence of transplant-related mortality at Day 100. This outcome will be monitored using a Sequential Probability Ratio Test (SPRT) for binary data as described below. The SPRT conserves type I error at 5% across all of the monthly examinations. No additional control of the type I error across multiple treatment groups will be used.

The cumulative incidence of TRM at Day 100 will be monitored separately for each arm. Each month, the null hypothesis that the cumulative incidence of TRM at Day 100 is ≤ 15% will be tested against the alternative that it is > 15%. This null hypothesis value comes from CIBMTR data on RIC unrelated adult donor transplants, in which Day 100 TRM is 11% (95% confidence interval 6%-17%) for 7/8 HLA-matched unrelated peripheral blood stem cell transplants and 9% (95% confidence interval 5%-14%) for double cord blood transplants. Day 100 TRM will be monitored using a SPRT for binary outcomes. The SPRT can be represented graphically. At each interim analysis, the total number of patients enrolled is plotted against the total number of patients who have experienced transplant-related mortality. The continuation region of the SPRT is defined by two decision boundaries. Only the upper boundary will be used for monitoring the study to protect against high incidences of TRM. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that the TRM incidence is higher than predicted by the observed number of patients enrolled on study. Otherwise, the SPRT continues until enrollment reaches the target goal. The SPRT for TRM was developed from the following SPRT:

A SPRT contrasting 15% versus 25% 100-day incidence, which results in decision boundaries with a common slope of 0.197 and an upper intercept of 4.258, with nominal type I and II errors of 6% and 10%, respectively.

The actual operating characteristics of this truncated test, shown in Table 5.3.2, were determined in a simulation study that assumed uniform accrual of 205 individuals over a four-year time period.

TABLE 5.3.2: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR 100 DAY TRM FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

True 100-Day Incidence	15%	20%	25%
Probability Reject Null	0.052	0.464	0.933
Mean Month Stopped	49.6	38.7	21.7
Mean # Endpoints in 100 Days	29.6	30.2	19.9
Mean # Patients Enrolled	197.9	151.3	79.3

For example, the testing procedure for a treatment which continues into Phase III testing rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day TRM incidence is 15%, and 93% 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 $\beta = 0.07$. When the true 100-day TRM incidence is 25%, on average, the DSMB will be consulted 22 months after opening, when 20 events have been observed in 79 patients.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status (Leukemia in CR1 vs. CR2+, Lymphoma in CR vs. PR), CMV status, HCT-comorbidity index, time from diagnosis to transplantation, cytogenetic at diagnosis (AML and ALL), HLA matching, prior autologous transplant, number of regimens prior to transplant (lymphoma only), cell dose/kg, and haplo donor relationship. Between group comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test. A secondary analysis of all outcomes will adjust for age, performance status, primary disease, risk status, and CMV status, in addition to any other demographic and baseline characteristics which are statistically different between treatment arms ($p<0.1$).

5.5. Analysis Plan

5.5.1. Analysis of the Primary Endpoint

The primary outcome of the trial is PFS at 2 years after randomization. The primary null hypothesis of the study is that there is no difference in PFS between the treatment arms at 2 years. In the primary analysis, the intention-to-treat principle will be used. The primary analysis will be performed using the difference in Kaplan-Meier estimates for PFS at 2 years. A 95% confidence interval for the difference in PFS at 2 years will also be constructed.

5.5.2. Analysis of Secondary Endpoints

5.5.2.1. Secondary analysis of PFS

Several secondary analyses of PFS will be conducted. In addition to a point-wise comparison at 2 years, Kaplan-Meier curves will be constructed for each treatment arm. Additional analyses to be performed will depend on an assessment of the original assumption of nonproportional hazards assumed in the study design. A Cox proportional hazards model will be fit to PFS and graphical diagnostics and time-dependent covariates will be used to assess the presence of nonproportional hazards between treatment groups. If there is no evidence of nonproportional hazards, a relative risk will be estimated from the Cox model both unadjusted and adjusted for other covariates. If there appears to be nonproportional hazards, several analyses will be conducted. First, confidence bands for the difference in PFS will be constructed. Second, a comparison of PFS post 2 years will be conducted using the linear combination test proposed by Logan et al.[23] This method directly compares the PFS curves starting at 2 years, and accounts for patients enrolled early in the study having additional follow-up past 2 years. Finally, an adjusted analysis of PFS at 2 years will be conducted using the adjusted PFS probabilities proposed by Zhang et al.[24]. The adjusted PFS probabilities are estimated using a Cox proportional hazards model, stratified on treatment. Age, performance score, disease, disease risk, CMV status, and any other covariates which are significantly different between the treatments ($p<0.1$) will be used in any adjusted analyses. Finally, PFS will also be described in each arm from the time of transplant.

5.5.2.2. Overall survival

Overall survival curves will be estimated using the Kaplan-Meier estimator. Overall survival at 2 years will be compared between treatment arms using the difference in Kaplan-Meier estimators. A secondary analysis of survival will be performed by assessing proportional hazards and performing subsequent analysis based on the results of that assessment, using the same methods as those described in Section 5.5.2.1. Overall survival will also be described in each arm from the time of transplant.

5.5.2.3. Treatment-related mortality

Incidence of TRM will be estimated using the cumulative incidence function, treating relapse/progression as a competing risk. Incidence of TRM will be compared between the treatment arms using Gray's test.[25] In a secondary analysis, TRM will be compared between arms using a Cox proportional hazards model with treatment as the main effect. Age, performance score, disease, disease risk, CMV status, and any other baseline characteristics which are significantly different between arms will be included as covariates in the Cox model to adjust for potential imbalances. TRM will also be described in each arm from the time of transplant.

5.5.2.4. Relapse/progression

Incidence of relapse/progression will be estimated using cumulative incidence function, treating death in remission as a competing risk. Incidence of relapse/progression will be compared between the treatment arms using Gray's test. In a secondary analysis, relapse/progression rates will be compared using a Cox proportional hazards model with treatment as the main effect. Age, performance score, disease, disease risk, CMV status, and any other significantly imbalanced characteristics will be adjusted for. Relapse/progression will also be described in each arm from the time of transplant.

5.5.2.5.Hematologic recovery

Incidence of neutrophil and platelet engraftment from the time of transplant will be estimated using the cumulative incidence function with death prior to engraftment as the competing risk. Incidence of neutrophil engraftment at 56 days and incidence of platelet engraftment at 100 days will be compared between the treatment arms using a pointwise comparison of the cumulative incidence probabilities.

5.5.2.6. Donor cell engraftment

Donor chimerism at Days 28 and 56 after transplantation in each treatment arm will be described numerically as median and range for those evaluable as well as according to proportions with full (> 95%), mixed (5-95% donor cells), graft rejection (< 5%), or death prior to assessment of donor chimerism. The proportions alive with ≥ 5% donor chimerism will be compared between the two groups using the chi-square test.

5.5.2.7. Acute GVHD of grades II-IV and III-IV

Cumulative incidence of acute GVHD will be estimated from the time of transplant using the cumulative incidence function, treating death prior to acute GVHD as the competing risk. Cumulative incidence of acute GVHD will be compared between treatment arms using Gray's test.

5.5.2.8. Chronic GVHD

Cumulative incidence of chronic GVHD from the time of transplant will be estimated using the cumulative incidence function, treating death prior to chronic GVHD as the competing risk. Cumulative incidence of chronic GVHD will be compared between treatment arms using Gray's test.

5.5.2.9. Incidence of primary graft failure

The proportions of patients alive at Day 56 but with primary graft failure will be described and compared between the treatment arms using the chi-square test or Fisher's exact test as appropriate.

5.5.2.10. Incidence of secondary graft failure

The cumulative incidence of secondary graft failure out of those who had initial engraftment will be described using the cumulative incidence estimator, treating death and disease relapse/progression prior to secondary graft failure as a competing event.

5.5.2.11. Incidence of toxicities grade ≥ 3 per CTCAE version 4.0

All Grade ≥ 3 toxicities will be tabulated by grade for each treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as well as cumulative over time.

The cumulative incidence of Grade ≥ 3 toxicity will be compared between treatment arms at Days 28, 56, 180, 365, and 730.

5.5.2.12. Incidence of infections

The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after transplant. The cumulative incidence of severe, life-threatening, or fatal infections, treating death as a competing event, will be compared between the two treatment arms at 6, 12, and 24 months. A secondary analysis of infections requiring hospitalization will be conducted in a similar way.

5.5.2.13. Hospital admission and length of stay

The number of hospital readmissions, the number of patients experiencing hospital readmissions, and the average length of stay for both hospital readmissions and the initial transplant hospitalization will be described. The number of days alive and not hospitalized will be used to examine the total duration of hospitalization in the first 6 months accounting for mortality. These distributions will be compared between the two groups using Mann-Whitney tests.

5.5.2.14. Health-Related Quality of life

HQL at each time point will be summarized using simple descriptive statistics (mean, SD). HQL among survivors at each time point will be compared between treatment arms in an initial analysis using two sample t-statistics. The missing data pattern of the HQL measurements will be examined using graphical techniques and logistic regression models conditional on survival. At each time point, estimates of the difference in HQL between the treatments conditional on survival at that time point will be obtained using inverse probability of censoring weighting with independent estimating equations[26] to account for missing data.

5.6.Subgroup Analysis

Subgroup analyses will be conducted for 2 year PFS according to disease, disease risk and age. Interaction tests between treatment group and subgroup will be conducted using a logistic regression model with treatment, subgroup, and a treatment*subgroup interaction term. If there

is censoring present prior to 2 years, a logistic regression model for 2 year PFS using pseudovalues will be used. A Bonferroni adjusted significance level of 0.05/3=0.0167 will be used for each interaction test to account for multiple testing. If a significant interaction is identified, plots of Kaplan-Meier estimates of PFS by treatment will be shown separately for each level of the subgroup.

CHAPTER 6

6. ETHICS AND REGULATORY

6.1. Good Clinical Practice Guidelines

The DCC and the clinical investigators assure that the clinical study is performed in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996, the Declaration of Helsinki (Recommendations guiding physicians in Biomedical Research involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000, Seoul 2008, Fortaleza 2013) and applicable regulatory requirements.

6.1.1. Patient Consent

A conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principal investigator or other designated physician.

6.1.2. Patient Withdrawal

6.1.2.1. Patient withdrawal from intervention

Participation in the trial is voluntary. Patients will be advised that they may voluntarily withdraw from the study at any time and will be instructed to notify the investigator. Patients may choose to withdraw for any reason(s). Patients are not obligated to reveal their reason(s) for withdrawal to the DCC.

6.1.2.2. Patient withdrawal from data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected and notified to the DCC in writing. In this event details should be recorded in the patient's hospital records, no further CRFs must be completed and no further data sent to the sponsor.

6.1.2.3. Patient Removal From Study

The investigator has the right to terminate the participation of any subject at any time, if s/he deems it in the partients's best interest. The reason and circumstances for study discontinuation will be documented by the site and sent to the DCC.

Reasons for study discontinuation might be:

- Intolerable side effects of the study product.

- Changes in medical status of the patient such that the Investigator believes that patient safety will be compromised or that it would be in the best interest of the patient to stop
  treatment.
- Pregnancy.
- Withdrawal of consent.
- Relevant non-compliance with the protocol.

6.1.3. Confidentiality

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

6.1.4. 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 leukemia and lymphoma in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

6.2. Protocol Amendments

All protocol amendments containing substantive changes must be reviewed and accepted by members of the DSMB before distribution to Clinical Centers. The review may take place at a DSMB meeting, on an arranged conference call, or by ballot.

Once approved by the DSMB, participating centers (and the FDA if applicable) will be notified of approved protocol amendments by an e-mail announcement from the DCC. Amendment documents may be included with the e-mail announcement and will be posted on the BMT CTN website. The documents will include:

1. A summary of protocol changes
2. A revised protocol with changes highlighted
3. A second version with the changes fully incorporated into the document
4. A rationale for changes may be provided

Other types of amendments containing non-substantive changes may be released to Centers before DSMB notification or deliberation. These changes will be reviewed at the next regularly scheduled DSMB meeting or conference call.

The DCC PIs will determine the appropriate review process in collaboration with the NHLBI Project Officer.

Clinical Centers are responsible for implementing all amendments according to institutional policy.

6.3. Protocol Deviations

Clinical centers should inform the DCC of any major protocol deviations. These will be submitted to the DSMB on a semi-annual basis.

6.4. Premature Termination of the Trial

The sponsor has the right to discontinue the study due to relevant medical or administrative reasons. Participants who still receive medication during the time of discontinuation will undergo a final visit which has to be documented in the CRF.

Possible reasons for discontinuation by the sponsor are:

- failure in recruiting participants,
- data quality is insufficient,
- unforeseen circumstances at the study site that make the continuation of the study impossible,
- early prove of superiority or non-inferiority of a treatment group,
- occurrence of unjustifiable risks or toxicity,
- new scientific knowledge that does not justify continuation of the clinical study.

6.5. Publication Policy

Manuscripts reporting the results of this trial will be prepared and submitted to a reputable peer-reviewed medical journal in accordance with basic ethical principles, including preservation of the accuracy of the results and making both positive and negative results publicly available. In all publications the confidentiality of patients' data will be ensured.

Data analysis and authorship will be conducted according to the BMT CTN MOP. No clinical trial results are released, presented or published without approval from the Publications Committee, the BMT CTN DCC, NHLBI and NCI.

The study is registered in the clinical trials database (www.clinicaltrials.gov) which is accessible to the public. The ClinicalTrials.gov number NCT01597778 allocated to this trial will be quoted in any publications resulting from this trial.

By signing this study protocol, the investigators accept that the results of this clinical trial can be presented to national and international authorities. They also accept that in this context their name, address, qualification and grade of involvement in this trial will be published

APPENDIX A

ABBREVIATIONS

APPENDIX A

ABBREVIATIONS

AdvantageEDC^{SM} – Proprietary electronic data capture system
AE – Adverse Event
ALL – Acute Lymphoblastic Leukemia
ALT – Alanine Aminotransferase
AML – Acute Myeloid Leukemia
ANC – Absolute Neutrophil Count
AST – Aspartate Aminotransferase
B-ALL – Acute B Lymphoblastic Leukemia
BM – Bone Marrow
BMT CTN – Blood and Marrow Transplant Clinical Trials Network
RIC – Reduced Intensity Conditioning
CBC – Complete Blood Count
CCr – Creatinine Clearance Rate
CD15 – Cluster of Differentiation 15
CD3 - Cluster of Differentiation 3
CD33 - Cluster of Differentiation 33
CDC – Centers for Disease Control
CEA – Cost Effectiveness Analysis
cGVHD – Chronic Graft Versus Host Disease
cGY - Centigray
CHOP±R – Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone +/- Rituximab
CI – Confidence Interval
CIBMTR – Center for International Blood and Marrow Transplant Research
CMV - Cytomegalovirus
CNS – Central Nervous System
CR - Complete Remission
CsA – Cyclosporin A
CT – Computed Tomography
CTCAE – Common Terminology Criteria for Adverse Events
CVP±R – Cyclophosphamide/Vincristine Sulfate/Prednisone +/- Rituximab
DCC – Data and Coordinating Center
DHAP±R – Dexamethasone/Cytarabine/Cisplatin +/- Rituximab
DLCO – Diffusing Capacity of the Lung for Carbon Monoxide
DLI – Donor Lymphocyte Infusion
DMSO – Dimethyl Sulfoxide
DNA – Deoxyribonucleic Acid
DSMB – Data Safety Monitoring Board
dUCB – Double Umbilical Cord Blood
EBV – Epstein Barr Virus
EKG - Electrocardiogram
ESHAP±R – Etoposide, Methylprednisolone, Cytarabine, Cisplatin +/- Rituximab
FDA – Food and Drug Administration

FDG - Flurodeoxyglucose
FEV1 – Forced Expiratory Volume 1
FHCRC – Fred Hutchinson Cancer Research Center
FISH – Fluorescence In Situ Hybridization
FK-506 - Tacrolimus
FLAG – Fludarabine+High-dose Cytarabine+G-CSF
FLT3-ITD – FLT3-Internal Tandem Duplication
FLT3-TKD – FLT3- Tyrosine Kinase Domain
FVC – Forced Vital Capacity
G-CSF – Granulocyte Colony Stimulating Factor
GFR – Glomerular Filtration Rate
GI - Gastrointestinal
GINA – Genetic Information Nondiscrimination Act
GVHD – Graft versus Host Disease
haplo-BM – Haploidentical Bone Marrow
HCG – Human Chorionic Gonadotropin
HCT-comorbidity – Hematopoietic Cell Transplant Comorbidity
HepA – Hepatitis A
HepB – Hepatitis B
HepC – Hepatitis C
HHV-6 – Human Herpesvirus 6
HiDAc – High Dose Intermittent Ara-C
HIPAA – Health Insurance Portability and Accountability Act
HIV – Human Immunodeficiency Virus
HLA – Human Leukocyte Antigen
HPLC – High Performance Liquid Chromatography
HQL – Health-related Quality of Life
HSCT – Hematopoietic Stem Cell Transplant
HTLV1 – Human T-Lymphotrophic Virus 1
IBW – Ideal Body Weight
ICE±R – Ifosfamide+Carboplatin+Etoposide+/- Rituximab
IRBs – Institutional Review Boards
ITT – Intension To Treat
IUD – Intrauterine Device
IV - Intravenous
LDH – Lactate Dehydrogenase
MDS – Myelodysplastic Syndrome
MMF – Mycophenolate Mofetil
MOP – Manual of Procedures
MUD – Matched Unrelated Donor
NCBI – National Center for Biotechnology Information
NCCN – National Comprehensive Cancer Network
NCI – National Cancer Institute
NIH – National Institutes of Health
NMDP – National Marrow Donor Program
OHRP – Office for Human Research Protections

OS – Overall Survival
PCR – Polymerase Chain Reaction
PET – Positron Emission Tomography
PFS – Progression Free Survival
PI – Principal Investigator
PO – Per Os (by mouth)
PR – Partial Response
QALY – Quality-adjusted Life Year
RBC – Red Blood Cell
SCTOD – Stem Cell Therapeutic Outcomes Database
SD – Standard Deviation
SPRT – Sequential Probability Ratio Test
T-ALL – T-cell Acute Lymphoblastic Leukemia
TBI – Total Body Irradiation
TID – ter in die (three times/day)
TRM – Treatment Related Mortality
UCB – Umbilical Cord Blood
ULN – Upper Limit of Normal
WBC – White Blood Cell

APPENDIX B

CONSENT FORMS

PATIENT INFORMED CONSENT

DONOR INFORMED CONSENT

DONOR ASSENT

Informed Consent to Participate in Research

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity(RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Your Name: _____

Study Title: A Multi-Center, Phase III, Randomized Trial of Reduced Intensity(RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Protocol: BMT CTN #1101

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

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

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this research because we want to learn more about reduced-intensity transplants that use a mismatched donor. These results will help us understand if one kind of mismatched donor is better or if there is no difference at all.

This study will take at least 4 years and will include about 400 participants. Your study participation will last for **3 years** after your transplant.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

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

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

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

A stem cell transplant is the only treatment at this time that may cure your disease. An **allogeneic** transplant uses blood-making cells from a family member or an unrelated

donor to remove and replace your abnormal blood cells. Your doctor may recommend that you have a transplant that uses lower amounts of chemotherapy and radiation. This type of transplant is also called a **reduced intensity**, **non-myeloablative**, or "**mini**" transplant. Because of your age or health problems and because you do not have a matched donor, you may have a higher chance of health problems from a standard stem cell transplant that uses high doses of chemotherapy and/or radiation.

Recent studies by the BMT CTN suggest the results are very similar for reduced-intensity transplants when they use either mismatched cord blood or use mismatched bone marrow from a family member.

There is no guarantee or promise that this procedure will be successful.

3. Study Purpose

We are inviting you to take part in this study because you have a cancer of the blood or lymph glands and a stem cell transplant is a treatment option.

Tissue typing shows that you do not have a completely matched donor available in your family. You also do not have a matched donor outside of your family who can donate when you need them to. However, you do have two other donor choices available for a transplant: (1) partially matched units of unrelated cord blood, and (2) a family donor who is a partial match.

We are doing this research to learn more about reduced-intensity transplants that use a mismatched donor. We will use either cord blood from an unrelated donor or bone marrow from a family member, and then compare the transplant results.

These results will help us understand if one kind of mismatched donor is better or if there is no difference at all.

4. Right to Ask Questions and/or Withdraw

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

[insert contact info for site PI]

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

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

5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for several years after you finish your treatment.

Before You Start Your Treatment

We will ask you to take quality of life surveys. The surveys will ask about:

- Any side effects of your treatment
- Any health problems
- How well you can do things that are important to you
- How you relate to other people
- Your feelings.

You may skip any questions you wish.

We will also ask you to provide optional Blood Samples for Future Research (see **Section 18: Optional Blood Samples for Future Research**).

Randomization

We will use a computer to randomly assign you to 1 of 2 study groups. One group will receive partially matched cord blood from an unrelated donor, and one group will receive bone marrow from a partially matched family member. You will have an equal chance of being placed in either group.

During Your Treatment

- **Conditioning Regimen Before Transplant (chemotherapy and radiation)**

You will be treated with a type of chemotherapy called **fludarabine**, which is given daily for 5 days. If you receive cord blood, you will also be given a type of chemotherapy called **cyclophosphamide** for 1 day. If you receive bone marrow, you will be given cyclophosphamide for 2 days.

After the chemotherapy is completed, you will receive a small dose of radiation to your whole body (**Total Body Irradiation**) in a single dose. The chemotherapy and radiation may cause side effects. Some of these side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

If you receive cord blood, and have not had cytotoxic chemotherapy within the last 3 months or an autologous transplant within the last 2 years, you will receive a slightly higher dose of radiation (300 cGy instead of 200 cGy). This slightly higher dose of radiation has shown hematopoietic recovery is comparable to that seen with low dose radiation for patients who have had chemotherapy in the last 3 months or an autologous transplant in the last 2 years.

- **Reinfusion of Stem Cells (Transplant)**

On your transplant day, if you receive cord blood, it will be given to you through your catheter like a blood transfusion. If you receive bone marrow, your family donor will have his or her marrow collected in the operating room. The donated marrow may be taken to a laboratory where red cells will be removed. The donor cells will be given to you through your catheter and will travel to your bone marrow where they will start to make healthy, new blood cells.

If you receive cord blood you will start to take the immune suppressing drugs **cyclosporine** and **mycophenolate mofetil (MMF)** for 3 days before transplant. These drugs may help prevent a complication called **graft versus host disease** (**GVHD;** see **Section 6: Risks and Discomforts**).

If you receive bone marrow, you will be given another dose of cyclophosphamide on Days 3 and 4 after your transplant. You will start to take the immune suppressing drugs **tacrolimus** and MMF to help prevent GVHD on Day 5 after your transplant.

In both study groups (partially matched cord blood from an unrelated donor or bone marrow from a partially matched family member), you will continue to take MMF for about 5 weeks and cyclosporine or tacrolimus for up to 6 months.

If you receive cord blood, you will be given **filgrastim (G-CSF)** through your catheter or by injection under your skin beginning on day 1 after your transplant. If you receive bone marrow, you will be given filgrastim (G-CSF) beginning on Day 5 after your transplant. Filgrastim speeds up the recovery of white blood cells. In both study groups, you will receive filgrastim daily until your white blood cells have recovered.

The immune suppressing drugs and filgrastim may cause side effects. These side effects may be life-threatening (see **Section 6: Risks and Discomforts**).

If needed, you will receive blood transfusions to maintain normal blood cell levels and antibiotics to treat or prevent infection. You may also receive extra nutrients and pain drugs during or after your transplant. They will be given to you through your catheter.

- **Health Evaluations**

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

Health evaluations after treatment:

1) Physical exam to assess toxicities, and infections weekly until Day 56 and then at Days 180, 365, and 730.
2) Physical exam to assess GVHD weekly until Day 90 and then at Days 180, 365, and 730.
3) Routine blood tests (cell counts and liver and kidney function) weekly until Day 56 and then at Days 180, 365, and 730.
4) Blood or bone marrow tests to find the amount of donor cells in your body on Days 28 and 56. This is also called *chimerism*.
5) Restaging tests to see how much cancer you have after treatment on Day 730.
6) A quality of life survey (see Before You Start Your Treatment**)** at Days 365 and 730.
7) Optional blood samples for future research (see **Section 19: Blood Samples for Future Research**).

- **Long-term follow-up**

Data regarding your clinical situation after 2 years may be obtained from the CIBMTR, which captures information on all US transplants.

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to very serious.

The risks and discomforts in participating in this study will be similar to what you may have with blood or marrow cell transplant if you do not participate in this trial. Other complications from transplants, such as graft-versus-host disease (GVHD) and infections happen equally in patients who have either type of regimen.

Your health care team will give you medicines to help lower side effects such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or may never go away.

Risks Related to Medications or Total Body Irradiation Used in Conditioning Regimens

All chemotherapy and radiation treatments used as conditioning regimens in this study are commonly used in allogeneic hematopoietic cell transplantation.

TABLE 1 – Risks and Side Effects

Likely	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Cyclophosphamide (Cytoxan®)

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with increased risk of infection ▪ Temporary hair loss ▪ Nausea ▪ Vomiting ▪ Loss of appetite ▪ Sores in mouth or on lips ▪ Diarrhea ▪ Stopping of menstrual periods in women ▪ Decreased sperm production in men ▪ Decreased platelet count (mild) with increased risk of bleeding ▪ Blood in urine	▪ Anemia ▪ Temporary tiredness ▪ Damage to the fetus if you become pregnant while taking drug	▪ Scarring of lung tissue, with cough and shortness of breath ▪ Severe heart muscle injury and death at very high doses ▪ New (secondary) cancers

Fludarabine (Fludara®)

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with risk of infection ▪ Decreased platelet count with increased risk of bleeding ▪ Anemia ▪ Tiredness ▪ Nausea ▪ Vomiting	▪ Diarrhea ▪ Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet ▪ Changes in vision	▪ Pneumonia ▪ Agitation or nervousness ▪ Confusion ▪ Cough ▪ Difficulty breathing ▪ Weakness ▪ Severe brain injury and death

Filgrastim (G-CSF; Neupogen®)

Likely	Less Likely	Rare, but Serious
▪ Ache or pain inside the bones ▪ Increased levels of liver enzymes and uric acid in the blood ▪ Low number of platelets in the blood ▪ Headache ▪ Tiredness	▪ Local irritation (skin) at the injection site ▪ Nausea	▪ Allergic reaction ▪ Low fever ▪ Enlargement or rupture of the spleen ▪ Worsening of pre-existing skin rashes

Mycophenolate mofetil (MMF; CellCept®)

Likely	Less Likely	Rare, but Serious
▪ Miscarriage ▪ Birth defects ▪ Diarrhea ▪ Damage to unborn baby ▪ Limited effectiveness of birth control ▪ Stomach pain ▪ Upset stomach ▪ Vomiting ▪ Headache ▪ Tremors ▪ Low white blood cell count with increased risk of infection ▪ Increased blood cholesterols ▪ Swelling of the hands, feet, ankles, or lower legs	▪ Anemia ▪ Rash ▪ Difficulty falling asleep or staying asleep ▪ Dizziness ▪ Uncontrollable hand shakes	▪ Difficulty breathing ▪ Unusual bruising ▪ Fast heartbeat ▪ Excessive tiredness ▪ Weakness ▪ Blood in stool ▪ Bloody vomit ▪ Change in vision ▪ Secondary cancers, such as lymphoproliferative disease or lymphoma ▪ Progressive Multifocal Leukoencephalopathy

Total Body Irradiation

Likely	Less Likely	Rare, but Serious
▪ Fatigue ▪ Hair loss ▪ Infertility ▪ Loss of appetite ▪ Mouth sores ▪ Nausea	▪ Vomiting ▪ Cataracts ▪ Inflammation of the parotid glands ▪ Skin pigmentation (reversible) ▪ Stunted Growth ▪ Low white blood cell count with increased risk of infection ▪ Low platelet count with increased risk of bleeding ▪ Anemia	▪ Diarrhea ▪ Lung fibrosis ▪ Second cancers

Tacrolimus (Prograf®; FK-506)/Cyclosporine

Likely	Less Likely	Rare, but Serious
▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors ▪ Increases in cholesterol and triglyceride	▪ Nausea ▪ Vomiting ▪ Liver problems ▪ Changes in how clearly one can think ▪ Insomnia ▪ Unwanted hair growth ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Dizziness ▪ Red blood cell destruction

It is very important that you do not eat grapefruit or drink grapefruit juice while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are *Fresca, Squirt,* and *Sunny Delight*.

Risks and Toxicities Related to Transplant

The following problems may occur as a result of cord blood or marrow transplant. These risks may occur whether a transplant was done as part of the study or not:

1. Slow recovery of blood counts. The red blood cells, white blood cells, and platelets can be slow to recover after blood or marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. To speed the recovery of the white cells as much as possible you will receive Filgrastim.

2. Graft failure. The cord blood or bone marrow stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10-15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. If your counts do not recover, you may need to receive a second transplant. Graft failure can be fatal.

3. Graft-Versus-Host Disease (GVHD). GVHD results from the bone marrow or cord blood cells in the graft recognizing your body as foreign and attacking it. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it.

Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

4. Other complications. Other complications may include:

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

b. Serious infections. Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will be prescribed certain drugs to reduce the chance of those infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

c. Relapse of disease or a new blood cancer. Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases, a new blood cancer may develop from the donor cells. Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10

years after treatment, or 6 years on average.

The risk of developing a new blood cancer after allogeneic blood or marrow transplant is probably less than 2%. However, if you receive bone marrow, your donor's marrow is exposed to the chemotherapy drug, cyclophosphamide, after the transplant. There is a risk that a blood cancer may develop in your donor's blood cells. This risk is unknown, but it may be as high as 5%. If cancer develops in your donor's blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

d. Risk to the unborn. The treatments in this study have <u>not</u> been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must refrain from all acts of vaginal sex (abstinence) or use two forms of effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD. Effective birth control is defined as the following:

1. Consistent use of birth control pills
2. Injectable birth control methods (Depo-Provera, Norplant)
3. Tubal sterilization or male partner who has undergone a vasectomy
4. Placement of an IUD (intrauterine device)
5. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

<u>Reproductive Risks</u>

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

If you are a woman and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use two effective methods of birth control or abstinence during your transplant and continue until you are finished with your GVHD prevention treatment.

If you are a man, your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

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

<u>Unforeseen Risks</u>

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about reduced-intensity transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

Additional Information about MMF

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills less effective and increase your chances of becoming pregnant while you are taking it.
- If you could become pregnant, you must use 2 effective forms of birth control or abstinence for 4 weeks before starting MMF, during treatment, and for 6 weeks after stopping MMF.
- In this study, you will be assigned to receive MMF for about 5 weeks, so you should not become pregnant during that time. If you think you might be pregnant or could be become pregnant during the upcoming 5 weeks, you should not join the study.

Other Treatments or Drugs

Some drugs react with each other. It is important to tell the study doctor or staff about any other drugs or treatments you are taking. This includes over-the-counter drugs, vitamins and herbal treatments.

It is also important that you tell the study staff about changes to any of your drugs during the study.

For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

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

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant
- An allogeneic blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about reduced-intensity transplant as a treatment for people with a blood cancer and who have a mismatched donor. This information could help people with a blood cancer who may need a transplant in the future.

9. New Information Available During the Study

During this study, the study doctors may learn new information about the study drug or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer take part in the study, or that you may not want to continue in the study.

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

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

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

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

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

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)
- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- Study investigators

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

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

11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.

- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs (see **Section 6: Risks and Discomforts**) too soon after transplant, your body could reject the donor stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

- If you decide to leave this study after the start of treatment, or your doctor asks you to leave the study for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study results, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

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

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to receive payment by signing this Consent Form.

13. Compensation or Payment

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

14. Costs and Reimbursements

Most of the visits for this study are standard medical care for your allogeneic transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for the costs of standard treatment in this study.

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

You or your insurance will not be charged for tests that are only done for research on this study.

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

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

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

15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert name and contact detail]

16. Contact Someone about Your Rights

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

[Insert appropriate contact details]

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

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

17. Cost-effectiveness Research

Study purpose: The study doctors want to learn more about the costs of the two types of transplant that are being tested in the larger transplant study: 1) partially matched units of unrelated cord blood and 2) family donors who are a partial match. This research will help doctors know which type of transplant is more cost effective.

Lead study doctor: Scott Ramsey of the Fred Hutchinson Cancer Research Center in Seattle is the lead study doctor for the cost-effectiveness research. Dr. Ramsey is a medical doctor and well-known health economist.

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

1) Type

2) Provider

3) Policy number

4) Group number

5) Policy holder's name and date of birth

We will also want to know about your out-of-pocket transplant costs (costs not covered by your insurance). The out-of-pocket costs you and your family have to cover are important in understanding the overall cost of transplant, so we want to collect information this information as well. For example, we want to know how much you spend on:

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

2) Travel and lodging

3) Cost of time away from work for both you and your caregivers (family and friends).

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

How we will use your health insurance information: After you have finished the transplant study, we will use your insurance information to learn about the reimbursements your health insurer made and calculate the cost of your transplant. Illness and transplant-related costs happen before the transplant and go on for many years after, so we want to collect reimbursement information for the 12 months before your transplant, and for the 2 years following.

Privacy, confidentiality and use of information: Only the study doctors at the Fred Hutchinson Cancer Research Center will have access to your health insurance and out-of-pocket cost information (study data). To maintain your confidentiality, we will not link your name to the study data. Also, all of the study doctors signed a confidentiality agreement and promised to keep electronic data protected under passwords and physical data (paper or other media such as CDs) in secure facilities (for example, on-campus locked offices and locked filing cabinets).

Collecting the study data: We will collect your health insurance and out-of-pocket information using an online questionnaire and diary. You will get a user ID number and password to log on to the system. The system was designed to be very user friendly, but we will help you with the online questionnaire and diary over the phone if needed. We will also send email reminders. The option to complete a mail-out survey will also be available.

As stated above, <u>we will collect reimbursement information starting 12 months before your transplant until 2 years after.</u>

<u>We will collect out-of-pocket costs 1 month after your transplant, and again 4 and 7 months after your transplant date</u>. We think each online entry will take between 5 and 25 minutes, but this depends on how much information there is to enter.

Help from your caregiver(s): We ask that you give us the name(s) and contact information of your main caregiver(s). This

may be your spouse, partner, parent, adult child or sibling, and friends. You may not feel like using the online diary when you're recovering from your transplant, so we ask that your caregiver(s) help enter this information

We also want to know the time your caregiver(s) spend caring for you after your transplant and the time they spend away from work or school.

Be sure to talk to your caregiver(s) about this study and get their permission before giving us their name and contact information. If you give us the name of your caregiver(s), we will explain the study to them and what they would need to do. They will also get their own consent form to participate in this study.

Risks to participating: The risks to participating in the cost-effectiveness study are small. We will make every effort to keep your health insurance and out-of-pocket cost information private. We will only use this data to get reimbursement information. A possible risk is the loss of confidentiality about your medical information, but the chance of this happening is very small.

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

If you provide out-of-pocket costs, we will give you a summary of these costs at the end of the study. This may be helpful information for tax reporting.

Right to ask questions and/or withdraw: You do not have to be part of the cost-effectiveness research study. Your involvement is totally voluntary and deciding not to be part of this study will not affect the medical care or services you are receiving. You can also leave the study at any time.

For more information: Jordan Steelquist, Fred Hutchinson Cancer Research Center, Seattle (206)-267-7438 or email:jsteelqu@fredhutch.org.

18. Blood Samples for Research (Optional)

This section of the informed consent form is about future research studies that will use blood samples from people who are taking part in the main study. You may choose to give blood samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give blood samples for future research studies.

There are no major risks associated with drawing blood. Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In rare cases, a blood draw

can cause fainting. Only trained people will draw your blood.

If you agree to provide blood samples, here is what will happen:

a.) We will collect five extra blood samples at the same time you have routine blood tests done. The amount of blood collected from you is about 4 tablespoons (50mL) each time. If you weigh less than 50 kg, the amount of blood collected will be based on your weight (1 mL per kg).

b.) We will collect samples at five different dates in the study: Prior to transplant, Day 28, Day 56, Day 180, and Day 365.

c.) The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to your name or other identifying information by future researchers testing your samples.

d.) Samples stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical information will be made available outside of this network.

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

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

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

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

- We will only store samples from people who give us permission.
- Research is meant to gain knowledge that my help people in the future. You will not

get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.

- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.
- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

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

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

Health Insurance Portability and Accountability Act 1 (HIPAA[1]) Authorization to use and disclose research purpose

A. Purpose:

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

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

B. Individual Health Information to be Used or Disclosed:

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

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

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

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

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

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

Principal Investigator and the researcher's staff

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data and coordinating center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration

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

(FDA) and the Office of Human Research Protections (OHRP)

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

E. Right to Refuse to Sign this Authorization:

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

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

F. Right to Revoke:

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

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

G. Potential for Re-disclosure:

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

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

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

PROTOCOL NUMBER: BMT CTN #1101

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

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____
Participant Name Date

_____ _____
Signature Date

Statement of Consent for Cost Effectiveness Research

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

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

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

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

_____ _____

Signature Date

Statement of Consent for Research Samples

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

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

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

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

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

_____ _____

Signature Date

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

_____ _____

Name of Counseling Physician Date

_____ _____

Signature of Counseling Physician Date

Donor Informed Consent to Participate in Research

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Your name:_____

Study Title: Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

Protocol: BMT CTN #1101

Co-Investigator: Ephraim Fuchs, M.D.
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Co-Investigator: Paul O'Donnell, M.D., Ph.D.
Massachusetts General Hospital Cancer Center55 Fruit St, Boston, MA 012141Phone: 508-274-7430Email: pvodonnell@mgh.harvard.edu

Co-Investigator: Claudio Brunstein, M.D.
University of Minnesota Medical Center
420 Delaware Street SE, MMC 286, Minneapolis, MN 55455
Phone: 612-624-5620 Email: bruns072@umn.edu

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

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

1. Introduction

This informed consent form is about future research studies. These studies will use blood and bone marrow samples from people who take part in the main study titled BMT CTN #1101. You must be 18 years of age or older to give bone marrow samples for future research.

You may choose to give blood and marrow samples for these future research studies if you want to. Your family member can still be a part of the main study even if you say 'no' to giving blood and marrow samples for future research.

The main study will use either umbilical cord blood (cord blood) from an unrelated donor or bone marrow from a family member (you), and then compare the transplant results. These results will help us understand if one kind of mismatched donor is better or if there is no difference at all.

If you agree to give blood and marrow samples (marrow from donors 18 and older only) , we will collect the blood sample at the same time you have routine blood tests done and the marrow sample at the same time you donate marrow. We hope to collect samples from 200 bone marrow donors who are a part of the main BMT CTN #1101 study.

This Consent Form will tell you about the purpose of the samples for future research, the possible risks and benefits, other options available to you, and your rights as a research participant.

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

- Being in any research study is voluntary.
- You will not directly benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you give blood and marrow samples for future research, you can change your mind at any time.
- If you decide to quit the study, it will not affect your care or the care of your family member at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to provide blood and marrow samples for future research. If you decide to join, please sign and date the end of the Consent Form.

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

We wish to collect blood and marrow samples from donors (marrow from donors age 18 and older only) to be used in future research. The research that may be done with your blood and marrow is not designed to help you but it may help people who have cancer or other diseases in the future

2. Study Purpose

We are collecting extra blood and marrow samples for future research because we want to learn more about reduced-intensity transplants that use a mismatched donor.

Samples may also be used in the future by researchers with the BMT CTN and other organizations

3. Right to Ask Questions and/or Withdraw

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

[insert contact info]

Giving blood and marrow samples for future research is voluntary. You can choose not to give samples, or change your mind at any time. If you choose not to take part or change your mind, it will not affect your donation process or the treatment of your family member in the main study in any way.

If you change your mind, your blood and marrow samples will not be used for other research studies or tested further.

Your study doctor and study staff will be available to answer any questions that you may have about giving samples for future research.

4. Study Treatments and Tests

If you agree to give blood and marrow samples (marrow from donors age 18 and older only), here is what will happen:

a.) We will collect 1 extra blood sample at the same time you have routine blood tests done. The amount of blood collected from you is about 4 tablespoons (50 mL). If you weigh less than 50 kg, the amount of blood collected will be based on your weight (1 mL per kg).

b.) If you are age 18 or older, we will also collect up to 1 tablespoon (10 mL) of bone marrow when you donate for your family member. 3-5 mL will be saved for future research.

c.) The blood and marrow samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores, and sends out samples for approved studies. All samples will be given a unique bar code that cannot be linked to you by researchers testing your samples.

d.) Samples stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

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

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

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

or link you to your information or research samples.

5. Risks and Discomforts

There are no major risks to having your blood drawn. It can be uncomfortable to have your blood taken and it can sometimes leave a bruise. In rare cases, you might faint. Only trained people will take your blood.

There is not a major risk to give extra research samples of bone marrow when the samples are collected at the same time you donate bone marrow.

Information about the bone marrow donation process for this study can be found in a separate consent form. Your transplant doctor or study coordinator will give you a copy of the donation consent form.

The donation consent form has more information about the steps to donate, and the risks and side effects of the donation process. Only trained people will collect your bone marrow.

6. Possible Benefits

You will not directly benefit from taking part in this study. The information from this study will help doctors learn more about reduced-intensity transplant as a treatment for people with a blood cancer and who have a mismatched donor. This information could help people with blood cancers who may need a transplant in the future.

7. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and

confidential. (Name of Transplant Center) and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

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

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

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

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

8. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the blood draw or the marrow collection. The study sponsor may decide to end the study at any time. If we ask you to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You become unable to donate bone marrow to your family member.
- The study is stopped for any reason.

9. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ [investigator's name(s)] or study staff if you feel that you have been injured because you provided blood and marrow samples for future research. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get all available medical treatment if you are injured as a result providing blood and marrow samples for future research. You, or your health plan, or your family member's health plan will be charged for this treatment. The study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this Consent Form.

10. Payment and Study Costs

You will not be paid for your participation in the research study or for providing blood and marrow samples for future research. You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

The visits to collect these samples are standard for bone marrow donors and will be billed to your family member's insurance company.

Your family member's insurance will not be charged for tests that are only done for research on this study. The costs of shipping and storing your blood and bone marrow samples will be paid by the BMT CTN.

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

11. For More Study Information

If you need more information about providing blood and marrow samples for future research, or if you have problems while you are participating in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert name and contact details].

12. Contact Someone About Your Rights

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

[Insert appropriate contact details].

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

For more information about your rights about providing blood and marrow samples for future research, call the _____[name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

Health Insurance Portability and Accountability Act (HIPAA)[2] Authorization to use and disclose research purpose

A. Purpose:

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

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

B. Individual Health Information to be Used or Disclosed:

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

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information:

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

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

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

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

Principal Investigator and the researcher's staff

<u>Study Sponsors</u>

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center

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

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

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

E. Right to Refuse to Sign this Authorization:

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

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

F. Right to Revoke:

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

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

G. Potential for Re-disclosure:

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

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

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: Reduced Intensity (RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies

PROTOCOL NUMBER: BMT CTN #1101

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I have read and understood this Consent Form. The nature and purpose of providing blood and marrow samples for future research has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to give blood and marrow samples (marrow samples from donors age 18 and older only) for future research.
- I understand that I may not directly benefit from providing samples for future research.
- I understand that, while information gained during research may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss giving blood and marrow samples for future research with a family member or friend.
- I understand that I can change my mind at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

Complete Appropriate Item Below, A or B

A. Adult Donor's Consent	**B. Parent's Permission for Minor Donor**
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to give blood and marrow samples for this study.	I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to give a blood sample for this study.
_____ **Signature of Adult Donor & Date Signed**	_____ **Signature of Parent(s)/Guardian & Date Signed**
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM _____ THROUGH _____.	If other than parent, specify relationship: _____

_____ _____

Signature of Investigator & Date Signed **Signature of Witness & Date Signed**

Pediatric Assent to Provide Extra Samples for Research

Study Title: **A Multi-Center, Phase III, Randomized Trial of Reduced Intensity(RIC) Conditioning and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies**

Protocol: **BMT CTN 1101**

A. Why am I here?

Your bone marrow is a match for a person in your family who needs a transplant. Your bone marrow grows inside your bones. It helps your body make blood and keeps you healthy. A transplant will collect some of your marrow and give it to a person who needs it to make new, healthy cells. Your body will make more marrow afterwards.

If you give us your permission, we would like to have an extra sample of your blood. We would collect the extra sample at the same time you have other blood tests done. We want to save the samples and use them for research in the future.

B. Why are you collecting an extra sample of blood?

Research with blood samples will help us learn more about transplant and other diseases. We will keep all of the extra samples private and store them in a place called a Repository. Your name will not be on the samples. Doctors and other researchers can ask to use the samples in the Repository as a part of their research.

C. What will happen to me?

If you say it is OK for us to collect an extra blood sample for research, we will ask you for:

- An extra blood sample. We would collect the extra sample at the same time as you have other blood tests done.

We will watch you carefully for side effects, fevers, infections or other problems.

D. Will it hurt?

When you have your blood taken with a needle, it may feel like a pinch. It will hurt for a minute and sometimes the place where the needle went might be red and sore. You might get a little bruise from the needle but it goes away in a few days.

E. Will the study help me?

Giving the blood sample for research will not help you.

F. What if I have questions?

You can ask any questions that you have about giving an extra blood sample. If you forget to ask a question and think of it later, you can call [*insert office number*].

G. Do I have to be in this study?

If you do not want to give an extra blood sample, you need to tell us and your parent or guardian. Your doctor will not be angry or upset if you do not want to join. You can still give bone marrow to the person in your family who needs it. They will still get the exact same care.

You can say yes now and change your mind at any time.

Please talk this over with your parents before you decide if you want to give an extra blood sample for research. We will also ask your parents to give their permission for you to give an extra sample for research.

Writing your name on this page means that you agree to give an extra blood sample and know what will happen to you. If you change your mind, all you have to do is tell the person in charge.

You and your parent or guardian will get a copy of this form after you sign it.

_____

Signature of Child Date

_____

Signature of Researcher Date

APPENDIX C

LABORATORY PROCEDURES

OPTIONAL RESEARCH SPECIMENS

APPENDIX C

LABORATORY PROCEDURES

OPTIONAL RESEARCH SPECIMENS

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

Patient samples will be collected both prior to the initiation of treatment and at four post-treatment time points as specified in the table below. Peripheral blood and bone marrow product samples will also be collected from HLA-haploindentical related donors and stored to support future research studies. All research samples will be collected and shipped same-day to the BMT CTN Repository for processing and sample aliquot storage. Sample collection and shipping procedures are detailed in the BMT CTN 1101 Laboratory Sample Guide.

Optional Research Samples						
Subject	**Research Sample Type**	**Time Points**	**Sample Quantity**	**Sample Processing & Storage Site**	**Stored Material**	**Purpose**
HLA-Haploidentical Related Donor	Peripheral Blood	Pre-BM Donation	50 mL (donors <50kg 1 mL/kg up to 50kg)	BMT CTN Repository	Plasma	Undefined Future Research
					Viable PBMC	
	Stem Cell Product (BM) (Donors ≥18 only)	Product to be Infused	3-5 mL	BMT CTN Repository	Viable BMMC	
Patient	Peripheral Blood	Pre-conditioning	50 mL (patients <50kg 1 mL/kg up to 50 Kg	BMT CTN Repository	Plasma	Undefined Future Research
					Viable PBMC	
					Granulocytes	
		Post-transplant Day 28, 56, 180, 365	50 mL (patients <50kg 1 mL/kg up to 50 kg)	BMT CTN Repository	Plasma	
					Viable PBMC	

APPENDIX D

APPROVED CYTOTOXIC CHEMOTHERAPY REGIMENS

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APPROVED CYTOTOXIC CHEMOTHERAPY REGIMENS

Patients must have received either

a. At least one cycle of at least one of the following cytotoxic chemotherapy regimens (or regimen of similar intensity) within 3 months of enrollment (measured from the start date of chemotherapy)
    i. Multi-agent chemotherapy (e.g. CVP±R, CHOP±R, ICE±R, DHAP±R, ESHAP±R, …)
    ii. Chemotherapy regimens like those that are given as induction or consolidation of acute leukemia (7+3, HiDAc, mitoxantrone+etoposide, FLAG, FLIG, and others)
    iii. Single drug alkylator agent (cyclophosphamide ≥1.5 g/m^2 or equivalent)
    iv. Bendamustine
    v. Single agent alemtuzumab or brentuximab vedotin

    Antineoplastic agents that are **not** considered adequate cytotoxic chemotherapy include:
    i. Single agent steroids
    ii. Single agent monoclonal antibody ± steroids with the exception of alemtuzumab
    iii. Single agent hypomethylating agent (e.g. azacytidine)
    iv. Single agent antimetabolite ± steroids (e.g. low dose methotrexate, low dose cytarabine)
    v. Single agent proteasome inhibitor ± monoclonal antibody (except for alemtuzumab or brentuximab vedotin) ± steroids
    vi. Hydroxyurea
    vii. Localized radiation therapy
    viii. Interferon
b. Autologous hematopoietic stem cell transplantation < 2 years prior to enrollment.

Please consult with the protocol chairs for any drugs or regimens not listed above.

APPENDIX E

REFERENCES

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REFERENCES

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