



BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning (NST) and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors in Patients with Hematologic Malignancies

**BMT CTN PROTOCOL 0604
VERSION 2.0**

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PROTOCOL SYNOPSIS – BMT CTN 0604

A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning (NST) and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors for Patients with Hematologic Malignancies

- Study Chairperson:** Claudio Brunstein, MD
- Primary Objective:** The primary objective is to determine overall survival 180 days after double cord blood transplantation using a non-myeloablative preparative regimen.
- Secondary Objectives:** Patients enrolled in this study will be followed for the following endpoints: neutrophil and platelet recovery, graft failure, acute graft versus host disease (GVHD), chronic GVHD, incidence of infection, treatment-related mortality, time to relapse/progression, overall survival and current progression-free survival.
- Study Design:** This study is a Phase II, multi-center prospective study of non-myeloablative conditioning and transplantation of double UCBs from unrelated donors in patients with:
- 1) Acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, and Burkitt's lymphoma in remission.
 - 2) Relapsed lymphoma including marginal zone B-cell lymphoma, follicular lymphoma and chemotherapy large-cell lymphoma, Hodgkin's lymphoma.
- Accrual Objective:** The target sample size is 50 patients.
- Accrual Period:** The estimated accrual period is three years.
- Eligibility Criteria:** Patients 21-70 years of age or < 21 years old and ineligible for BMT CTN #0501 with the diagnosis of a hematologic malignancy and with two partially HLA-matched UCB units. Units must be HLA-matched at 4 of 6 HLA-A and B (intermediate resolution molecular typing) and DRB1 (high resolution molecular typing) with each other and 4 of 6 with the recipient. Each unit must contain a minimum pre-cryopreserved, nucleated cell dose of 1.5×10^7 per kilogram. Patients may not have an available HLA 6/6- or 5/6-matched sibling.

Adequate organ function defined as: 1) left ventricular ejection fraction > 35%; 2) DLCO, FEV₁, FVC > 50% predicted; 3) total bilirubin ≤ 2.5 mg/dl, and ALT, AST, and alkaline phosphatase all < 5 x upper limit of normal (ULN); 4) serum creatinine within normal range for age, or if serum creatinine outside normal range for age, then renal function (creatinine clearance or GFR by Cockcroft-Gault formula) > 40 mL/min/1.73m²; 5) Karnofsky/Lansky performance score 60 to 100; and 6) if applicable, > 3 months since a previous autologous transplant.

Treatment Description:

The preparative regimen will consist of:

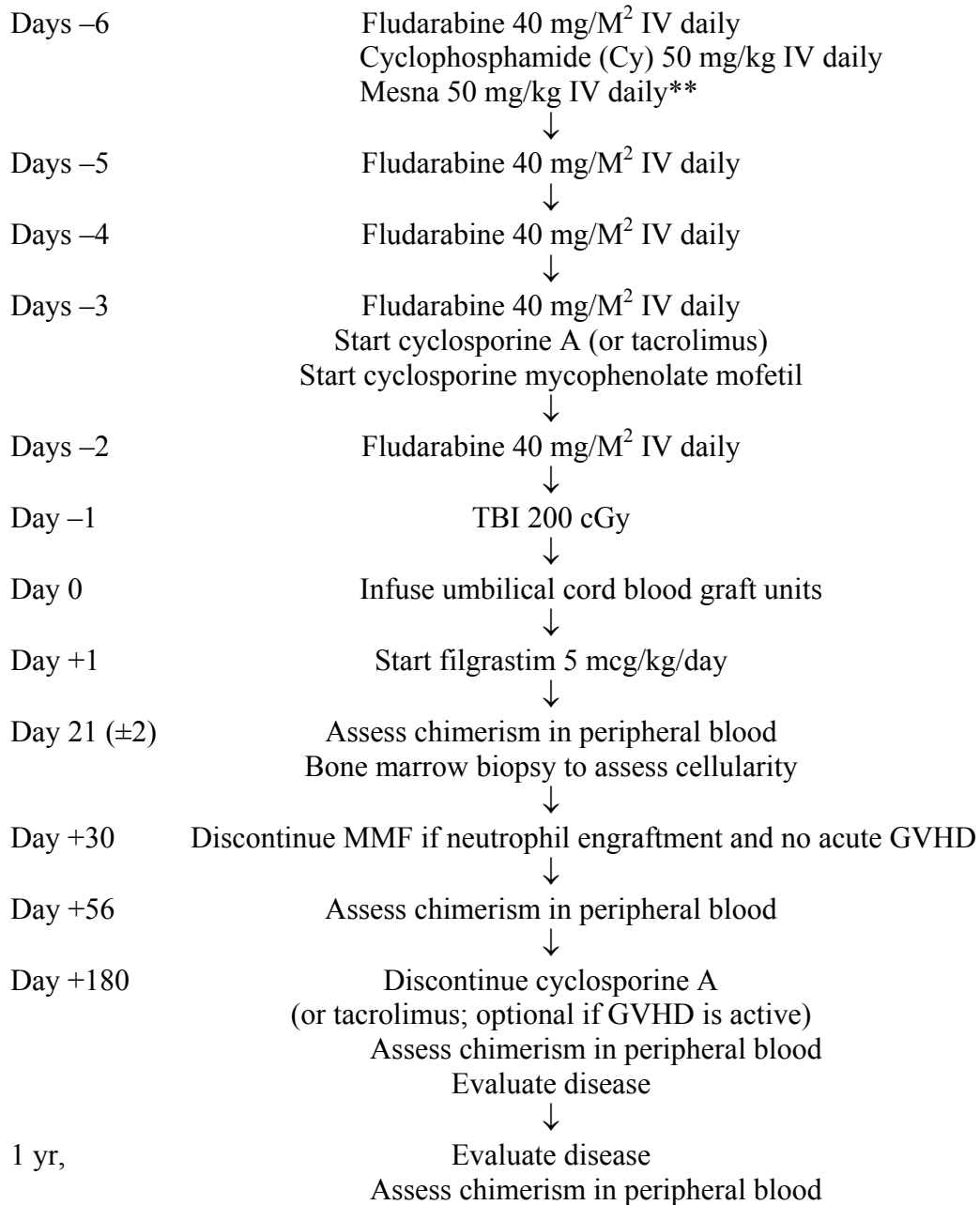
- Fludarabine 40 mg/m² IV Days –6, -5, -4,-3, -2
- Cyclophosphamide 50 mg/kg IV Day -6
- Total Body Irradiation (TBI) 200cGy Day –1
- Day 0 will be the day of the double UCB transplant

The GVHD prophylaxis regimen will consist of:

- Cyclosporine beginning Day –3 with dose adjusted to maintain a level of 200-400 ng/mL
- Mycophenolate mofetil (MMF) 1 gram IV TID if > 50 kg or 15 mg/kg IV TID if < 50 kg beginning Day-3 until Day 30 or 7 days after engraftment whichever day is later.

Study Duration:

Patients will be followed for one year post-transplant.

TREATMENT SCHEMA*

* Refer to Section 2.6 for complete instructions on medication administration.

** Or as per institutional standards.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Overview

Several small pilot studies have shown that umbilical cord blood (UCB) can mediate sustained donor engraftment after a reduced intensity conditioning regimen^{1, 2, 3, 4, 5}. Since most patients eligible for reduced intensity transplantation are adults, identifying an UCB graft with an adequate cell dose has been a limitation. In order to overcome this limitation, some centers^{1, 5} have adopted the strategy of using double umbilical cord blood grafts, similar to what was described successfully in the myeloablative setting⁶. We propose a Phase II study to determine whether the encouraging preliminary results of double UCB transplantation with a reduced-intensity conditioning regimen at single institutions is reproducible in a multi-center setting. This study will target adults with hematologic malignancies who are not candidates for a myeloablative conditioning regimen either as result of their age or associated co-morbidities.

1.2. Background

UCB grafts contain sufficient numbers of hematopoietic stem cells (HSC) for transplantation as evidenced by durable hematopoietic and immune reconstitution of UCB cell derived donor cells after myeloablative therapy. A recent survey by the Institute of Medicine found that more than 180,000 UCB units have been banked and more than 6,000 unrelated donor UCB transplantations have been performed. UCB transplants offer several advantages over adult donor bone marrow or peripheral blood stem cell transplants, including:

1. Rapid availability;
2. Absence of risk to the mother or infant donor;
3. Reduced incidence of transmission some blood-borne infectious disease agents (e.g., Epstein-Barr virus [EBV], cytomegalovirus [CMV]);
4. Reduced donor attrition;
5. Lower rates of grade 3-4 acute graft versus host disease (GVHD) in the setting of donor-recipient HLA mismatch (as compared to recipients of unrelated donor marrow and peripheral blood).

1.2.1. Unrelated Donor UCB Transplantation: Clinical Results

Since the first UCB transplantation performed by Gluckman et al. in 1988 in a child with Fanconi anemia⁷, there are several reports documenting the feasibility and efficacy of HLA-matched and mismatched unrelated donor UCB. The first repository of unrelated donor UCB was established in New York in 1993^{8, 9}. Currently, private and publicly funded UCB banks worldwide store an estimated 250,000 cryopreserved and publicly available HLA-A, B, and DRB1 typed units¹⁰. Several findings emerge from review of the literature.

Engraftment. Reported rates of neutrophil recovery after single UCB transplantation range from 65-92%^{10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23}. Findings consistently reported with single donor UCB transplants include the following: 1) hematopoietic recovery is slower and less complete than after bone marrow transplantation^{14, 23, 24}; 2) time to neutrophil and platelet recovery is cell dose dependent with more rapid recovery in those receiving graft containing a higher cell dose. In a report by Gluckman et al.¹², a graft nucleated cell dose > 3.7 x 10⁷/kg was associated with faster neutrophil recovery (25 vs. 35 days). Similarly, Rubinstein et al.^{19, 20} demonstrated that a step-wise increase in graft nucleated cell dose was associated with progressively faster neutrophil recovery. This study and others²² have shown graft CD34+ cell dose also predict the speed of hematopoietic recovery. It is widely believed that there is a threshold cell dose required for consistent engraftment; the proposed threshold varies from 2.5-4.9 x 10⁷/kg^{20, 25, 26}. Recent data also suggest that the deleterious effect of HLA-mismatching may be, at least in part, minimized by increasing the cell dose^{25, 27}.

Graft-versus-host disease. The reported incidence of acute graft-versus-host disease (GVHD) range from 33-44% for grades II-IV and 11-22% for grades III-IV acute GVHD^{12, 14, 19, 22, 28}. The incidences of chronic GVHD range from 0-25%^{12, 14, 19, 22}. These results are particularly notable since most UCB donor-recipient pairs are mismatched at 1 or 2 HLA-loci. However, most recipients of UCB transplants are young and younger age is also associated with lower rates of GVHD. However, most studies demonstrate none or a weak association between HLA disparity and occurrence of GVHD. Although few in number, Rubinstein et al.²⁰ did report a significantly lower rate of acute GVHD in recipients of HLA-matched grafts with no further increase observed in those with increasing HLA disparity (1 vs. 2 vs. 3 antigen mismatches). Associations between HLA-match and chronic GVHD are not reported.

Survival. The probability of survival after single UCB transplantation ranges from 18-78%^{12, 14, 19, 22}. Differences among studies are in part explained by marked differences in patients and their disease characteristics. However, nearly all studies demonstrate a significant relationship between UCB cell dose and survival. The association between HLA match and survival is more controversial, perhaps because of limited patient numbers and recipient age. Laughlin et al.¹⁶ studied 68 adult recipients of 0-3 antigen HLA-mismatched UCB transplants found no association between degree of HLA-mismatch and overall survival. In contrast, in two series by Rubinstein et al. (initially 562 patients, subsequently updated to 862 patients) and Wagner et al., a significant association between HLA-mismatch and survival was observed^{19, 20, 22}.

In the myeloablative setting, two registry-based studies^{29, 30} compared UCB to unrelated donor marrow transplantation for adult patients. One study included adults with acute lymphoblastic and myeloid leukemia, chronic myelogenous leukemia and myelodysplastic syndrome who received matched unrelated donor bone marrow (n=367), mismatched unrelated donor bone marrow (n=83), and mismatched UCB (n=150) grafts after myeloablative conditioning²⁹. In multivariate analysis, treatment-related death, treatment failure, and were similar between mismatched UCB and mismatched unrelated bone marrow recipients, but both had inferior outcomes when compared to matched bone marrow. A study facilitated by the Eurocord-Netcord included patients with acute leukemia who receive UCB (n=98) or 6/6 HLA matched unrelated marrow (n=582) grafts³⁰. In multivariate analysis, this study showed no significant

difference in regards to treatment-related mortality, relapse, leukemia-free survival, and overall survival between the two cohorts. In the single center study Takahashi et al³¹ studied 113 adult patients with hematological malignancies who underwent either unrelated donor bone marrow (n=45) or UCB (n=68) transplantation. They reported lower TRM (9 vs. 29%, p=0.02) and superior disease-free survival (74 vs. 44%, p<0.01) for recipients of UCB grafts.

1.2.2. Double UCB Transplantation

It is clear that cell dose is a critical determinant of hematopoietic recovery and early mortality after single unrelated donor UCB transplantation¹⁴. However, unlike bone marrow or peripheral blood stem cell transplantation where large numbers of cells may safely be harvested, the number of cells obtained from a single UCB unit is limited and fixed. Since the number of UCB cells needed to safely transplant a patient is dependent on the recipient's body weight, adolescents and adults (typical weight > 50 kg) require a larger cell dose than children who weigh considerably less. The limitation of cell dose is a major obstacle in the application of UCB transplantation in adolescents and adults.

Various methods of augmenting UCB cell dose have been considered^{1, 6}. One strategy is to infuse two UCB units. This strategy has been piloted in studies at the University of Minnesota primarily in adult patients who received two UCB units that were partially HLA-matched with the recipient (4-6/6 HLA match) and with each other. The hypothesis was that higher cell dose would enhance hematopoietic recovery. In a Phase I-II study, 23 consecutive patients (median age 24 years [range: 13-53]; weight 73 kg [48-120]; 57% male; 61% CMV positive) were transplanted with two UCB units. All patients received cyclophosphamide 120 mg/kg, fludarabine 75 mg/m² and TBI 1320 cGy pre-transplant and cyclosporine, mycophenolate mofetil (MMF) and filgrastim (G-CSF) after UCB infusion.

Engraftment. The incidence of sustained donor engraftment was 100% at a median of 23 days (range 15-41) post-transplantation. All patients had complete donor chimerism and there were no secondary graft failures. By Day 180, the probability of platelets > 50 x 10⁹/L was 71% (95% CI: 47-95%). These data demonstrate the safety of double UCB infusion in terms of engraftment, a previous concern because of the theoretical possibility of bi-directional immunological rejection.

Chimerism. In this series, 16 (76%) recipients had persistence of only one UCB unit by Day 21. While the remaining five patients (24%) had evidence of both units at Day 21 (median total donor chimerism 91% [range 64-100%]), one unit predominated. Skewed engraftment progressed such that evidence of 'double chimerism' was observed in only two patients at Day 60, and in none by Day 100 (n=17). The relative percent viability, order of infusion, ABO match, gender match, infused cell dose and HLA match of the UCB units did not predict which unit would predominate.

GVHD and Treatment-related Mortality (TRM). Rates of grade II-IV and III-IV acute GVHD were 65% (95% CI 42-88) and 17% (95% CI 2-32), respectively. Of the three patients with grade III-IV acute GVHD, one had involvement of skin only, one of skin and gut, and one of skin and liver. All responded to immunosuppression. Five patients have had chronic GVHD (all

extensive) for a cumulative incidence of 23% (95% CI 6-40%). The 6-month TRM rate was 22% (95% CI 5-39%).

Disease-free Survival (DFS). With a median follow-up of 10 months (range: 3.5 months-2.5 years), the probability of DFS at 1 year is 57% (95% CI 35-79%). For those in remission at the time of transplantation (n = 15), DFS was 72% (95% CI 49-95%) versus 25% (95% CI-64%), respectively (P=0.04) (Figure 1.2.3.1). Causes of death were GVHD/infection (n=3), GVHD/organ failure (n=2), hemorrhage (n=1), and relapse (n=3).

Summary. These results indicate that co-infusion of two UCB units is safe and may improve on engraftment rates anticipated after transplantation with an available single UCB unit.

1.2.3. Reduced Intensity UCB Transplantation

Hematologic malignancies are typically diagnosed during adult life with the median age of presentation in the 6th and 7th decades of life³². Age has been previously shown to increase the risk of treatment-related morbidity and mortality after hematopoietic stem cell transplantation^{33, 34}. As compared to children, adults are more like to have co-existing clinical problems at transplantation which increases the likelihood of treatment-related complications³⁵. Lastly, treatment options for hematologic malignancies have grown in number and many patients to have had extensive prior therapy by the time they are referred for transplantation^{36, 37, 38}. A growing number of reports have shown related and unrelated donor transplantation using a reduced intensity conditioning regimen is feasible and safe for a population of patients who would normally be offered only palliative care^{39, 40, 41, 42, 43, 44}.

Several reports, summarized in Table 1, have shown that UCB is an acceptable source of hematopoietic stem cells containing functional T cells that are able to mediate sustained donor engraftment after a reduced intensity conditioning regimen^{1, 2, 3, 4, 45, 46, 47, 48}. The median age at transplantation in these studies ranges from 47 to 59 years, an older population as compared to reports of myeloablative UCB transplantation. The median infused nucleated cell dose ranges from 2.4 to 4.0 x 10⁷/kg reflecting the higher cell dose required to proceed to transplantation in adults as well as the utilization of double UCB unit grafts.

Engraftment. The median time to neutrophil recovery ranged between 9 to 21 days and platelet recovery to 20 x 10⁹/L between 32 and 43 days. Graft failure rates ranged between 6% to 24%. In a recent report⁴⁸, patients who received cyclophosphamide/fludarabine/TBI 200 cGy conditioning regimen had better engraftment, lower treatment-related mortality and improved disease-free survival.

GVHD and TRM. Rates of grades II-IV GVHD after transplantation with reduced intensity conditioning and two UCB units range between 40 to 60%;^{1, 5, 45} rates of grades III-IV GVHD is up to 20%⁴⁵ and chronic GVHD, from 12 to 50%. Treatment-related mortality rates range from 14 to 46%.

Relapse and Survival. Relapse rates after reduced intensity UCB transplants range from 5 to 30%,^{3, 45, 47} but one must consider the heterogeneity of diseases included in each of the studies

shown below in Table 1. Survival rates after reduced intensity transplantation with a single UCB unit is reported to be between 33% and 37%,^{3,4} whereas for patients receiving two UCB units 40 to 70%^{5,45}.

In summary, available data show encouraging results after UCB transplantation with reduced intensity preparative regimens suggesting that UCB is an effective source of hematopoietic stem cells for patients who require an allogeneic transplantation with such a regimen but lack a suitable related or unrelated donor.

Table 1. Overview of adult reduced intensity umbilical cord blood transplant studies.

AUTHOR [ref]	n	Preparative Regimen	Median Age (range)	Infused NCD X10 ⁷ /kg (range)	Infused CD34 cell dose x10 ⁶ /kg (range)	Median time to ANC>500/μL (days)	Graft Failure (%)	Median time to platelet count recovery (Days) (>20 X 10 ⁹)	aGVHD II-IV (%)	cGVHD (%)	Relapse rate (%)	TRM (%)	Survival (%)
Barker et al * [1]	21	Bu/Flu/TBI	49 (22-65)	2.6 (1.6-3.8)	3.7 (1.1-8.1)	26	24	24%(20) at 6 months	44	21	NR	48 at 100 days	39 at 1 year
	22	Cy/Flu/TBI	49 (24-58)	3.2 (1.1-5.1)	4.3 (1.1-10)	9.5	6	80%(20) at 6 months			NR	28 at 100 days	
Brunstein et al* [45]	95	Cy/Flu/TBI	50 (18-69)	3.6 (1.1-6.8)	4.5 (0.7-18.8)	12	13	NR	61	25	31	18 at 180 days	44 at 2 years
Morii et al [4]	14	Cy/Flu/TBI Bu/Flu/TBI	57 (31-72)	2.6 (2.1-3.8)	NR	21	14	43	21	50	NR	19	37% at 1 year
Missawa et al [2]	12	Cy/Flu/TBI	49 (19-63)	2.55 (2.26-3.33)	0.91 (0.6-2.0)	17	16	32	62.5	33	NR	41.7	NR
Rocha et al [48]	65	Multiple ‡	47 (16-76)	2.4	NR	20	12 ‡	35	27	NR	NR	46	NR
Miyakoshi et al [3]	30	Flu/Mel/TBI	59 (20-70)	3.1 (2.0-4.3)	0.7 (0.2-2.5)	17.5	7	39	27	23	11	27	33 at 1 year
Ballen et al+ [5]	21	Flu/Mel/ATG	49 (24-63)	4.0 (2.9-5.1)	1.9 (0.6-9.7)	20	14	41	40†	12	5	19 at 180 days	71

Adapted from Brunstein CG & Wagner JE. Vox Sanguinis 2006, 91: 195-205.

UCB, umbilical cord blood; NCD, nucleated cell dose; ANC, absolute neutrophil count, aGVHD, acute graft-vs.-host disease; cGVHD, chronic graft-vs.-host disease; TRM, treatment related mortality, Bu/Flu/TBI, busulfan, fludarabine, and total body irradiation; Cy/Flu/TBI, cyclophosphamide, fludarabine, and total body irradiation; Flu/Mel/TBI, fludarabine, melphalan, and total body irradiation.

* The 22 patients who receive Cy/Flu/TBI in the series by Barker et al are included in the series by Brunstein et al.

+ Study included patients receiving multiple unit UCB grafts.

† The incidence of grades II-IV acute GVHD for patient who received tacrolimus/sirolimus posttransplantation immunosuppression was 29%.

‡ cyclophosphamide (Cy)/fludarabine (FLU)/total body irradiation 2Gy (TBI) was given to 33 patients, Flu/Cy or Melphalan(Mel) in 11 , Flu+Busulfan (<8mg/kg) associated or not to other drugs in 13 , Flu/TBI (2GY) in 3 and other

1.2.3.1. Rationale for the proposed study

Donor availability is a significant obstacle for patients who need an allogeneic transplant but lack a suitably matched relative. In addition, patients who are older and/or with co-morbidities are at a higher risk of treatment-related morbidity and mortality. Pilot studies have consistently shown superior engraftment, lower treatment-related mortality, and encouraging survival rates after reduced intensity double UCB transplantation. Currently, the University of Minnesota has the largest single-center experience with use of a non-myeloablative regimen for double UCB transplantation. This regimen consists of cyclophosphamide 50 mg/kg, fludarabine 200 mg/m², and total body irradiation 200cGy. Our data indicate 87% sustained donor engraftment, 18% TRM at 6-months, and a 3-year overall survival rate of 44% (Table 1). The proposed study will determine whether these results can be reproduced in a multi-center setting.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a multi-center, Phase II study to assess the safety and efficacy of double UCB transplantation using a non-myeloablative preparative regimen. The purpose is to determine whether results in a single center setting can be duplicated in a multi-center setting. If the results of this therapy are acceptable it will lead to a randomized trial comparing different graft sources in the unrelated donor setting.

2.2. Hypotheses and Specific Objectives

2.2.1. Hypotheses

Primary Hypothesis: 180 day survival after UCB transplantation using a reduced intensity preparative regimen is higher than 60%, similar to what is observed after unrelated bone marrow/peripheral blood stem cell transplantation using reduced intensity regimens.

Secondary Hypotheses:

1. More than 80% of engrafting patients will achieve $\geq 95\%$ donor chimerism by Day 56 after transplant.
2. The incidence of Grades III-IV GVHD will be less than 30%.

2.2.2. Study Objectives

The primary objective is to determine overall survival at 180 days after double UCB transplantation using a non-myeloablative preparative regimen. Secondary objectives include estimating overall and progression-free survival one year after transplantation, treatment-related mortality, incidence of neutrophil and platelet recovery, incidence of graft failure, cumulative incidence acute and chronic GVHD, incidence of infections, and cumulative incidence of relapse/progression. The proportion of patients able to find acceptable donors and the proportion proceeding to transplant will also be described.

2.3. Inclusion Criteria

Patients fulfilling the following criteria will be eligible to enroll on this study:

1. Age: Subjects 21-70 years old. Subjects 1-21 are also eligible if they are ineligible for BMT CTN #0501.
2. UCB units will be selected according to the algorithm in described under Treatment Plan, below. Each unit must supply a minimum of 1.5×10^7 /kg pre-cryopreserved nucleated cell dose.

3. Patients must have two partially HLA-matched UCB units. Each unit must match at a minimum of 4 of 6 at HLA-A, -B, -DRB1 loci with the recipient. This may include 0-2 antigen mismatches at each A or B (at the antigen level) or DRB1 (at the allele level) loci. Each unit must be a 4-6 HLA-A, B, and DRB1 antigen matched to each other, not necessarily at the same loci as with the recipient. All typing will be done using molecular typing. Though molecular level typing will be available a match is defined at intermediate resolution for HLA-A and -B and at high resolution for -DRB1 for this study. An adult unrelated donor search is not required for a patient to be eligible for this protocol if the clinical situation dictates an urgent transplant. Clinical urgency is defined as 6-8 weeks from referral to transplant center or low-likelihood of finding a matched, unrelated donor.
4. Patients must have received cytotoxic chemotherapy within 3 months of consent date (measured from the start date of chemotherapy).
5. Acute Leukemias (includes T lymphoblastic lymphoma) in 2nd or subsequent CR (see remission definition in Chapter 3):
 - a. Acute Lymphoblastic Leukemia in high risk CR1 as defined by at least one of the following:
 - i. Adverse cytogenetics such as t(9;22), t(1;19), t(4;11), MLL rearrangements,
 - ii. White blood cell counts of greater than 30,000 wbc/mcL,
 - iii. Patients over 30 years of age, or
 - iv. Time to Complete Remission was greater than 4 weeks.
 - b. Acute Myelogeneous Leukemia in high risk CR1 as defined by at least one of the following:
 - i. Greater than 1 cycle of induction therapy required to achieve remission,
 - ii. Preceding myelodysplastic syndrome (MDS),
 - iii. Presence of Flt3 abnormalities,
 - iv. FAB M6 or M7 leukemia, or
 - v. Adverse cytogenetics for overall survival such as
 - Those associated with MDS
 - Complex karyotype (≥ 3 abnormalities)
 - Any of the following: inv(3) or t(3;3), t(6;9), t(6;11), + 8 [alone or with other abnormalities except for t(8;21), t(9;11), inv(16) or t(16;16)], t(11;19)(q23;p13.1).
 - c. Acute Leukemias in 2nd or subsequent CR.
 - d. Biphenotypic/Undifferentiated Leukemias in 1st or subsequent CR.
6. Burkitt's lymphoma: second or subsequent CR.

7. Lymphoma:
 - a. Chemotherapy-sensitive (complete or partial response; see response criteria in Chapter 3) large cell, Mantel Cell or Hodgkin's lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are ineligible for an autologous transplant.
 - b. Marginal zone B-cell lymphoma or follicular lymphoma that has progressed after at least two prior therapies (excluding single agent Rituxan).
8. Patients with adequate physical function as measured by:
 - a. Cardiac: Left ventricular ejection fraction at rest must be $> 35\%$, or shortening fraction $> 25\%$.
 - b. Hepatic: Bilirubin ≤ 2.5 mg/dL; and ALT, AST and Alkaline Phosphatase ≤ 5 x upper limit of normal (ULN).
 - c. Renal: Serum creatinine within normal range for age, or if serum creatinine outside normal range for age, then renal function (creatinine clearance or GFR) > 40 mL/min/1.73 m².
 - d. Pulmonary: FEV₁, FVC, DLCO (diffusion capacity) $> 50\%$ predicted (corrected for hemoglobin); if unable to perform pulmonary function tests, then O₂ saturation $> 92\%$ on room air.
9. Performance status: Karnofsky/Lansky status scale ≥ 60 .

2.4. Exclusion Criteria

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

1. HLA-matched related or 7 or 8/8 HLA allele matched (HLA-A, - B, -Cw, - DRB1) related donor able to donate.
2. Prior autologous hematopoietic stem cell transplant < 3 months from enrollment;
3. Pregnancy or breastfeeding;
4. Evidence of HIV infection or known HIV positive serology.
5. Current uncontrolled bacterial, viral or fungal infection (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).
6. Prior allogeneic hematopoietic stem cell transplant.
7. Patients with a history of primary idiopathic myelofibrosis.

2.5. Graft Selection

Selection of Unrelated UCB Grafts:

1. Unit selection is based on cryopreserved nucleated cell (NC) dose & HLA-A, B, and DRB1-matching by molecular techniques (intermediate resolution for HLA-A and B, and high resolution for DRB1).

2. If the units are red cell-depleted, the minimum cryopreserved nucleated cell (TNC) dose of each unit must be $\geq 1.5 \times 10^7/\text{kg}$ (actual body weight). If the unit was NOT red cell-depleted, the minimum cryopreserved TNC dose of each unit must be at least 2.0×10^7 TNC/kg.
3. All patients will receive two UCB units.
4. Once the minimum cell dose requirement is achieved, units must be $\geq 4/6$ HLA matched with the patient and to each other but not necessarily at the same loci.
5. Above the cell dose threshold of 1.5×10^7 TNC/kg (or 2.0×10^7 TNC/kg for units that were not red cell-depleted), HLA-match will take priority in unit selection. However, within the best available HLA match grade (e.g. 5/6), units with the largest TNC should be chosen.
6. Double mismatches at any given locus should be avoided.

2.6. Treatment Plan

All patients will receive the same preparative therapy as shown in Table 2.6

TABLE 2.6-PREPARATIVE REGIMEN

Day –6	Fludarabine 40 m/m ² IV over 30-60 minutes Cyclophosphamide 50 mg/kg IV over 2 hours
Day –5	Fludarabine 40 m/m ² IV over 30-60 minutes
Day –4	Fludarabine 40 m/m ² IV over 30-60 minutes
Day –3	Fludarabine 40 m/m ² IV over 30-60 minutes
Day –2	Fludarabine 40 m/m ² IV over 30-60 minutes
Day –1	TBI 200 cGY
Day 0	UCB Transplant

2.6.1. Study Drugs

2.6.1.1. Fludarabine

Fludarabine 40 mg/m²/day IV x 5 days, total dose 200 mg/m². Fludarabine will be dosed according to the recipient’s actual body weight, unless the actual body weight is greater than or equal to two times their ideal body weight, in which case the protocol team must be consulted for instruction. For patients who have a creatinine clearance < 70 ml/min/1.73 m², or prior CNS disease, or prior brain radiation, and/or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%.

2.6.1.2. Cyclophosphamide

Cyclophosphamide 50mg/kg x 1 day to be administered on Day -6. Uroprotection can be administered according to institutional guidelines. Mesna is recommended to accompany pre-transplantation Cy, but is not required. Administration of IV fluids prior to cyclophosphamide dosing is recommended: 2 mL/kg/hr for 4 hours before and 24 hours after cyclophosphamide. It is recommended that fludarabine should be the first chemotherapy drug administered on Day -6, followed by the administration of cyclophosphamide, to allow for fludarabine to be infused at approximately the same time each day.

2.6.1.3. Cyclophosphamide dose adjustments

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 below for formulas).

Ideal Body Weight (IBW) Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Adjusted Ideal Body Weight Formula:

$AIBW = IBW + [(0.25) \times (ABW - IBW)]$

2.6.1.4. Total body irradiation (TBI)

Total body irradiation: 200 cGy will be administered in a single fraction on Day -1. Radiation sources and dose rates will be determined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources.

2.6.2. Immunosuppressive Therapies

2.6.2.1. Cyclosporine A (CSA)

CSA will be administered beginning on Day -3 and doses will be adjusted to maintain a 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. CSA can be administered per institutional practice. Tacrolimus may be substituted for cyclosporine if the patient has a hypersensitivity reaction to cyclosporine.

Dose adjustments will be made on the basis of toxicity and low CSA levels with a trough level of < 200 ng/mL. Once the patient can tolerate oral medications and has a normal gastro-intestinal transit time, CSA will be converted to an oral form at 2-3x the current IV dose. CSA dosing will be monitored and altered as clinically appropriate.

Patients will receive CSA 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 may be used as an alternative to CSA. Tacrolimus will be given at a dose of 0.02 mg/kg every 24 hours as a continuous intravenous infusion beginning on Day –3. An effort will be made to convert the tacrolimus to oral dosing at 2-3 times the total 24-hour intravenous dose, split into 2 doses given every 12 hours as soon as clinically feasible. The target trough level is 5-10 ng/mL.

2.6.2.2. Mycophenolate mofetil (MMF)

MMF will be given at a dose of 1 gram IV q 8 hours if > 50 kg or 15 mg/kg IV q 8 hours if < 50 kg beginning the morning of Day –3. (If renal failure and GFR < 25 mL/min, do not exceed 1 gram q 8 hours). Dose adjustments are not necessary for liver disease. MMF should be given IV until patient can tolerate oral medications and has a normal gastro-intestinal transit time. Tablets or suspension may be used to achieve calculated doses.

MMF should be continued until Day +30 or 7 days after engraftment, whichever day is later, if acute GVHD has not occurred. If GVHD occurs before Day 30, continue MMF until control of GVHD and treat GVHD according to institutional protocols. Methylprednisolone, 2 mg/kg divided q12H IV, is suggested as initial therapy. If no response after 7 days, treat with second line agents per institutional guidelines.

2.6.3. UCB Infusion

Following the administration of the preparative therapy, all subjects will undergo UCB transplantation. Under no circumstances is the cord blood to 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 cord blood infusion. Vital signs should be monitored before beginning the infusion and periodically during administration. The two units for double UCB transplantation are infused one after the other with no need for interval between units.

The BMT CTN Manual of Procedures should be followed for requesting, receiving and characterizing the cord blood unit for infusion. Contingency plans for UCB units which cannot be infused (due to viability, etc.) will be made according to institutional policies. These plans may include obtaining marrow from a haploidentical relative, supportive care, acquisition of another compatible UCB unit, following local institutional practices or autologous marrow back up.

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 recommended 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.

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 ziplock bag and thawed rapidly in a 37°C waterbath. The ziplock 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.

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

2.6.3.1. Pre-infusion medication and hydration regimen

The pre-medication and hydration regimen will be given following institutional guidelines.

2.6.4. Supportive Care

Patients will receive transfusions, 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 prevent herpes simplex, cytomegalovirus (CMV), Pneumocystis carinii, and fungal infections.

Transfusion thresholds for blood product support will be consistent with BMT CTN MOP and standard institutional guidelines. All blood products will be irradiated.

2.6.5. Growth Factors

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 $\geq 2,000/\text{mm}^3$ for three consecutive days. G-CSF should then be titrated to maintain $\text{ANC} > 1,000/\text{mm}^3$. G-CSF may be given by IV or subcutaneously.

2.6.6. 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 non-transplant 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 that 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.

UCB Graft Infusion:

Potential toxicities associated with the infusion include DMSO toxicity and side effects from red cells. These may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, headache, allergic reaction, presence of DMSO taste and odor, hemoglobinuria, and acute renal failure. Due to the washing and processing steps, these toxicities are unlikely.

Cyclosporine A:

Cyclosporine may cause: nephrotoxicity, seizures, hypertension, hirsutism, thrombotic microangiopathy, electrolyte imbalances, paresthesias/neuropathy, gingival hyperplasia, transient-blindness, and hepatic and renal dysfunction.

Mycophenolate Mofetil:

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

Growth Factor or G-CSF (Filgrastim, Neupogen):

G-CSF may cause: Bone pain, insomnia, headaches, dyspnea, body aches, rash, fever, splenomegaly allergic reaction, fatigue, edema and nausea/vomiting.

Graft Failure:

Based on historical data, there could be a 15% chance of graft failure. Contingency plans are recommended and include obtaining marrow from a haploidentical relative, supportive care or acquisition of another compatible UCB unit.

2.6.7. Management of Slow Engraftment and Graft Failure

Slow engraftment and graft failure should be handled according to institutional guidelines.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is overall survival at 180 days from the time of transplantation.

3.2. Secondary Endpoints

3.2.1 Neutrophil Recovery

Neutrophil recovery is defined as achieving an ANC $\geq 500/\text{mm}^3$ for three consecutive measurements on 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

3.2.1.1. Primary graft failure

Primary graft failure is defined as $< 5\%$ donor chimerism on all measurements prior to and day-100.

3.2.1.2. Secondary graft failure

Secondary graft failure is defined initial recovery followed by neutropenia with $< 5\%$ donor chimerism. If no chimerism assays were performed and ANC is $< 500/\text{mm}^3$, then it will be counted as a secondary graft failure.

3.2.1.3. Platelet recovery

Platelet recovery is defined as the first day of a minimum of three consecutive measurements on different days such that the patient has achieved a platelet count $> 20,000/\text{mm}^3$ and $> 50,000/\text{mm}^3$ with no platelet transfusions in the preceding seven days. The first day of the three measurements will be designated the day of platelet engraftment.

3.2.2. Donor Cell Engraftment

Donor cell engraftment is defined as donor chimerism $> 5\%$ on Day >56 after transplantation. Chimerism should be evaluated on Days ~ 28 , ~ 56 , ~ 100 , ~ 180 and ~ 365 after transplantation. Chimerism may be evaluated in whole blood or mononuclear fraction.

3.2.3. Acute Graft-versus-Host Disease

The probabilities 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.

3.2.4. Chronic Graft-versus-Host Disease

Chronic GVHD will be scored according to the BMT CTN MOP. The time to onset of limited and extensive chronic GVHD will be recorded.

3.2.5. Progression-free Survival

Progression-free survival is defined as the minimum time interval to relapse/recurrence/progression, to death or to last follow-up.

3.2.6. Treatment-related Mortality (TRM)

The probability of TRM will be estimated at Day 100, 180, and 1 year. An event for this endpoint is death without evidence of disease progression or disease recurrence. Documented disease progression or recurrence is the competing event.

3.2.7. Infections

Infections will be reported by anatomic site, date of onset, organism and resolution, if any. For definitions, see the BMT CTN MOP. Patients will be followed for infection for 1 year post-transplant.

3.2.8. Relapse and Residual Disease

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 malignancy consistent with pre-transplant features.

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 will not be sufficient to meet the definition of relapse in the context of this study. Data on tapering immunosuppression, administering chemotherapy or biological agents to attempt reducing the tumor load 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. If there are no circulating blasts, but the marrow contains 5-20% blasts, a repeat bone marrow examination \geq one week later demonstrating > 5% blasts is necessary to meet this criterion for relapse; or,
4. The appearance of new dysplastic changes within the bone marrow; or,
5. The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

Lymphoma – Relapse will be diagnosed when there is:

1. Appearance of any new lesion more than 1.5 cm in any axis post-transplant, 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 \geq 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. 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).

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 measurable 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 identified 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

Abbreviations: CR, complete remission; FDG, [¹⁸F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

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

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.

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 (AdvantageEDCSM). The following procedures should be followed:

1. Prior to initiation of conditioning regimen and prior to shipment of UCB units, but no more than 14 days prior to initiation of conditioning regimen, an authorized user at the transplant center enters the patient demographics and Segment A of the Enrollment Form in AdvantageEDC. The eligibility screening (Segment A) includes a question confirming that the patient (or legal guardian) signed the informed consent.
2. If the patient is eligible, a patient number is generated and displayed.
3. 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

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 ± 2 days
2 week	14 ± 2 days
3 week	21 ± 2 days
4 week	28 ± 2 days
5 week	35 ± 2 days
6 week	42 ± 2 days
7 week	49 ± 2 days
8 week	56 ± 2 days
6 month	180 ± 28 days
12 month	365 ± 28 days

Criteria for Forms Submission: 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 within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data 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.

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 #0604 must be indicated on the SCTOD pre-transplant registration form, if applicable. Additionally, CIBMTR pre- and post- transplant 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.

Weekly 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 56 post-transplant for GVHD. After Day 56 patients will be assessed at each follow-up visit (Day 180 and 365) for the presence of GVHD.

4.2.2. Adverse Event 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. Expected AEs will be reported using NCI’s Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

4.2.3. Patient Assessments

Table 4.2.3 summarizes patient clinical assessments over the course of the study.

4.2.3.1. Pre-transplant evaluations

The following observations are considered standard evaluations for transplant eligibility and should be determined < 4 weeks before initiation of conditioning therapy, unless otherwise noted.

1. History, physical examination, height and weight.
2. Karnofsky/Lansky performance status.
3. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST.
4. 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.
5. High resolution HLA typing, if not already performed.
6. EKG, < 6 weeks before initiation of conditioning therapy.
7. Left ventricular ejection fraction or shortening fraction, < 6 weeks before initiation of conditioning therapy.
8. DLCO, FEV1, and FVC or O₂ saturation. < 6 weeks before initiation of conditioning therapy.
9. Bone marrow aspirates for pathology and cytogenetics and/or biopsy.
10. β -HCG serum pregnancy test for females of childbearing potential.
11. Chest imaging (Chest X-Ray or Chest CT) as clinically indicated.
12. Peripheral blood for pre-transplant RFLP analysis to establish a reference profile of host hematopoiesis.
13. Lymphomas (large cell, B- cell, and Hodgkin's): Whole Body PET/CT as clinically indicated.

4.2.3.2. Post-transplant evaluations

The following evaluations are considered standard evaluations for transplant recipients:

1. History and physical exam to assess GVHD and other morbidity weekly until Day 56 post-transplant, then at six months, and one year post-transplant. GVHD evaluation and grading to be in keeping with BMT CTN MOP.
2. CBC at least three times a week from Day 0 until ANC > 500 mm³ for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until 12 weeks, then six months, and one year post-transplant.
3. Creatinine, bilirubin, alkaline phosphatase, ALT, AST, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, and then at six months, and one year post-transplant.

4. Peripheral blood on Day ~28, ~56, ~180, ~365 for post-transplant chimerism assay.
5. Bone marrow aspirate at Day 21 if WBC < 500. If there are an insufficient number of cells for chimerism assay on Day 21, repeat on Day 28.
6. Immunizations will be given per institutional guidelines.
7. Toxicity assessments at Day 28, 56, 6 months, and 1 year.
8. Disease status evaluation required at Day 56, 6 months, and 1 year. Testing to determine disease status should follow pre-transplant evaluation process. Disease status evaluation before Day 56 should follow institutional practices. Bone marrow biopsy and aspirate to pathology is required for disease status evaluation at Days 56 and 365.

TABLE 4.2.3: SUMMARY OF PATIENT CLINICAL ASSESSMENTS

Study Assessments/ Testing	Baseline	Days after Transplantation										
		7	14	21	28	35	42	49	56	180	365	
History, physical exam, weight, height, and Karnofsky/Lansky performance status	X	X	X	X	X	X	X	X	X	X	X	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											
EKG, LVEF, or shortening fraction	X											
DLCO, FEV1 and FVC or O ₂ saturation	X											
Bone marrow biopsy and aspirate for pathology ⁴	X			X	X				X	X	X	
Chest X-ray	X											
β-HCG serum pregnancy test (females only)	X											
GVHD and other morbidity assessments ⁵		X	X	X	X	X	X	X	X	X	X	X
Toxicity assessments	X				X				X	X	X	
Chimerism ⁶	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 12 weeks post-transplant.
- ² Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly until Day 28. Blood chemistries performed weekly after Day 28 until 12 weeks post-transplant.
- 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.
- ⁴ Bone marrow biopsy and aspirates to pathology required at Day 21 if WBC < 500. Day 28 only to be done if slow neutrophil recovery to evaluate for graft failure. Cytogenics and flow cytometry should be sent as clinically indicated by patient’s diagnosis. Baseline, Day 56 and Day 365 are required; Day 180 is optional.
- ⁵ GVHD and other morbidity assessments performed weekly until Day 56 post-transplant, and then at Day 180 and 365.
- ⁶ Chimerism will be measured by RFLP or microsatellite. On Day 28 chimerism tests will be performed on whole or mononuclear fraction peripheral blood.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

The study is a Phase II, non-randomized, multi-center trial. It is designed to assess the overall survival 180 days after double umbilical cord blood transplantation using a non-myeloablative preparative regimen in patients undergoing a partially HLA mismatched unrelated donor transplant. The sample size is 50 patients for this trial. Patients with acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, Burkitt's lymphoma or large-cell lymphoma, Hodgkin's lymphoma, marginal zone B-cell lymphoma, and follicular lymphoma, and which is chemotherapy sensitive are eligible. A primary purpose of this study is to determine if results from a single center study can be duplicated in a multi-center setting.

5.2. Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Accrual will be reported by race, ethnicity, gender, and age.

5.3. Study Duration

Patients will be followed by BMT CTN personnel for a minimum of one year post-transplant. Additional follow-up will be available through routine CIBMTR mechanisms (see Section 4.2.1).

5.4. Randomization

There is no randomization aspect to this trial.

5.5. Primary Objective

The primary endpoint is the overall survival (OS) probability at 180 days post-transplant. The choice of this endpoint is based on CIBMTR registry data reported by Giralt et al (Biol Blood Marrow Transpl 2007; 13:1083) for unrelated adult donor transplants. In this study the probability of 6-month survival was 60%. The primary analysis will be on all transplanted patients. Death will be considered as an event for this endpoint. Based on historical data the 180 day survival is expected to be 60%. The study is designed to rule out survival percentages below 40%.

5.6. Sample Size and Power Considerations

The sample size is 50 patients for this trial. Table 5.6.1 provides 90% confidence intervals for a variety of true underlying proportions. For example if 30 of the 50 patients survive (60% observed survival percentage) the length of the confidence interval is 22.8%. The percentages above and below 60% are intended to represent other plausible OS percentages.

This is an exploratory study with a decision rule that a further Phase III study would be warranted if the lower bound of a 90% confidence interval for the survival estimate is above 40%. The probability to rule out OS percentages of a certain size is known as “power”. Table 5.6.2 provides the probability (or power) that the lower bound of a 90% two-sided confidence interval for the OS probability will be greater than a threshold of 70%, 65%, 60%, 55%, 50%, 45% or 40%. Based on the table below, there is 84% power at $\alpha = .05$ to reject the null if the true percentage is 40%.

TABLE 5.6.1: CONFIDENCE INTERVAL LENGTHS AND POSSIBLE CONFIDENCE INTERVALS FOR VARIOUS OBSERVED OVERALL SURVIVAL PROBABILITIES

N	Overall Survival (OS) %	Length of 95% Confidence Interval	Possible Confidence Intervals	
50	70	21.3	59.3	80.7
50	65	22.2	53.9	76.1
50	60	22.8	48.6	71.4
50	55	23.1	43.4	66.6
50	50	23.3	38.4	61.6
50	45	23.1	33.4	56.6
50	40	22.8	28.6	51.4

The OS probability estimate will be based on the Kaplan-Meier product limit estimator using Greenwood’s formula as the variance estimate. In the absence of censoring, the Kaplan-Meier estimate reduces to the simple binomial proportion.

TABLE 5.6.2: PROBABILITY OF RULING OUT A THRESHOLD OF SIZE T FOR VARIOUS TRUE UNDERLYING OVERALL SURVIVAL PERCENTAGES

N	True Overall Survival %	Probability of Ruling Out Overall Survival Percentages of Size T						
		T=70%	T=65%	T=60%	T=55%	T=50%	T=45%	T=40%
50	70		0.14	0.33	0.68	0.86	0.98	0.99
50	65	0.19		0.12	0.39	0.62	0.88	0.96
50	60	0.44	0.16		0.16	0.34	0.67	0.84
50	55	0.71	0.39	0.13		0.13	0.39	0.61
50	50	0.90	0.66	0.34	0.16		0.16	0.34
50	45	0.98	0.87	0.61	0.39	0.13		0.13
50	40	0.99	0.97	0.84	0.67	0.34	0.16	

5.7. Interim Analysis and Stopping Guideline

Interim analyses for efficacy will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately six-month intervals. Monitoring of 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 guideline serves as trigger for consultation with the DSMB for additional review.

Two safety endpoints for this study are treatment-related mortality (TRM) and graft failure. The rate of TRM will be monitored up to 100 days post-transplant and the rate of graft failure will be monitored up to 56 days post-transplant. Monitoring will be performed monthly beginning after the third month of enrollment until enrollment is closed. At least three events must be observed in order to trigger review. Each month, the null hypothesis that the 100-day TRM rate is less than or equal to 30% is tested. Similarly, the null hypothesis that the 56-day graft failure rate is less than or equal to 12% is tested. Primary graft failure, secondary graft failure and second transplants will be counted as events for this stopping guideline. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for each endpoint, as described in greater detail below and in Appendix D.

This sequential testing procedure conserves type I error across all of the monthly examinations for a single endpoint, but not across the multiple safety endpoints. Thus for a single endpoint, the type I error is approximately 5%, and across two safety endpoints, the study-wide type I error

is $< 10\%$. The rationale for not conserving type I error across multiple safety endpoints is twofold. First, adjusting the size of the test for multiple comparisons would reduce statistical power to detect adverse outcomes, which seems imprudent. Secondly, the procedure is a guideline for requiring additional review by the Data and Safety Monitoring Board, and is not a formal “stopping rule” that would mandate automatic closure of study enrollment.

The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints (e.g., patients experiencing TRM). The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring to protect against excessive 100-day TRM. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum of 50 patients.

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

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRTs:

- A SPRT contrasting 30% versus 50% 100-day rate of TRM results in decision boundaries with a common slope of 0.54 and the intercepts are -1.74 and 1.46 , with nominal type I and II errors of 10% and 15%, respectively.
- A SPRT contrasting 12% versus 30% 56-day rate of graft failure results in decision boundaries with a common slope of 0.69 and the intercepts are -1.43 and 1.20 , with nominal type I and II errors of 10% and 15%, respectively.

The actual operating characteristics of the truncated test, shown in Table 5.7.1, were determined in a simulation study that assumed uniform accrual of 50 individuals over a three-year time period, and exponential time to failure after registration. Since 100,000 replications were used, the estimates have two digits of precision.

TABLE 5.7.1: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 100,000 REPLICATIONS**TREATMENT-RELATED MORTALITY**

True 100-Day Rate	30%	35%	40%	45%	50%
Probability Reject Null	0.07	0.20	0.41	0.66	0.86
Mean Month Stopped	34.5	32.3	28.5	23.5	18.5
Mean # Endpoints in 100 Days	13.8	15.0	15.1	14.0	12.1
Mean # Patients Enrolled	48	45	40	33	26

GRAFT FAILURE

True 56-Day Rate	12%	15%	20%	25%	30%
Probability Reject Null	0.07	0.16	0.44	0.72	0.90
Mean Month Stopped	34.5	32.6	27.3	21.1	15.6
Mean # Endpoints in 56 Days	5.6	6.6	7.4	7.1	6.3
Mean # Patients Enrolled	48	45	38	30	22

For example, the testing procedure for TRM rejects the null hypothesis in favor of the alternative 7% of the time when the true 100-day TRM rate is 30%, and 86% of the time when the rate is 50%. This corresponds to a type I error rate of $\alpha = 0.07$ and a type II error rate of $\beta = 0.14$. When the true 100-day TRM rate is 50%, on average, the DSMB will be consulted 18.5 months after opening, when 12 events have been observed in 26 patients.

The testing procedure for graft failure rejects the null hypothesis in favor of the alternative 7% of the time when the true 56-day graft failure rate is 12%, and 90% of the time when the rate is 30%. This corresponds to a type I error rate of $\alpha = 0.07$ and a type II error rate of $\beta = 0.10$. When the true 56-day graft failure rate is 30%, on average, the DSMB will be consulted 15.6 months after opening, when 6 events have been observed in 22 patients.

5.8. 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, HLA match, disease type and stage, remission status and number, number of prior treatments, prior autologous transplantation (yes or no), serum bilirubin level, serum creatinine level, donor age, donor gender, and donor ethnicity.

5.9. Analysis of Primary Endpoint

The primary analysis will consist of estimating the 180 day overall survival probability based on the Kaplan-Meier product limit estimator. The 180 day overall survival probability and confidence interval will be calculated. All registered patients will be considered for this analysis.

5.10. Analysis of Secondary Endpoints

1. **Overall survival:** The overall survival distribution at one and two years after transplantation will be estimated by the Kaplan-Meier curve. All patients will be followed for a minimum of two year post-transplant for mortality.
2. **Neutrophil recovery:** To assess the incidence of neutrophil recovery from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to neutrophil recovery will be considered a competing risk.
3. **Platelet recovery:** To assess the incidence of platelet engraftment from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to platelet engraftment will be considered a competing risk.
4. **Chimerism:** The degree of total donor chimerism will be assessed on Days 28, 56, and 180 and 365 after transplantation.
5. **Graft failure:** To assess the incidence of primary and secondary graft failure a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to graft failure will be considered as a competing risk.
6. **Acute GVHD:** To assess the incidence of grades II-IV and grade III-IV acute GVHD from day of transplant. The first day of acute GVHD onset at a certain grade will be used to calculate a cumulative incidence curve for that acute GVHD grade. An overall cumulative incidence curve will be computed along with a 95% confidence interval at 100 days post-transplant with graft failure, disease progression and death considered a competing risk.
7. **Chronic GVHD:** To assess the incidence and severity of extensive chronic GVHD from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at one and two years post-transplant. The first day of clinical onset of extensive chronic GVHD will be used. Death, disease progression or graft failure prior to occurrence of chronic GVHD will be considered a competing risk.
8. **Treatment-related mortality:** Treatment-related mortality at 100 days, six months, and one year will be estimated. Disease progression is considered a competing risk.
9. **Relapse/progression:** To assess the incidence of relapse/progression from day of transplant, a cumulative incidence curve will be computed along with a 95% confidence interval. Death prior to relapse or progression will be considered a competing risk.
10. **Progression-free survival:** To assess current progression-free survival, the one and two year progression-free survival probability after transplantation and 95% confidence interval will be calculated based on the Kaplan-Meier product limit estimator.

5.11. Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. The type and severity of adverse events will be analyzed.

APPENDIX A

HUMAN SUBJECTS

1. Subject Consent

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

2. Confidentiality

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

3. Participation of Women and Minorities and Other Populations

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 strategies.

APPENDIX B

CONSENT FORMS

PATIENT INFORMED CONSENT

Informed Consent to Participate in Research

A Multi-Center, Phase II Trial of Non-myeloablative Conditioning and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors for Patients with Hematologic Malignancies

Your name: _____

Introduction

You are being invited to participate in a clinical trial. A clinical trial is a research study to answer specific medical questions. The information from this study may help future patients. This form tells you about the study. In addition, the study doctor (the person in charge of the research) will explain the study to you.

This is a consent form for a research study. You are being asked to take part in this study because you have leukemia or lymphoma that has failed other treatment or it is not likely to respond to other treatment. These diseases can be treated and sometimes cured with very high doses of chemotherapy and radiation therapy given to kill leukemia or lymphoma cells. However, this treatment also harms normal cells in the bone marrow. We and other transplant centers have the most experience using a donor who is a “perfect” or close to perfect “tissue match”. However, tissue typing shows that a completely or partially matched donor is unavailable within your family. A completely matched unrelated donor transplant is an option, we either have not been able to find a good match or we are concerned that your disease may worsen in the time it takes to find one.

The bone marrow is the body’s “blood factory.” It makes the cells that circulate in the blood, including: red blood cells (which carry oxygen), white blood cells (which fight infection), and platelets (which prevent bleeding). The bone marrow can be fixed by giving “hematopoietic or blood stem cells” donated by someone else. This is called a hematopoietic stem cell transplant. Blood stem cells are the “parent cells” of the bone marrow that produce all the blood cells. For a transplant to be successful, the donor blood stem cells must have a tissue type that is completely or closely matched to the patient’s tissue type. These genetic markers are like a “finger print” and help our immune system to determine which cells belong to the body and which do not. For patients needed a transplant that do not have a family donor who is a match (has the same tissue type), blood stem cells from unrelated donors can be used.

Blood stem cells are found in bone marrow and in umbilical cord blood. Umbilical cord blood is the blood left over in the placenta (afterbirth) after a baby is born. Usually this blood is thrown out with the placenta. Over the past 15 years, we have learned how to collect and freeze cord blood cells to be used for transplants at a later time. A cord blood unit is the cord blood cells

collected and stored from a single placenta. Cord blood units have been used for more than 6,500 transplants performed around the world.

This trial will use two cord blood units for transplantation to determine if disease survival is better using a non-myeloablative preparative regimen than using intense doses of chemotherapy and radiation therapy. Two cord blood units are being used as the numbers of blood cells in one unit are too few to allow successful growth of these cells.

Principal Investigator Contact Information at your Institution

Name/Title/Phone number/

Contact information for emergencies after hours or on weekends or holidays:

Name/Phone number/

Who is conducting this study?

The research in this study is paid for by the National Institutes of Health (NIH), which supports the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The BMT CTN will direct the research study. All decisions about how the study is done are made independently by the BMT CTN and NIH.

Why is this study being done?

Before a standard transplant, patients receive high doses of chemotherapy and possibly radiation therapy. This treatment is called a preparative regimen or a conditioning regimen. The preparative regimen destroys the diseased cells (such as cancer cells). It also destroys the patient's immune system so it cannot attack the donor's cells during transplant.

In contrast, the preparative regimen for a reduced-intensity transplant (sometimes referred to as a "mini-transplant") does not destroy many diseased cells. It is just strong enough to weaken the patient's immune system so it cannot attack the donor's cells. The donor's cells grow a new immune system. The new immune system destroys the diseased cells. The cells for a mini-transplant can come from a family member, an unrelated donor, or a cord blood unit.

The information collected from this study will help doctors and future patients make better treatment choices.

How many people will take part in the study?

A total of 50 patients will participate in this study. This study will be done many different medical centers in the United States, including [Center Name/Location].

What will happen if I take part in this research study?

Your treatment will start six days before you are to receive your double UCB transplant. You will begin taking a drug called fludarabine, by IV, once a day for five days. You will also receive cyclophosphamide (Cytosan®), another chemotherapy drug, by IV on the sixth day before transplant. On the day before transplantation you will receive a low dose of total body irradiation (TBI). The purpose of this treatment is to allow your body to accept the donor cells without rejecting them. After this treatment is completed, your donor's stem cells will be given to you through your central venous catheter.

Starting three days before your transplant, you will be given cyclosporine (also called Gengraf®) twice a day and Mycophenolate mofetil (also MMF or CellCept®) three times a day. Cyclosporine and MMF are given to prevent your body from rejecting your donor's stem cells and to help decrease the risk of developing a complication called graft-versus-host-disease (GVHD). GVHD is a condition where your donor's immune cells attack your skin, liver, intestines and potentially other organs. Some patients develop very severe GVHD, which can be fatal. In certain transplant centers patients may be given tacrolimus (also called FK-506 or Prograf®), another approved drug that helps prevent GVHD.

Because the chance of developing GVHD can persist many months after an unrelated double UCB transplant, you will continue to receive MMF for 30 days and cyclosporine or tacrolimus for 180 days after your transplant. While you are taking cyclosporine or tacrolimus, blood tests to monitor the amount of cyclosporine or tacrolimus in your blood will be done at least weekly for the first several weeks and your dose of cyclosporine or tacrolimus may be adjusted if necessary to maintain the proper level in your blood.

Blood tests will be performed frequently to evaluate your response to treatment and possible side effects of treatment. If necessary, platelet and red cell transfusions will be given to maintain adequate levels and antibiotics will be given to treat or prevent infection. You may also require intravenous nutritional support and pain medications during or after transplantation. You will be monitored closely for any signs and symptoms of GVHD.

You will receive treatment for any infections according to medical standards.

If, at any time during this study, your cancer worsens, you will be taken off study. Other treatment options will be discussed with you at that time.

How long will I be in this study?

Your treatment will last approximately 2-3 months at this center but possibly longer if there are complications. We would like to see you in clinic for follow-up at 6 months, if possible, and then one year post-transplant.

However, we would like to keep track of your medical condition for the rest of your life. We will do this by contacting you and the doctor providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us

know whether there are any unexpected long-term side effects of treatment. Many transplant centers include this type of long-term follow-up as part of their regular care.

Can I stop being in this study?

Yes. You can decide to stop at any time. If you wish, you may withdraw from the study but still receive UCB transplant. If you withdraw from the study after you have had some or all of the pre-transplant treatments and decide to have no transplant at all, then your blood counts may not return and you could die.

If you decide to withdraw from the study, we ask that you tell your doctor. If you withdraw, there will be no penalty or loss of benefit to which you are entitled and you will continue to receive medical care. The medical staff will continue to tell us about your progress for three years after your transplant. If you do not want this, you must specifically tell your doctor.

If you have any questions about your rights as a study subject, you may contact the Institutional Review Board (IRB) at [number].

Can the Principal Investigator withdraw me from this research study?

You can be taken off the study (with or without your consent) for any of these reasons:

- The study treatment does not work for your type of cancer
- You develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications
- You are unable to meet the requirements of the study (for example, you cannot take the medicine as prescribed or you refuse follow up)
- New information about the study drugs or other treatments for cancer becomes available.
- The study is cancelled

What side effect or risks can I expect from being in the study?

Likely Side Effects	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 Side Effects	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 Side Effects	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
<ul style="list-style-type: none"> • Decreased white blood cell count with increased risk of infection • Temporary hair loss • Nausea • Vomiting • Loss of appetite • Sores in mouth of 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 	<ul style="list-style-type: none"> • Anemia • Temporary tiredness • Damage to the fetus if you become pregnant while taking drug 	<ul style="list-style-type: none"> • Scarring of lung tissue, with cough and shortness of breath • Severe heart muscle injury and death at very high doses • Secondary cancers

Fludarabine (Fludara®)

Likely	Less Likely	Rare, but Serious
<ul style="list-style-type: none"> • Decreased white blood cell count with risk of infection • Decreased platelet count with increased risk of bleeding • Anemia • Tiredness • Nausea • Vomiting 	<ul style="list-style-type: none"> • Diarrhea • Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet • Changes in vision 	<ul style="list-style-type: none"> • Pneumonia • Agitation/nervousness • Confusion • Cough • Difficulty breathing • Weakness • Severe brain injury and death

G-CSF (Neupogen®)

Likely	Less Likely	Rare, but Serious
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Local irritation (skin) at the injection site • Nausea 	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Miscarriage • Birth defects • Diarrhea • Stomach pain • Damage to unborn baby • Limited effectiveness of birth control • 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 	<ul style="list-style-type: none"> • Anemia • Rash • Difficulty falling asleep or staying asleep • Dizziness • Uncontrollable hand shakes 	<ul style="list-style-type: none"> • Difficulty breathing • Unusual bruising • Fast heartbeat • Excessive tiredness • Weakness • Blood in stools • Bloody vomit • Changes in vision • Progressive Multifocal Leukoencephalopathy

Total Body Irradiation (TBI)

Likely	Less Likely	Rare, but Serious
<ul style="list-style-type: none"> • Fatigue • Nausea 	<ul style="list-style-type: none"> • Vomiting • Cataracts • Low white blood cell count with increased risk of infection • Low platelet count with increased risk of bleeding • Anemia 	<ul style="list-style-type: none"> • Diarrhea • Secondary cancers

Cyclosporine (Gengraf®)/Tacrolimus (Prograf®)

Likely	Less Likely	Rare, but Serious
<ul style="list-style-type: none"> • Kidney problems • Loss of magnesium, calcium, potassium • High blood pressure • Tremors • Increases in cholesterol and triglyceride 	<ul style="list-style-type: none"> • Nausea • Vomiting • Liver problems • Changes in how clearly one can think • Insomnia • Unwanted hair growth • Confusion 	<ul style="list-style-type: none"> • Seizures • Changes in vision • Dizziness • Red blood cell destruction

Most of the problems described above, we anticipate to be common are temporary and treatable.

Risks and Toxicities Related to Standard Transplant Procedures

Risks of Umbilical Cord Blood Transplantation

The following problems may occur as a result of transplantation of cord blood. These are risks that would be present whether such 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 bone marrow transplantation. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. Although infections can be treated with drugs, they can be very dangerous or fatal.
- 2. Graft Failure.** The umbilical cord blood cells (the “graft”) may fail to grow inside your body. Past experience suggests that there can be up to a 15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. Graft failure can be fatal. Should this happen, you will NOT receive additional stem cells from the same cord blood donor. However, you may be able to receive a second transplant with stem cells from another person (e.g. different umbilical cord blood donor or an adult donor).
- 3. Graft-versus-host Disease (GVHD).** This condition results from the bone marrow cells 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 medication to prevent and/or treat it.

There are two forms of GVHD: acute GVHD (occurs in the first 3 months after transplant) and chronic GVHD (after the first 3 months). 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 (i.e. taking a small sample of tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

- 4. Genetic Disease within the Cord Blood Cells.** It is possible that certain genetic diseases (for example, thalassemia or immunodeficiency) may be passed through the umbilical cord blood stem cells. While these diseases are very rare, each umbilical cord blood unit can only be tested for a few of the many possible genetic diseases. To reduce this possibility, cord blood is not collected from babies that have genetic diseases running in their family.
- 5. Incorrect Labeling of the UCB.** Though rare, it is possible that incorrect labeling of an umbilical cord blood unit could occur so that you receive the wrong unit. To avoid this, the umbilical cord blood unit is re-typed to ensure that the tissue type of the donor and you are as previously reported (i.e., when the donor unit is confirmed). If the umbilical cord blood unit does not have an attached segment for us to re-type, there are several ways the unit labeling can be confirmed.

- 6. Other Complications.** Other complications that can result from the transplantation procedure not specifically related to one specific drug or the bone marrow stem cells or this study include:
- a. Damage to the vital organs in your body.** This could result in problems in any body organ, such as heart, lungs, liver, gut, kidneys and bladder, brain, etc. The lungs and the liver are particularly vulnerable. Some patients will experience severe lung problems due to infections and/or due to a reaction of the lungs to the chemotherapy and radiation. Rarely patients can suffer veno-occlusive disease of the liver (VOD). This complication results from high doses of chemotherapy and/or radiation. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, abdominal swelling, and abdominal pain. Although many patients recover completely, these complications may cause permanent damage or even death.
 - b. Serious infections.** Full and complete recovery of your immune system may take many months following the initial recovery of your cell counts. During this time, there is an increased risk of infections. You will be prescribed certain medications to reduce the chance of those infections. However, preventative treatments are not always effective. 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. Recurrence of disease, or development of a new blood cancer.** Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases (<2% of patients receiving a transplant) a blood cancer may arise from cells of the donor.
 - d. Risk to the unborn.** The treatments in this study have NOT 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 have the potential of becoming pregnant must use some form of effective birth control while receiving chemotherapy, TBI, and GVHD prophylaxis. Effective birth control is defined as the following:
 - 1) Refraining from all acts of vaginal intercourse (ABSTINENCE)
 - 2) Consistent use of birth control pills
 - 3) Injectable birth control methods (Depro-Provera, Norplant)
 - 4) Tubal sterilization or male partner who has undergone a vasectomy
 - 5) Placement of an IUD (intrauterine device)
 - 6) Use, with every act of intercourse, of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam.
 - e. Sterility and future childbearing potential for men and women.** Chemotherapy and/or irradiation may affect your ability to have children. Male patients may become sterile (unable to produce sperm) and should discuss with their doctor regarding sperm banking prior to transplantation. Female patients who have attained puberty may find that their menstrual cycle becomes irregular or stops permanently.

However, this DOES NOT MEAN THAT YOU CANNOT BECOME PREGNANT, and you must use some effective method of birth control during transplant and afterwards until you are off GVHD prophylaxis. Damage to reproductive tissue may result in infertility (inability to have children). It is not known if the damage could result in birth defects. You should discuss these risks and options in detail with your doctor before entering this study.

7. **Unknown or Unexpected Side Effects.** As with any treatment, there may be unknown and/or unexpected side effects from a non-myeloablative double UCB transplant. We may learn new things about non-myeloablative UCB 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.
8. **Additional information regarding MMF**
 - a. MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
 - b. MMF can limit the effectiveness of birth control pills and thus increase your chances of becoming pregnant while you are taking it.
 - c. In this trial you will be assigned to receive MMF for approximately 5 weeks and therefore you should not become pregnant during that time. If you think you might be pregnant or could become pregnant during the upcoming 5 weeks, you should not enroll in this trial.

Are there benefits to taking part in the study?

This research study is examining the treatment results of non-myeloablative preparative regimen along with UCB transplantation in unrelated donors. The knowledge gained from this study may help future patients who need a umbilical cord blood stem cell transplant, but there is no expectation that you will benefit from participating in the study.

As a result of the umbilical cord blood transplant, your disease may be put in remission or continue in remission.

What other choices do I have if I do not take part in this study?

Participation in this study is entirely voluntary. You don't have to be in this study. What you decide will not affect current or future health care you receive at this institution. Before you decide to be in this study, you and the medical staff will discuss other options available to you, including:

- Chemotherapy
- A bone marrow transplant from a tissue-typed partially mismatched related donor
- Transplantation from an adult unrelated donor, if one can be identified that would be a good match for you
- No therapy to try to control your leukemia/lymphoma but treatment to make sure you remain comfortable for the remainder of your life

What are the costs of taking part in this study?

You and/or your insurance company will pay all medical expenses relating to, or arising from, UCB transplantation. You will not be billed for tests that are only done for research purposes.

You will not be paid to be in this study.

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

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

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

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

What if I am injured as a result of being in this study?

In the event that this research activity results in an injury, treatment will be available. This treatment includes first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed to your insurance company. If you think you have suffered a research related injury, let the study doctors know right away. Unexpected side effects or accidents might result in your getting sicker than anticipated. All available medical care will be provided to you, but you and your insurance company are responsible for the costs of all such care.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you. You will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information that may affect your health or your willingness to stay in the study.

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

Will my medical information be kept private?

Your participation in this research study will be kept private and confidential. 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.

Organizations with access to your research and medical records:

- /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

Scientific and medical findings resulting from a study may be presented at meetings. They may be published so that the information can be useful to others. You will not be identified in these presentations and publications.

Information related to or resulting from your transplant will be reported to the CIBMTR. The CIBMTR is a voluntary organization of basic and clinical scientists working together to gather results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

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

HIPAA¹ authorization to use and disclose individual health information for research purposes

- a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher’s staff to use and disclose my individual health information for the purpose of conducting the research study entitled: *A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning (NST) and Transplantation of Partially HLA-Mismatched 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 conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).
- c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher’s staff may obtain 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 Investigators and the researcher’s staff at the University of Minnesota.
 - Staff/laboratories identified in the protocol for the evaluation of other laboratory samples
 - National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
 - Blood and Marrow Transplant Clinical Trials Network (BMT CTN), 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
 - 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)

¹ 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 public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Others:

- 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 research-related treatment that is provided through the study. However, 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. This authorization does not have an expiration date.

Is there an expiration date for keeping my records?

Study records will be kept indefinitely by the transplant center for re-analysis and follow-up. If you have questions about the keeping of your research records or access to your files, please call /name/ at /number/.

Will researchers benefit from me being in this research study?

Your doctors have no money invested and will not get any financial gain from this study. Presenting research results may help the career of a doctor. Therefore, the doctors running this research study may benefit when the results are presented at scientific meetings or in the scientific press.

Consent for Treatment:

I have been informed about this study’s purpose, procedures, possible benefits and risks. I have been given a chance to ask questions and have had them answered to my satisfaction. I understand that I can ask more questions at any time.

I voluntarily agree to participate in this study.

By signing this consent form, I have not given up any of the legal rights which I otherwise would have as a subject in a research study.

Signature of Subject *Date*

Print Name of Subject

Signature of Legally Authorized Representative *Date*

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

Counseling Healthcare Professional *Date*

Use of an Interpreter: Complete if the subject is not fluent in English and an interpreter was used to obtain consent:

Print name of interpreter: _____ Date: _____

Signature of interpreter: _____

An oral translation of this document was administered to the donor in _____ (state language) by an individual proficient in English and _____ (state language). See the attached short form addendum for documentation.

ASSENT FORM***A Multi-Center, Phase II Trial of Non-Myeloablative Conditioning and Transplantation of Umbilical Cord Blood (UCB) from Unrelated Donors for Patients with Hematologic Malignancies***

You have leukemia or lymphoma. Leukemia and lymphoma are cancers of the blood cells made in your body's "blood factory", which is called the bone marrow. These cancers are treated with special medicines. These medicines are called chemotherapy. They kill cancer cells. If chemotherapy doesn't kill all of the cancer cells, a special and stronger treatment called a transplant may be needed.

During some transplants, you receive a very large amount of chemotherapy medicines and radiation therapy to kill the cancer cells in your body. These chemotherapy drugs are so strong that they also kill many normal cells in your blood and bone marrow. In a mini-transplant you will still get chemotherapy medicines and radiation therapy, but you will get smaller doses of these medicines. A smaller amount of your cancer cells will be killed, but your body will be able to heal itself faster and attack the cancer cells. Your doctors think that a mini-transplant is the best treatment for you. They believe that it will increase your chance of cure.

You can be transplanted with blood cells from a baby's umbilical cord. Umbilical cord blood is the extra blood left over after a baby is born. It used to be thrown away. We know now that it contains blood-forming cells like the ones found in bone marrow. Cord blood can be collected after a baby is born and stored for future use. Collecting cord blood does not hurt the baby or Mom. When a patient, like you, needs a transplant, cord blood can be removed from storage and sent to your hospital for your transplant. There have been many transplants using umbilical cord blood.

Transplant Procedure

Before the transplant, you will be given the drugs cyclophosphamide and fludarabine. These drugs will be given through a central line – an IV that will be placed in your chest. If you do not already have a central line, we will put one in as a surgical procedure. A central line makes it easier for you to receive drugs and for drawing blood for tests. You will also get radiation to your whole body the day before your transplant. After you have received these drugs and radiation, new blood cells from umbilical cord blood will be given through your central line. When the blood gets into your body, you may feel sick to your stomach but that will go away quickly. You will be in the hospital for about four weeks after the cord blood cells are given to you while we are waiting for the cord blood cells to grow up inside your body and for you to recover from the chemotherapy and radiation. You will need to be on a number of medications during your transplant, which will either be given through your line or will be taken by mouth.

It will be necessary to check your blood and bone marrow after the transplant to make sure the cord cells are growing in your body. Your doctors will do blood tests and bone marrow tests. Blood tests will usually be done by taking blood through your line.

Risks/Discomforts

The drugs and radiation may cause hair loss, nausea and vomiting, and diarrhea. Your blood counts will fall and you may get fevers, infections or start bleeding. You may also get mouth sores. These are temporary and you will feel better as your new bone marrow grows.

During the period your new bone marrow is growing back after the cord blood transplant, you may need to get antibiotics since you will not be able to fight infections. You may also need to get blood transfusions since your new bone marrow will not be making new blood cells right away. It is possible that your new bone marrow will not grow back. This is unlikely but if it did happen, it may even be necessary to do a second transplant. You may get graft-versus-host disease (GVHD), which happens when transplanted cells attack your body causing skin rash, vomiting, diarrhea and liver problems. These problems could be mild, or they could be very serious. Your doctors will do their best to make you feel better and keep you safe.

The above information has been explained to me. My questions have been answered.

I agree to participate in this study.

Patient

Parent

Physician

Witness

Date

APPENDIX C

LABORATORY PROCEDURES

1. HLA TYPING

Before Transplantation: HLA typing will be performed for all patients and donors in American Society of Histocompatibility and Immunogenetics (ASHI)-approved laboratories designated by the transplant centers. HLA typing must be performed by DNA methods for HLA-A, and -Band DRB1 at high resolution (allele level).

After Transplantation: High resolution HLA typing of cryopreserved patient and UCB samples (from the wash or unused attached segments) is conducted as an ongoing research study by the NMDP. Data will be shared with the BMT CTN.

2. CHIMERISM

Samples of peripheral blood or marrow are collected from the patient and samples from the UCB pre-transplant for chimerism studies according to institutional standards. Patient samples are also collected on Day ~28, ~60, ~180 and ~365 post-transplant. Chimerism will be measured by RFLP or microsatellite. FISH should not be used to assess chimerism. Donor chimerism after transplantation shall be measured on samples of whole blood or mononuclear fraction.

APPENDIX D**DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED
EXPONENTIAL DATA****Background – The Sequential Probability Ratio Test**

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

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$, and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N | \theta_j) \equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0) \leq \alpha$ and $\Pr_1(\text{reject } H_0) \leq \beta$, and for which $E_j(N)$ are finite, $j=0,1$, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the x_1, x_2, \dots are independent and identically distributed (i.i.d.) with density function $f(x, \theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1 (> \theta_0)$ has non-decreasing power function.

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

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

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of treatment-related mortality (TRM) at 100 days is less than or equal to 30% versus the alternative hypothesis that it is greater than or equal to 50%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 5%, and that the test provide 80% power to reject the null hypothesis under a specified alternative that the true rate is 50%. A maximum sample size of 50 patients will be permitted.

Let us assume that the survival times, T_1, T_2, \dots, T_n , are completely observed (uncensored) and are i.i.d. with exponential density function $f(T, \theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 100-day survival rate of 70% translates into a mean survival of 0.768 years ($\theta_0 = 1.303$), and 50% translates into a mean survival of 0.395 years ($\theta_1 = 2.532$).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0 : \theta = \theta_0 = 1.303$ versus $H_1 : \theta = \theta_1 = 2.532$. However, since the log-likelihood ratio for the

exponential, $\log \prod_i^n f(x_i; \theta_1) - \log \prod_i^n f(x_i; \theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0) \sum_i^n T_i$, is a

monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ . Thus the SPRT is a one-sided level .05 test of a composite null ($H_0 : \theta \leq \theta_0 = 1.303$) versus a composite alternative ($H_1 : \theta \geq \theta_0 = 1.303$), with power of $1 - \beta = .80$ at the selected alternative $\theta = \theta_1 = 2.532$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\log \theta_0 - \log \theta_1)/(\theta_0 - \theta_1) = 0.541$, and intercepts $\log A/(\theta_0 - \theta_1) = -2.256$ and $\log B/(\theta_0 - \theta_1) = 1.270$, for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the cumulative sum of failure times, $\sum_i^n T_i$, is recomputed, and plotted against the current sample size, n . When this graph crosses the lower boundary, the null hypothesis is rejected.

The maximum sample size of 50 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 50 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 50 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for TRM is constant over the first 100 days post-transplant, and

we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 100 day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, T_1, T_2, \dots, T_n , with censored failures times, x_1, x_2, \dots, x_n , and the current sample size, n , with the number of observed failures, d .

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 50 patients to the study, and that the final analysis takes place 100 days after the last patient is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s , ranging from 0 to 3 years 100 days, the sum of observed time on study, $\sum_i^n X_i(s)$ is plotted against the number of observed failures, $d(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the lower boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 100-day TRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in survival at Day 100 from 70% to 50%, with type I and II errors of 5% and 20%. Since only the lower boundary is used for monitoring, the continuation region of the test was bounded below by a line with a slope of 0.541 and intercept of -2.256 . The effect of truncation is to reduce the power of the test. In order to compensate for this, we raise the lower boundary to make it easier to cross. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of -1.741 , corresponding to setting parameters α and β to 10% and 15%, result in empirical type I and II error rates of about 5% and 20%.

Table D-1 Operating Characteristics of Sequential Testing Procedures from a Simulation Study with 100,000 Replications**Treatment-Related Mortality (TRM)**

True 100-Day Rate	30%	35%	40%	45%	50%
Probability Reject Null	0.07	0.20	0.41	0.66	0.86
Mean Month Stopped	34.5	32.3	28.5	23.5	18.5
Mean # Endpoints in 100 Days	13.8	15.0	15.1	14.0	12.1
Mean # Patients Enrolled	48	45	40	33	26

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of TRM on or before Day 100 was 30%, the test crossed the lower boundary in 7119 of 100,000 replications, for an estimated type I error rate of 7%. When the true rate of TRM on or before Day 100 was 50%, the test failed to cross the boundary in 14226 of 100,000 replications, for an estimated type II error rate of 14%. And on average, the boundary will be crossed at 18.5 months, when 26 patients will be enrolled to the study.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 100 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 100 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 100 days were high, the exponential test would reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.

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