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 $1.5 \times 10^7$ 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, $FEV_1$, 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 Cockroft-Gault formula) > 40 mL/min/1.73$m^2$; 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/$m^2$ 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*

| | |
|---|---|
| Days –6 - | Fludarabine 40 mg/M$^2$ IV daily<br>Cyclophosphamide (Cy) 50 mg/kg IV daily<br>Mesna 50 mg/kg IV daily** |
| | ↓ |
| Days –5 - | Fludarabine 40 mg/M$^2$ IV daily |
| | ↓ |
| Days –4 - | Fludarabine 40 mg/M$^2$ IV daily |
| | ↓ |
| Days –3 | Fludarabine 40 mg/M$^2$ IV daily<br>Start cyclosporine A (or tacrolimus)<br>Start cyclosporine mycophenolate mofetil |
| | ↓ |
| Days –2 - | Fludarabine 40 mg/M$^2$ IV daily |
| | ↓ |
| Day –1 - | TBI 200 cGy |
| | ↓ |
| Day 0 - | Infuse umbilical cord blood graft units |
| | ↓ |
| Day +1 - | Start filgrastim 5 mcg/kg/day |
| | ↓ |
| Day 21 (±2) | Assess chimerism in peripheral blood<br>Bone marrow biopsy to assess cellularity |
| | ↓ |
| Day +30 | Discontinue MMF if neutrophil engraftment and no acute GVHD |
| | ↓ |
| Day +56 - | Assess chimerism in peripheral blood |
| | ↓ |
| Day +180 | Discontinue cyclosporine A<br>(or tacrolimus; optional if GVHD is active)<br>Assess chimerism in peripheral blood<br>Evaluate disease |
| | ↓ |
| 1 yr, | Evaluate disease<br>Assess chimerism in peripheral blood |

* 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 setting[6]. 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 anemia[7], 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 units[10]. 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 $10^7$/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 others[22] 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 $10^7$/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 conditioning[29]. 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) grafts[30]. 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 al[31] 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 transplantation[14]. 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/m$^2$ 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 $10^9$/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 6$^{th}$ and 7$^{th}$ decades of life[32]. 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 complications[35]. 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 $10^7$/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 $10^9$/L between 32 and 43 days. Graft failure rates ranged between 6% to 24%. In a recent report[48], 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 NCDX$10^7$/kg (range) | Infused CD34 cell dose x$10^5$/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/rATG | 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, Fly/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/$m^2$, 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 ≥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 $1.5 \times 10^7$/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 $m^2$.
   d. - Pulmonary: $FEV_1$, FVC, DLCO (diffusion capacity) > 50% predicted (corrected for hemoglobin); if unable to perform pulmonary function tests, then $O_2$ 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).

**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/.

**HIPAA[1] 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 $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$ decides in favor of $H_1$ or $H_0$ if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1) / f(x_i;\theta_0)$ is the likelihood ratio, and $c_\alpha$ is determined to have the size $\alpha$. 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 $\alpha$ and $\beta$ of rejecting $H_0$ when $\theta = \theta_0$, and of accepting $H_0$ when $\theta = \theta_1$, respectively, and the expected sample size $E(N \mid \theta_j) \equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0) \le \alpha$ and $\Pr_1(\text{reject } H_0) \le \beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities $\alpha$ and $\beta$ minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2, ...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing $\theta_0$ against $\theta_1 (> \theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities $\alpha$ and $\beta$, 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 $\theta$. The sample size distribution is very highly skewed, $Var(N) \approx [E(N)]^2$. Thus we will consider a truncated test with maximum sample size of $N_0$ and simulate to obtain the operating characteristics of the test.

**Derivation of the SPRT for 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, $T_1, T_2, ..., T_n$, 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, - $H_0 : \theta = \theta_o = 1.303$ 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 $\theta$. Thus the SPRT is a one-sided level .05 test of a composite null ($H_0 : \theta \le \theta_o = 1.303$) versus a composite alternative ($H_1 : \theta \ge \theta_o = 1.303$), 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, $T_1, T_2, ..., T_n$, with censored failures times, $x_1, x_2, ..., x_n$, 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 $\alpha$ and $\beta$ 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.

# APPENDIX E

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