



**A Phase III Randomized, Multicenter Trial Comparing
G-CSF Mobilized Peripheral Blood Stem Cell with Marrow
Transplantation from HLA Compatible Unrelated Donors**

**BMT CTN PROTOCOL 0201
Version 8.0**

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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0201

A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors

Principal Investigator: Claudio Anasetti, M.D.

Study Design: The study is designed as a Phase III, randomized, open label, multicenter, prospective, comparative trial of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) versus marrow from unrelated donors for transplantation in patients with hematologic malignancies. Recipients will be stratified by transplant center and disease risk and will be randomized to either the PBSC or marrow arm in a 1:1 ratio.

Primary Objective: The primary objective is to compare two-year survival probabilities between patients in the two study arms using an intent-to-treat analysis.

Secondary Objectives: Patients randomized to the two study arms and actually transplanted will be compared for the following endpoints (patients who do not receive a transplant will be excluded from the following analyses): survival, incidences of neutrophil and platelet engraftment, graft failure, acute graft-versus-host disease (GVHD), chronic GVHD, time off all immunosuppressive therapy, relapse, infections, adverse events, immune reconstitution, and quality of life. Donors in each arm of the study will be compared for time to return to baseline toxicity score, CBC and WBC differential values after donation and quality of life.

Eligibility Criteria: Eligible patients are up to 66.00 years of age, have acute leukemia, myelodysplasia, chronic myeloid leukemia, or other myeloproliferative disorders, adequate organ function, a 6/6 or 5/6 HLA-A, B and DRB1 matched unrelated donor, and are able to give signed informed consent prior to enrollment. Donors must be 18 years of age, meet National Marrow Donor Program (NMDP) criteria for donor eligibility and give informed consent prior to enrollment.

Treatment Description: Patients will receive one of four conditioning regimens as described in the protocol, at the discretion of the transplant physician. The GVHD prophylaxis regimen will be per institutional standard, but may not contain Phase I agents. The transplant physician must declare the conditioning and GVHD prophylaxis regimens prior to randomization to the PBSC versus marrow arm. Marrow cells will be collected from the donors using standard procedures. PBSC

donors will receive G-CSF ~10mcg/kg/d x 5 days and cells will be collected by a single large volume apheresis on Day 5, or two smaller volume apheresis procedures on Days 5 and 6. Marrow or blood cells will not be T-depleted or frozen prior to transplantation.

Accrual Objective: Patients who are candidates for transplantation of G-CSF–mobilized PBSC or marrow from HLA-compatible unrelated donors will be targeted for accrual. Approximately 275 patients will be accrued per study arm (total of 550 patients).

Accrual Period: The estimated accrual period is three years.

Study Duration: Patients and donors will be followed for two years for evaluation of the primary endpoint, with additional follow-up to three years after transplantation or donation for evaluation of certain secondary endpoints.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Rationale

Many studies of allogeneic marrow transplantation have shown that a higher dose of marrow cells correlates with more robust hematopoietic engraftment and lower mortality from infectious complications. Peripheral blood stem cells (PBSC) collected after mobilization with granulocyte colony stimulating factor (G-CSF) contain a larger number of CD34-positive (CD34) progenitors and total cells than bone marrow. These observations led to the hypothesis that transplantation of PBSC would lead to lower mortality compared to transplantation of marrow. In addition, PBSC grafts have a higher T cell content, predicting a possibly more powerful anti-leukemia effect. However, the higher T cell content of PBSC may also lead to increased incidence and severity of acute and chronic graft-versus-host disease (GVHD). This concern is especially serious when the donor is unrelated to the recipient. This prospective, randomized, multicenter clinical trial of unrelated donor transplantation will test the hypothesis that transplantation of PBSC leads to similar patient survival compared to transplantation of marrow.

1.2. Marrow Cell Dose Effect

Early in the history of hematopoietic stem cell transplantation, marrow cell dose was recognized as a limiting factor for engraftment and patient survival. In patients with aplastic anemia conditioned with cyclophosphamide and transplanted with marrow from HLA-identical siblings, infusion of fewer than 3×10^8 cells per kilogram (kg) was associated with increased risks of graft failure and death (1). The authors of that report suggested: “The greatest possible amount of donor marrow, perhaps supplemented by stem cells derived from the peripheral blood, should be obtained.” Subsequent studies have supported this concept. Improved survival was associated with transplantation of higher marrow cell doses in patients with acute myeloid leukemia (AML) in first remission (2). The number of hematopoietic precursor cells in T-replete marrow grafts was associated with better survival after transplantation from HLA-identical siblings (3). A higher number of CD34 cells, a population that includes hematopoietic progenitors, was associated with improved survival after T cell depleted (4), or T-replete marrow grafts from HLA-identical siblings (5).

Cell dose is limiting with transplantation of HLA incompatible unrelated cord blood (6, 7), and with transplantation of HLA incompatible related donor marrow (8). However engraftment across the HLA barrier was achieved with the use of T-depleted PBSC containing a large dose of CD34 cells (9).

Studies of unrelated donor transplants have shown similar results. In patients with acute leukemia receiving T-replete marrow from unrelated donors, transplantation of a marrow nucleated cell dose above $3.65 \times 10^8/\text{kg}$ was associated with faster neutrophil and platelet engraftment, decreased incidence of severe GVHD, less non-leukemic deaths and better

leukemia-free survival (10, 11). Similar findings were reported in children receiving unrelated donor transplants for chronic myeloid leukemia (CML) (12) or Hurler's syndrome (13). Thus, there is abundant evidence that marrow is a limiting source of hematopoietic progenitors for human transplantation. This supports the hypothesis that cell doses higher than the average marrow harvest might improve transplant outcome.

1.3. PBSC Characteristics

Hematopoietic precursors circulate in the peripheral blood at a low steady state concentration. However, administration of a recombinant growth factor, such as G-CSF, causes a rapid increase in hematopoietic progenitors in the circulation. Transplantation of G-CSF-mobilized PBSC can produce durable hematopoietic reconstitution when infused after myeloablative conditioning into autologous, syngeneic or allogeneic transplant recipients, and engraftment is more rapid with PBSC compared to marrow transplantation (14, 15, 16). After transplantation, PBSC can differentiate into mature hepatocytes and epithelial cells in the skin and gastrointestinal tract, indicating that they contain true stem cells (17). PBSC components collected after G-CSF administration contain two to five-fold greater numbers of CD34 cells compared to marrow, 10-fold greater numbers of T cells (18), 24-fold greater numbers of monocytes, 13-fold greater numbers of natural killer (NK) cells (19), and 5-fold greater number of plasmacytoid dendritic cells (20). Therefore, more rapid engraftment of PBSC compared to marrow grafts may not be entirely due to increased numbers of CD34 cells, but may result from altered properties of CD34 cells, or from the infusion of more cells belonging to other lineages. Clinical studies indicate that the risk of acute GVHD is perhaps increased after PBSC transplantation, but is definitely not as high as one would expect with the infusion of 1–2 logs more T cells as compared to marrow transplantation. Possible explanations are that T cells are functionally altered in G-CSF-mobilized PBSC or that infused accessory cells regulate T cell function (21, 22, 23). Thus, there are multiple quantitative and qualitative differences between PBSC and marrow transplants.

1.4. Safety of G-CSF in Normal Donors

The advantages for the donor of PBSC apheresis over marrow harvesting include the avoidance of general anesthesia and surgical complications. A randomized study of sibling transplantation demonstrated similar levels of physical discomfort for marrow and PBSC donors, but quicker resolution of symptoms for PBSC donors (24). The administration of G-CSF in doses up to 16 mcg/kg/day in normal donors has been associated with bone pain, malaise, myalgias, headache, leukocytosis and mild thrombocytopenia as common side effects (25). These are usually reversed within two days of discontinuing the drug. Self-limited laboratory abnormalities include elevated alkaline-phosphatase, lactate dehydrogenase, uric acid, alanine aminotransferase, γ -glutamyl transpeptidase, and decreased potassium and magnesium. G-CSF also causes transient hemostatic changes, including increases in prothrombin fragment, thrombin–antithrombin complex and D-dimer (26). Case reports have described rare events, such as myocardial infarction (27), or stroke (28), in association with G-CSF administration. These thrombotic complications have occurred in donors with a history of peripheral vascular disease or myocardial infarction and are unlikely to occur in healthy donors. Spontaneous spleen rupture constitutes an unusual and rare adverse event following G-CSF administration for PBSC collection from normal donors (29, 30). Preliminary National Marrow Donor Program (NMDP)

experience with PBSC collection from unrelated donors indicates a favorable short-term safety profile (31). The existence of late side effects from G-CSF will not be known until many donors are evaluated for a long period of time.

1.5. Results of Randomized Trials of PBSC versus Marrow from HLA-Identical Siblings

1.5.1. Engraftment

Eight randomized trials compared transplantation of mobilized PBSC and marrow from HLA-identical sibling donors (32, 33, 34, 35, 36, 37, 38, 39). Each of these trials enrolled 30 to 350 patients. Neutrophil engraftment occurred significantly earlier with PBSC in seven trials, and platelet engraftment occurred significantly earlier with PBSC in all trials.

1.5.2. Acute GVHD

The risks of acute grades II–IV GVHD were similar in seven trials, while the European Blood and Marrow Transplant (EBMT) study (40) noted a 13% greater incidence of grade II–IV GVHD and a 12% greater incidence of grade III–IV GVHD with PBSC. The following are differences among the trials that might explain the reason for discrepant results:

1. All trials utilized the combination of cyclosporine and methotrexate for GVHD prevention. However, the EBMT study omitted the Day 11 methotrexate from the regimen while the next two largest trials in the U.S. (41) and Canada (42) included the Day 11 methotrexate. In prior studies of marrow transplantation, the omission of Day 11 methotrexate increased the risks of GVHD (43).
2. The EBMT trial employed G-CSF post-transplant while the U.S. and the Canadian trials did not employ G-CSF. There is no obvious relationship between post-transplant G-CSF and GVHD.
3. The EBMT trial was the largest and therefore had the most statistical power to detect a difference.

1.5.3. Chronic GVHD

All trials suggested that PBSC transplantation was associated with more chronic GVHD, and three trials found a statistically significant increase of chronic GVHD with PBSC. The Day 11 dose of methotrexate was omitted in the three trials where PBSC led to a statistically significant increase in incidence of chronic GVHD. While this observation does not directly explain a higher incidence of chronic GVHD, patients who have acute GVHD are more likely to develop chronic GVHD and patients who do not receive the Day 11 dose of methotrexate are more likely to develop acute GVHD.

1.5.4. Survival and Relapse

The second and third largest trials, involving 228 and 172 patients in Canada and the United States (U.S.), respectively, showed statistically better survival or disease-free survival with PBSC. In the U.S. study, the survival difference of 13% at 2 years was greatest among patients with advanced hematologic malignancies. Both reduced transplant-related mortality and relapse contributed to the improved survival. In comparison to the other trials, the U.S. study enrolled a larger number of patients with advanced hematologic malignancies, where it found a benefit for PBSC. The U.S. trial failed to detect improved survival with PBSC in patients with early stage disease, perhaps because of the relatively small sample size or perhaps because both transplant-related mortality and relapse are lower in this group regardless of graft source. The Canadian trial enrolled patients with early leukemia, and found a significant survival advantage with PBSC of 10% at 2 years, primarily due to reduced non-relapse mortality. The EBMT trial enrolled almost exclusively patients with early leukemia, but showed no differences in disease-free survival or overall survival. Differences between the EBMT and the Canadian trials were discussed above. One interpretation of the results of these randomized trials is that the administration of post-grafting methotrexate using the full dose and schedule may be critical to prevent acute and chronic GVHD after PBSC transplantation and to realize the potential for PBSC to improve patient survival by 10–13% at 2 years (44).

1.6. Results of Phase II Studies of PBSC from Unrelated Donors

1.6.1. European Studies

Initial reports demonstrated the feasibility and potential safety of G-CSF-mobilized PBSC transplants from unrelated donors (45, 46, 47, 48). In matched-cohort studies by Ringden (49) and Remberger (50), PBSC achieved faster neutrophil and platelet engraftment compared to marrow transplantation, but there was no difference in acute GVHD, relapse, treatment-related mortality, or survival. Elmaagacli and colleagues (51) proposed that for patients with CML in chronic phase, PBSC transplants are associated with decreased relapse and improved survival when compared with bone marrow from HLA-compatible unrelated donors.

1.6.2. Preliminary NMDP Phase II Data in Unrelated Donor PBSC Transplants

A prospective study was conducted by the NMDP to test the feasibility of harvesting PBSC from volunteer donors and the safety of transplanting those PBSC to patients with hematological disorders. Donors were treated daily with G-CSF 10 mcg/kg and PBSC were harvested on Days 5 and 6. Cells collected on Day 5 were stored at 2-8°C. The two-day collection was transported at 2-8°C and infused fresh into the recipient. An interim analysis evaluated results of 222 transplants facilitated by 55 apheresis centers and 57 transplant centers over the first year of study. PBSC were obtained in a one-day (n=47) or two-day (n=175) collection. The median blood volume processed was 12 liters per day, and 24 liters per total collection. Transplant regimens varied according to institutional protocols. The incidence of engraftment was 96%, acute GVHD grades II-IV 47%, acute GVHD grades III-IV 33%, extensive chronic GVHD 36%, mortality from causes other than relapse 18% at 100 days and 41% at one year, relapse 26%, survival 35% and disease-free survival 32% at one year. Outcomes of PBSC and marrow

transplants conducted at the same institutions over the same period were compared. Multivariate analyses were used to adjust for differences in patient age, gender, cytomegalovirus serology, performance status, diagnosis and stage, interval from diagnosis to transplant, donor age, HLA matching, transplant center, year of transplant, conditioning and immunosuppressive regimen. PBSC were associated with faster neutrophil and platelet engraftment, similar risk of GVHD grades II-IV, increased GVHD grades III-IV, and similar rates of relapse, survival and disease-free survival (Table 1.6.2).

Table 1.6.2: Multivariate Analyses of Unrelated Donor Transplant Outcomes Assessing the Risks Associated with PBSC Compared to Bone Marrow

	Odds Ratio	95% Confidence Interval	p value
Neutrophil engraftment on Day 21	4.6	2.5-8.5	< 0.0001
Platelet engraftment on Day 21	5.2	3.1-8.8	< 0.0001

	Relative Risk	95% Confidence Interval	p value
Acute GVHD grades II-IV	1.3	0.9-1.7	0.12
Acute GVHD grades III-IV	1.7	1.2-2.5	0.004
Chronic extensive GVHD	1.3	0.8-1.9	0.26
Relapse	1.0	0.7-1.4	0.85
Disease-free survival	0.9	0.7-1.1	0.28
Overall death	0.8	0.6-1.0	0.10
Death first 100 days	0.6	0.4-0.8	0.003
Death beyond 100 days	1.2	0.8-1.7	0.39

Models were controlled for transplant center and year, recipient age, gender, diagnosis, Karnofsky score and CMV, donor age, HLA matching, conditioning and immunosuppressive regimens.

Since the survival model did not meet criteria for hazard proportionality over time, two separate models tested the association between PBSC and survival. Within the initial 100 days after transplantation, PBSC was associated with a lower hazard of death (RR 0.6, 95% C.I. 0.4-0.8, p=0.003), while after the 100 days there was no association (RR 1.2, 95% C.I. 0.8-1.7, p=0.39). When reduced-intensity transplants, defined by the use of whole body irradiation at a dose below 800 cGy, or the use of mycophenolate mofetil were excluded from the analysis, the proportional hazards assumption was no longer violated and PBSC was associated with a small and not statistically significant survival advantage at 100 days (RR=0.7, p=0.10) and similar overall survival (RR=0.95, p=0.73). A multivariable analysis restricted to PBSC recipients evaluated a potential association of CD34 cell dose with outcome. The analysis found that the highest quintile of CD34 cell doses (i.e. > 10⁷ per kg) was associated with an increased risk of chronic GVHD but had no association with survival. The lowest dose of CD34 cells (i.e. < 4 x 10⁶ per kg) was not associated with worse outcome.

We conclude that harvest and transplantation of PBSC from volunteer donors are feasible and, within the constraints of this initial study, appear at least as safe and effective as marrow grafts. Since this study was not randomized and the groups of patients who received PBSC and marrow differed for many variables, we cannot conclude with certainty that PBSC is better, worse, or the same as marrow. Although the benefits and risks of PBSC transplants from unrelated donors are not proven, the utilization of unrelated donor PBSC in the U.S. is increasing: from 223 in the year 2000, to 372 in the year 2001, to 523 in the year 2002. The continued rise in utilization of PBSC, in the absence of definitive data demonstrating any long-term advantages over marrow and concern about possible increased risks of chronic GVHD, supports the rationale for the timely conduct of a prospective randomized trial of PBSC versus marrow in unrelated donor transplantation.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a Phase III randomized, open label, multicenter clinical trial sponsored by the NMDP and the National Institutes of Health (NIH). The objective of the trial is to test the null hypothesis that there is no difference in overall survival after PBSC versus marrow transplants from HLA compatible unrelated donors. The study will compare G-CSF-mobilized PBSC transplantation with bone marrow transplantation from HLA-compatible unrelated donors for patients with leukemia, myelodysplastic or myeloproliferative syndromes. Conditioning and GVHD prophylaxis regimens will vary by center and within centers, however, the center must declare before randomization what regimens will be used for each patient. The primary endpoint of this trial is two-year survival following randomization. Secondary analyses will consider neutrophil and platelet recovery, acute and chronic GVHD, time off all immunosuppressive therapy, relapse, infections, adverse events and immune reconstitution. The trial will include evaluation of patient and donor quality of life, composition of the graft, and immune reconstitution. Accrual is anticipated for three years with a follow-up period of three years.

2.2. Hypothesis and Specific Objectives

2.2.1. Primary Hypothesis

The null hypothesis of this randomized clinical trial is that there is no difference in the two-year survival between PBSC and marrow transplantation. The alternative statistical hypothesis is that survival after PBSC transplantation differs from survival after marrow transplantation; no assumption is made about the direction of the difference.

2.2.2. Secondary Hypotheses

PBSC recipients will have faster hematopoietic recovery, improved immune reconstitution, lower risks of infection and relapse, higher risks of grades III-IV acute GVHD and chronic GVHD, and longer requirement for immune suppressive medications than marrow recipients. There will be no detectable difference in the physical, functional, psycho-emotional quality of life and the rate of return to work between PBSC and marrow recipients. There will be differences in the pattern of donor quality of life over time from donation between the groups, but no detectable differences in overall scores. PBSC donors will experience more rapid recovery from the donation with fewer prolonged painful or disabling complications than marrow donors. There will be no long-term impact on post-donation blood counts in either the PBSC or marrow group.

2.2.3. Study Objectives

The primary objective of the trial is to compare two-year survival rates of the two groups of patients starting from the time of randomization to the PBSC or marrow arm. Secondary objectives include comparisons of survival rates after transplantation and incidences of neutrophil and platelet recovery, acute GVHD, chronic GVHD, time off all immunosuppressive therapy, relapse, infections, adverse events, immune reconstitution and quality of life. Additional secondary objectives are to compare donor donation experiences and recovery and donor quality of life. In addition, the study will analyze variables affecting the composition of the graft, and assess the relationships between cell subsets in marrow or PBSC grafts and transplant outcomes.

2.3. Patient Eligibility for Randomization

2.3.1. Patient Inclusion Criteria

Diagnoses to be included:

1. Acute Myelogenous Leukemia at the following stages:
 - First Remission
 - Second Remission
 - Third or Subsequent Remission
 - Not in Remission

Complete remission will be defined as all of the following according to the revised recommendations of the international working group:⁵²

- A bone marrow aspirate containing spicules with < 5% blasts with a count of at least 200 nucleated cells and no Auer rods seen. If spicules are absent in the aspirate, a bone marrow biopsy should confirm that < 5% blasts are present.
- No evidence of a persistently abnormal leukemic population by flow cytometry.
- ANC > 1,000 μ L and platelet count > 100,000 μ L.
- No extramedullary leukemia.
- No blasts in peripheral blood.

2. Acute Lymphoblastic Leukemia at the following stages:
 - First Remission
 - Second Remission
 - Third or Subsequent Remission
 - Not in Remission

Complete remission will be defined as all of the following according to the revised recommendations of the international working group:⁵²

- A bone marrow aspirate containing spicules with < 5% blasts with a count of at least 200 nucleated cells and no Auer rods seen. If spicules are absent in the aspirate, a bone marrow biopsy should confirm that < 5% blasts are present.

- No evidence of a persistently abnormal leukemic population by flow cytometry.
 - ANC > 1,000 μ L and platelet count > 100,000 μ L.
 - No extramedullary leukemia.
 - No blasts in peripheral blood.
3. Chronic Myelogenous Leukemia at the following stages:
- Chronic Phase:
 - Stable, not hematologic remission: blasts present in marrow and/or PB, but disease does not qualify as accelerated or blast phase
 - Hematological remission: no blast cells or precursor cells in the blood or marrow
 - Partial cytogenetic remission: Ph+ metaphases >0% but < 35%
 - Complete cytogenetic remission: absence of Ph+ metaphases
 - Accelerated Phase - any one of the following symptoms:
 - WBC difficult to control (> 50 x 10⁹/L despite therapy)
 - Rapid doubling of WBC (< 5 days)
 - \geq 10% blasts in blood or marrow
 - \geq 20% blasts and/or promyelocytes in blood or marrow
 - \geq 20% basophils and/or eosinophils in blood
 - Anemia or thrombocytopenia unresponsive to standard treatment
 - Persistent thrombocytosis (> 1000 x 10⁹/L)
 - Cytogenetic abnormalities in addition to Ph+
 - Increasing splenomegaly
 - Marrow fibrosis
 - Blast Phase:
 - More than 30% blasts and/or promyelocytes in blood or bone marrow
 - More than 20% blasts
4. Myelodysplastic syndromes at the following stages:
- Refractory anemia
 - Refractory anemia with ringed sideroblasts
 - Refractory cytopenia with multilineage dysplasia
 - Refractory cytopenia with multilineage dysplasia and ringed sideroblasts
 - Refractory anemia with excess blasts-1 (5-10% blasts)
 - Refractory anemia with excess blasts-2 (10-20% blasts)
 - Myelodysplastic syndrome, unclassified
 - MDS associated with isolated del (5q)
5. Myeloproliferative diseases:
- Chronic Myelomonocytic Leukemia
 - Agnogenic Myeloid Metaplasia with Myelofibrosis (Idiopathic Myelofibrosis)
 - Juvenile Myelomonocytic Leukemia

6. Patients with therapy-related AML or MDS whose prior malignancy has been in remission for at least 12 months. If the remission is less than 12 months, Medical Monitor or Protocol Chair approval is required.
7. Signed informed consent
8. Age range: 0.00-66.00 years
9. Transplant Center location in the United States (U.S.) or Canada

2.3.2. Patient Exclusion Criteria

1. Patients with prior allogeneic or autologous transplants using any hematopoietic stem cell source will be excluded from this trial. Patients with secondary malignancies who have had a prior autologous transplant will be eligible. The prior autologous transplant must have been performed for the primary malignancy (such as lymphoma) and must have occurred 12 or more months prior to enrollment.
2. Diseases to be excluded are: lymphoma (11% of 2001 NMDP transplants), other malignant disorders (6%), and non-malignant disorders (9%). The diseases are excluded because they are rarely transplanted or are most often transplanted using reduced intensity regimens.

2.4. Additional Patient Exclusion Criteria for Transplant Conditioning

1. HIV infection
2. Pregnancy (positive serum β -HCG) or breastfeeding
3. Creatinine or bilirubin or ALT or AST greater than two times the upper limit of normal for the laboratory, whatever the etiology of the abnormal test except for isolated hyperbilirubinemia attributed to Gilbert's Syndrome
4. Pulmonary disease with FVC, FEV1 or DLCO parameters < 45% predicted (corrected for hemoglobin) or O₂ saturation < 92% of room air
5. Cardiac insufficiency or coronary artery disease requiring treatment
6. Active infection requiring systemic antibiotic therapy with antibacterial, antifungal or antiviral agents
7. Concomitant enrollment on Phase I study
8. Patients with prior malignancies except resected basal cell carcinoma or treated carcinoma in-situ. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Medical Monitor or Protocol Chair. Cancer treated with curative intent > 5 years previously will be allowed.

2.5. Donor Selection Criteria

The evaluation of donors shall be in accordance with existing NMDP Standards Policies and Procedures. All donors shall meet the health criteria for both marrow and PBSC donation.

2.5.1. Donor Inclusion

1. Matched for HLA-A, B and DRB1 antigens
 - One antigen mismatch at HLA-A, B or DRB1 is acceptable with or without mismatch at HLA-C
 - Typing is by DNA techniques: intermediate resolution for A, B and C, and high resolution for DRB1. HLA-C typing is mandatory but will not count in the match.
2. Signed informed consent. Donor must consent to both bone marrow harvest and G-CSF administration with apheresis. Donor must provide written informed consent to randomization for either marrow or PBSC collection.
3. Donor must have adequate peripheral venous access for leukapheresis or must agree to placement of a central catheter.
4. Donor center affiliation with NMDP.
5. Donor must be 18 years of age or older.
6. General donor inclusion criteria specified in the Donor Companion Manual.

2.5.2. Donor Exclusion

1. Females who are pregnant (positive serum β -HCG) or uninterruptible breastfeeding
2. Known allergy to G-CSF or to *E. Coli*-derived recombinant protein products
3. History of autoimmune disorders
4. History of deep vein thrombosis or venous thromboembolism
5. History of iritis or episcleritis
6. History of serious adverse reaction to anesthesia
7. Thrombocytopenia (platelets < 150,000 per mL) at baseline evaluation
8. Current treatment with lithium
9. Presence of sickle hemoglobin as demonstrated by appropriate testing such as hemoglobin electrophoresis
10. Donors receiving experimental therapy or investigational agents

2.6. Treatment Plan

2.6.1. Conditioning Regimens

Four broad groups of conditioning regimens will be included in the protocol:

1. Cyclophosphamide and Total Body Irradiation (CY-TBI)-based regimens that include at least 120 mg/kg cyclophosphamide and at least 1200 cGy of fractionated TBI.
2. Busulfan and cyclophosphamide (BU-CY)-based regimens that include at least 14 mg/kg busulfan orally or 11.2 mg/kg busulfan intravenously (14 x 0.8 correction factor) or a

targeted busulfan dosing strategy aimed at a serum concentration greater than 600 ng/mL at steady state and at least 120 mg/kg cyclophosphamide.

3. Fludarabine and melphalan (Flu-Mel)-based regimens that include a fludarabine dose of least 120 mg per m² and a melphalan dose of at least 140 mg per m².
4. Fludarabine, busulfan, and ATG (Flu-Bu-ATG)-based regimens that include a fludarabine dose of at least 120 mg/m², at least 8 mg/kg busulfan orally or 250 mg/m² busulfan intravenously, and at least 40 mg/kg equine ATG or 4 mg/kg rabbit ATG. Institutional standards should be followed for targeting plasma levels.

2.6.1.1. Additional drugs

Additional drugs including anti-T cell antibodies may be added at the transplant center's discretion with the exception of Alemtuzumab (Campath-1H) because of the impaired immune reconstitution and increased mortality observed with Alemtuzumab in combination with post-grafting cyclosporine and methotrexate that will be employed in this study (53).

2.6.1.2. Choice of conditioning regimen

Transplant centers may use different regimens for patients with different diseases as required by institutional protocol. However, the transplant center must declare before randomization what conditioning regimen and GVHD prophylaxis regimens will be used for each patient. The specified regimens will be used for the patient whether randomized to receive PBSC or marrow, unless there is approval from the Protocol Chair to alter the regimen.

2.6.1.3. Order of administration of cyclophosphamide and TBI

The order of administration of cyclophosphamide and TBI is at the discretion of the transplant center. Within each institution, all patients should receive the cyclophosphamide and TBI in the same order. If cyclophosphamide is given last, there should be at least a one-day rest period before the marrow or PBSC infusion.

2.6.1.4. TBI administration

Fractionated TBI will be administered according to the schedules utilized by the participating clinical centers. Radiation sources, dose rates, details of lung shielding, and sites receiving boost radiation will also be defined by the institution. TBI may be delivered from either linear accelerator or Cobalt sources. Lung shielding is preferred but not required during TBI. For institutions using lung shielding, an electron boost to the chest wall should be used, if necessary, to achieve a rib dose within the desired therapeutic range.

2.6.1.5. Cyclophosphamide administration

Cyclophosphamide will be administered intravenously. Mesna is allowed, but not required.

2.6.1.6. Cyclophosphamide and busulfan dose adjustments

Cyclophosphamide and busulfan dose adjustments for ideal body weight are recommended, but not required.

Ideal Body Weight Formulas:

Patients Over 18 Years

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

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

Patients 1 to 18 Years of Age

Less than 60 inches

IBW = $(ht^2 \times 1.65) / 1000$ where ht = cm, IBW = kg

More than 60 inches

Males IBW = 39.0 + [2.27 x (ht - 60)] where ht = inches, IBW = kg

Females IBW = 42.2 + [2.27 x (ht - 60)] where ht = inches, IBW = kg

2.6.1.7. Busulfan

Busulfan may be administered either orally or intravenously. Busulfan dose may be adjusted based on drug clearance estimated before or after starting the conditioning regimen.

2.6.1.8. Fludarabine

Fludarabine will be administered intravenously at the minimum total dose of 120 mg per m², divided into three or more doses administered once daily. Fludarabine is not recommended for patients with severe renal impairment, i.e., a creatinine clearance (CrCl) less than 30 milliliters/minute/1.73 square meter (mL/min/1.73 m²). For patients with moderate renal impairment (CrCl of 30 to 70 mL/min/1.73 m²), the fludarabine dose should be reduced by 20% to 50% (54). Fludarabine administration should be dosed based on the patient's actual body weight. It is recommended, though not required, that for patients weighing more than 100% of their IBW, fludarabine be dosed based on the adjusted ideal body weight (AIBW).

Ideal Body Weight Formulas:

See Section 2.6.1.6

Adjusted Ideal Body Weight Formula:

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

2.6.1.9. Melphalan

Melphalan will be administered intravenously at the minimum dose of 140 mg per m².

2.6.1.10. ATG

ATG will be administered at a dose of at least 40 mg/kg equine or 4 mg/kg rabbit. The Physician Desk Reference's manufacturer's guidelines should be followed for administration of ATG.

2.6.1.11. Allopurinol

Allopurinol is recommended for patients with high tumor bulk. A common regimen employs allopurinol at the daily dose of 300 mg, beginning at least six hours before the start of conditioning and until the day before marrow or PBSC infusion.

2.6.1.12. Intravenous hydration

Intravenous hydration is recommended to prevent tumor lysis syndrome in patients with bulky tumor and to prevent hemorrhagic cystitis in patients treated with cyclophosphamide. Hydration should begin at least 12 hours prior to the first dose of chemotherapy and continue for 24 hours following the last dose.

2.6.1.13. Testicular irradiation

Testicular irradiation with 400 cGy may be given to male patients with ALL or other acute leukemia according to local institutional practice.

2.6.1.14. Central Nervous System prophylaxis

Central Nervous System (CNS) prophylaxis will be given according to institutional practice.

2.6.2. GVHD Prophylaxis Regimen

The choice of GVHD prophylaxis regimen is by institutional preference. Any regimen or protocol may be used, with the exception that Phase I GVHD prophylaxis protocols are not allowed. The regimen and dosing employed must not be dependent on graft source assignment, i.e., marrow or PBSC.

The two most commonly used GVHD prophylaxis regimens following unrelated donor transplantation are:

1. Cyclosporine/methotrexate
2. Tacrolimus/methotrexate

The recommended doses and schedule of administration of cyclosporine, tacrolimus and methotrexate are as detailed in Sections 2.6.3 and 2.6.4. This information is provided only as a guideline.

Alternative or additional agents/dosing may be used per institutional preference. However, the use of Phase I agents is prohibited.

The transplant center will declare before randomization what GVHD prophylaxis regimen will be used for that particular patient. The declared regimen must be used whether the patient is randomized to receive PBSC or marrow. There is no requirement for the institution to use the same regimen for each subsequent patient enrolled.

2.6.3. Cyclosporine or Tacrolimus Treatment Regimen

Either cyclosporine or tacrolimus is administered beginning at least one day before transplantation for a minimum of six months. The initial dose should be based on the ideal body weight of the recipient. Subsequent doses are based on blood levels (see below). Determinations of blood levels should be performed at least once weekly for the initial three months. Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Dose reductions for high levels without toxicity should be conservative, e.g. 25%, to avoid inadequate immunosuppression.

If there is nausea and vomiting, the drug should be given intravenously. Patients with severe intolerance of cyclosporine may be placed on tacrolimus and vice versa.

2.6.3.1. Taper

Fifty or more days after transplantation, in the absence of GVHD, the dose is slowly tapered over a minimum of 20 weeks and discontinued.

2.6.3.2. Cyclosporine

The cyclosporine regimen for GVHD prophylaxis will initially employ an intravenous total daily dose of 3 mg/kg/day. Subsequent cyclosporine doses are adjusted to target whole blood levels between 150 and 450 nano (n)g/mL.

Oral formulations of cyclosporine have variable bioavailability (intestinal absorption), and Neoral appears to have a higher and more predictable bioavailability than other formulations. When a patient is switched from intravenous cyclosporine to Neoral (preferred) or other oral formulation, the dose is increased by 2.5-3 fold to adjust for the lower bioavailability of Neoral compared to intravenous cyclosporine.

Drugs that may affect cyclosporine levels:

1. Caspofungin, phenobarbital, phenytoin, rifampin, carbamazepine, rifabutin, St. John's Wort (**lowers levels**)
2. Glucocorticoids, fluconazole, voriconazole, ketoconazole, itraconazole, grapefruit juice, acetazolamide, amiodarone, amlodipine, amprenavir, bromocriptine, chloramphenicol, cimetidine, cisapride, clarithromycin, clotrimazole, danazol, diltiazem, erythromycin, ethinyl estradiol, metoclopramide, metronidazole, mibefradil, nefazodone, nelfinavir, tacrolimus, nifedipine, omeprazole, quinupristin/dalfopristin, ritonavir, saquinavir, theophylline, troleandomycin, verapamil (**increases levels**)

Per the voriconazole package insert, when initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary (55).

2.6.3.3. Tacrolimus

The tacrolimus regimen for GVHD prophylaxis will initially employ an intravenous total daily dose of 0.03 mg/kg/day. Subsequent tacrolimus doses are adjusted to target whole blood levels between 5 and 15 ng/mL. When a patient is switched from intravenous to oral tacrolimus, the dose is increased by 3-4 fold to adjust for the lower bioavailability of oral compared to intravenous tacrolimus.

Drugs that may affect tacrolimus levels are:

1. Caspofungin, phenobarbital, phenytoin, rifampin, carbamazepine, rifabutin, St. John's Wort (**lowers levels**);
2. Glucocorticoids, fluconazole, voriconazole, ketoconazole, itraconazole, grapefruit juice, amprenavir, bromocriptine, chloramphenicol, cimetidine, cisapride, clarithromycin, clotrimazole, danazol, diltiazem, erythromycin, ethinyl estradiol, metoclopramide, metronidazole, mibefradil, nefazodone, nelfinavir, nifedipine, omeprazole, quinupristin/dalfopristin, ritonavir, saquinavir, theophylline, troleandomycin, verapamil (**increases levels**).

Per the tacrolimus package insert, when initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary.(55)

2.6.4. Methotrexate Treatment Regimen

The regimen of methotrexate for GVHD prophylaxis will employ intravenous doses of 15 mg per m² on Day 1 post-transplant, and 10 mg per m² on Days 3, 6, and 11 post-transplant. The dose of methotrexate may be decreased per institutional standard practice to no less than 5 mg per m² on Days 1, 3, 6, and 11 post-transplant. Third space syndromes with large accumulation of ascites or pleural effusions are a contraindication to the use of methotrexate. Dose reductions should be made for renal, hepatic and mucosal toxicity. Determinations of blood levels are indicated 24-72 hours after administration in patients with impaired renal function. Leucovorin rescue should be considered in patients with decreased clearance, severe toxicity or fluid accumulation/effusions.

Drugs that may increase methotrexate levels are:

1. Non-steroidal anti inflammatory drugs
2. Penicillins
3. Diuretics

2.6.5. PBSC Mobilization and Collection

2.6.5.1. G-CSF Administration to Donors

G-CSF (filgrastim, Amgen) will be administered to the donor at a dose of ~10 mcg/kg/day subcutaneously for 5 consecutive days. Daily dose shall not exceed 1200 mcg/day, and volume per injection site shall not exceed 2.0 mL. G-CSF will be administered at approximately the same time each day for the first four days. The fifth dose should be given at least one hour prior to apheresis. There will be no additional, sixth dose of G-CSF in cases where a second PBSC collection is performed on Day 6. See Donor Companion Manual for G-CSF dose calculation and dose modification.

2.6.5.2. PBSC Collection and Evaluation

Apheresis shall begin on Day 5 of G-CSF administration.

Apheresis Devices and Central Catheters - Apheresis shall be accomplished using a continuous-flow apheresis device. Bilateral peripheral venous access will be used whenever possible. Donors with insufficient peripheral access may undergo placement of a central venous catheter. Central catheters should be inserted on the day of collection.

Anticoagulation - A citrate based anticoagulant such as acid citrate dextrose formula A (ACD-A) should be used unless there is a contraindication or sensitivity to this agent. Mononuclear cell apheresis collections are generally performed using citrate: whole blood ratios of 1:12 to 1:13. If a citrate to whole blood ratio of less than 1:13 is used, then additional ACD-A may be added to the component bag, either during apheresis or immediately after the procedure is completed.

CD34 Cell Dose - Typical requested CD34 cell doses are between 5-10 x 10⁶ per kg recipient body weight. Quantitation of the CD34 cell content of the product by the Apheresis Center on the day of apheresis is required.

Volume Processed – The volume processed shall be linked to the actual weight of the recipient as follows. For recipients weighing less than or equal to 35 kg, a single 12-liter apheresis shall be performed. For recipients weighing greater than 35 kg, the volume processed shall be 15 to 24 liters.

Single larger volume procedures are encouraged whenever possible. In a prospective randomized study, a single 25-liter PBSC collection yielded the same number of CD34 cells as two consecutive daily 15-liter procedures, and was associated with a marked reduction in inconvenience and discomfort for the donor (56). The following table provides a guide to

volume processed by weight of recipient. Volume processed refers to true whole blood volume, not including anticoagulant (see Table 2.6.5).

Table 2.6.5: Blood Volume Processed in Relation to Recipient Weight

Recipient Weight (kg)	Volume Processed (L)	Procedure
≤ 35	12	Single 12-liter apheresis
36 - 45	15	Single 15-liter apheresis
46 -55	18	Single 18-liter apheresis or two 12-liter procedures
56 - 65	22	Single 22-liter apheresis or two 12-liter procedures
> 65	24	Single 24-liter apheresis or two 12-liter procedures

Alternatively, centers may use an immediate pre-procedure blood CD34 cell count to determine the blood volume to be processed. If such calculations are used, the transplant center requested CD34 cell dose should be targeted as the minimum dose. If the requested dose is collected in the first apheresis procedure, a second collection will not be performed.

Prevention of Citrate Toxicity - Apheresis procedures in which greater than 12 liters of blood are processed should incorporate a method to prevent severe citrate toxicity. Such methods could include either (1) use of continuous infusion or intermittent bolus heparin administration, allowing use of lower citrate infusion rates, or (2) use of continuous infusion or bolus calcium salts (calcium chloride or calcium gluconate) (57). Please refer to the Donor Companion Manual for suggested algorithms for heparin or calcium salt administration.

Heparin should not be used in procedures requiring central venous catheter placement.

Product Volume and Sampling - The product should have a minimal volume of 200 mL. A 1.0 mL sample for CBC should be obtained by the Apheresis Center from the long tubing tail attached to the bag.

Processing, Storage and Shipment - If more than one PBSC procedure is performed, the first collection will be stored at 2-8° C overnight. No processing or freezing of the PBSC product shall be done by the apheresis facility. The transportation of PBSC components shall be in accordance with NMDP Standards. Products will be shipped in an NMDP-approved container that is charged with cold packs or similar material to provide an initial ambient temperature of 2-8° C. Dry ice shall not be used.

PBSC components will be infused within 12 hours of arrival at the Transplant Center.

Sample Collection - Each collection will be separately evaluated by the central reference laboratory for cellular composition in keeping with Appendix C and the BMT CTN Manual of Procedures (MOP) for graft characterization.

Records - Records of donation shall be maintained in accordance with NMDP Standards and shall include:

1. Evaluation of donor health
2. Dose of G-CSF administered per day
3. Volume and type of anticoagulant administered
4. Additional anticoagulant added to component
5. Volume of blood processed, total cell and differential count in product
6. Pre and post apheresis donor CBCs
7. Details of storage and shipping

2.6.6. Marrow Collection

Donors randomized to the marrow arm will have marrow harvested on Day 0.

Anesthesia - Either general or regional (epidural, spinal) anesthesia may be used.

Anticoagulation of the Marrow Product - Reagents used, including salt solutions and anticoagulants, shall be approved by FDA or similar regulatory agency for human infusion. Recommended anticoagulation techniques are 10 U/mL of preservative-free heparin or 10% (volume/volume) ACD-A or a combination of both. Anticoagulants to be used shall be agreed upon by the donor and transplant centers before initiation of the transplant conditioning regimen.

Volume and Cell Dose - Requested marrow cell dose will be 4×10^8 nucleated cells per kg of recipient body weight. This dose will be unattainable for many recipients because of donor and/or recipient factors, e.g., body size mismatches. The volume of marrow shall not exceed 20 mL per kg donor weight. The estimated cell dose and a planned donor marrow volume shall be agreed upon by the donor and transplant centers before initiation of the transplant conditioning regimen.

Blood Product Support - Donors shall store blood for autologous use in accordance with existing NMDP Standards.

The transfusion of autologous or homologous blood should be in accordance with appropriate medical practice. Homologous blood, if used, shall be irradiated to 2500 cGy.

Processing of Bone Marrow Products - No processing of bone marrow, other than anticoagulation, filtration, packaging, and labeling in preparation for transportation, shall be performed by the collection center. Processing of bone marrow for reduction of volume, plasma, red blood cells, or fat, may be performed by the transplant center.

Shipping of Bone Marrow - The transportation of bone marrow shall be in accordance with NMDP Standards. Products will be shipped in an NMDP-approved container that is charged

with cold packs or similar material to provide an initial ambient temperature of 2-8° C. Dry ice shall not be used.

The marrow will be infused within 12 hours of arrival at the Transplant Center.

Sample Collection - Each collection will be separately evaluated by the central reference laboratory for cellular composition in keeping with Appendix C and the BMT CTN Manual of Procedures (MOP) for graft characterization.

Records - Records of donation shall be maintained in accordance with NMDP Standards and include:

1. Evaluation of donor health
2. Volume and type of anticoagulant added to component
3. Volume of marrow, total cell and differential count in product
4. Pre and post marrow harvest donor CBCs
5. Details of storage and shipping

2.6.7. PBSC or Marrow Infusion

All patients will receive unmodified G-CSF mobilized PBSC or marrow on Day 0 with the following exceptions: plasma and red cell depletion are allowed for volume reduction or ABO incompatibility. CD34 cell selection or T cell removal are not allowed. PBSC or marrow is infused via a central venous catheter using standard blood infusion tubing.

There is no minimum cell dose for CD34 cells or nucleated cells in either arm. Similarly, there is no maximum cell dose. It is recommended that all products are infused entirely, but this is not required. Non-infusion of portion of the products will be documented. No portion of the donor marrow or PBSC should be cryopreserved if the CD34 cell count is $< 5 \times 10^6$ per kg recipient weight.

In the case that there is an unexpected change in the recipient's condition and the PBSC or marrow harvest cannot be cancelled, the transplant center is required to obtain an approval from the NMDP prior to cell cryopreservation. The patient and donor remain on study even if the transplant does not occur.

2.6.8. No Blinding of Marrow and PBSC Infusions

Rationale for Blinding - There are at least theoretical concerns that knowledge of the type of the stem cell product infused may influence the decision-making process of clinicians and nurses at the participating transplant centers. Patient knowledge may have an impact as well. This can introduce bias in the evaluation of transplant outcomes of interest. This could be avoided by stem cell manipulation (ordinarily at the collection center) aimed at making the two products indistinguishable upon infusion and asking recipients to agree via the consent form to refrain from asking about the product type. This was seemingly accomplished in at least one single-center study (58).

Logistical Challenges - There are logistical challenges translating what was successfully carried out at a single center into procedures followed by many donor and transplant centers. More importantly, blinding requires manipulation of the graft product and any additional stem cell manipulation introduces the potential for cell loss, clerical errors and infusion-related adverse events. The related risks for patients are hard to justify. Therefore, while acknowledging that blinding may be desirable, the decision was made not to pursue blinding in this Phase III study.

2.6.9. PBSC Collection or Marrow Harvesting for Additional Stem Cell Products

In the event of primary or secondary graft failure, additional PBSC collection or marrow harvesting from the original donor may be requested by transplant centers following established NMDP policies. The selection of PBSC or marrow for the second transplant is not bound to the randomization arm; it is the choice of the transplant center physician, and requires donor consent. If the same donor is selected, no less than 21 days should elapse between the two donations. If the donor is unwilling or unavailable for a second PBSC or marrow collection, alternative management strategies including transplantation from a second donor must be considered by the treating physician at the transplant center.

2.6.10. Supportive Care

All supportive care will be given in keeping with BMT CTN MOP and local institutional practice.

2.6.11. Growth Factors

It is recommended that patients not receive post-transplant growth factors before Day 21, except in the case of serious infection where hastening neutrophil recovery by 1-3 days may be critical for survival. If a transplant center chooses to give growth factors prior to Day 21 post-transplant, they should be given to all patients, regardless of whether receiving bone marrow or peripheral blood stem cells. After Day 21, G-CSF or granulocyte-macrophage colony stimulating factor (GM-CSF) should be given for severe neutropenia (ANC < 500/mcL), or as necessary to keep ANC > 1000/mcL.

2.6.12. Blood Products

Transfusion thresholds for blood product support will be consistent with BMT CTN MOP and standard institutional guidelines. All cellular blood products will be irradiated. Patients who are CMV negative will receive CMV negative or filtered blood products from study entry.

2.6.13. Prophylaxis against Infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peritransplant period according to the BMT CTN MOP. This will include:

1. Anti-bacterial prophylaxis: In keeping with the BMT CTN MOP and local institutional standards for allogeneic transplants. Prophylactic antibacterial antibiotics should be used for patients during the neutropenic (ANC < 500/mcL) period.
2. Pneumocystis carinii: Prophylaxis will start at the time of engraftment or on Day 30 post-transplant according to institutional preference. Prophylaxis should be continued until immunosuppressive drugs are discontinued.
3. Antifungal therapy: In keeping with the BMT CTN MOP and local institutional standards for allogeneic transplants.
4. HSV/VZV: Prophylaxis will begin with conditioning therapy and continue up to one year post-allograft as directed by standard institutional practice.
5. CMV: Monitoring and preemptive treatment strategy will be in accordance with the BMT CTN MOP and local institutional practice.

2.6.14. Intravenous Immune Globulin (IVIG)

IVIG administration will be left to local institutional standard practice.

2.6.15. Failure to Engraft

If the ANC has not reached 500/mcL by Day 21, G-CSF, GM-CSF or other cytokines may be utilized. If the ANC is < 100/mcL on Day 28 post-transplant, the patient should be considered for a second infusion of stem cells from the original donor or retransplantation from a different donor using appropriate Transplant Center protocols.

2.6.16. Post-transplant Donor Leukocyte Infusions (DLI)

DLI may be given to patients for a recurrent or a second malignancy according to institutional practice and in accordance with the NMDP policy, if the donor is available and provides consent. The use of DLI will be recorded and analyzed as a secondary endpoint.

2.6.17. Risks and Toxicities

Recipients of marrow or PBSC transplants incur risks from pre-transplant conditioning, the graft itself, and post-transplant therapies. All risks must be weighed against the risk of the malignancy for which the transplant is prescribed. Major risks following transplantation include:

1. Damage of any major organ may occur as a result of cumulative toxicity from anti-neoplastic therapy, the conditioning regimen, drug toxicity, infection, or GVHD.
2. Graft failure can result from genetic disparity between donor and recipient, insufficient immunosuppression of the recipient or poor cell dose.
3. GVHD can be either acute or chronic; both types predispose to infection.
4. Life-threatening infections may develop in patients with and without GVHD. These can be of a bacterial, viral, parasitic, or fungal nature.
5. Relapse of the underlying disease may occur, especially in patients with far advanced disease status at time of transplant.
6. All of these toxicities may be severe enough to result in death.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is **two-year survival** from the time of randomization after two years of follow-up. The event analyzed is death from any cause. Patients alive at the time of last observation will be censored.

3.2. Secondary Endpoints

3.2.1. Two-Year Post-transplant Survival

The endpoint is **two-year survival** from time of transplant. Only patients who receive their transplant are included. The event analyzed is death from any cause. Patients alive at the time of last observation will be censored.

3.2.2. Neutrophil Engraftment > 500/mcL

This is defined as achieving ANC > 500/mcL for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil engraftment. This endpoint will be evaluated through 100 days.

3.2.3. Primary Graft Failure

This is defined by lack of neutrophil engraftment by 100 days in patients surviving a minimum of 14 days.

3.2.4. Secondary Graft Failure

This is defined by initial neutrophil engraftment followed by subsequent decline in neutrophil counts < 500/mcL unresponsive to growth factor therapy.

3.2.5. Platelet Engraftment > 20,000 and 50,000/mcL Transfusion Independent

This is defined as achieving platelet counts > 20,000 and 50,000/mcL for consecutive measurements over seven days without requiring platelet transfusions. The first of the seven days will be designated the day of platelet engraftment. This endpoint will be evaluated through 100 days.

3.2.6. Acute GVHD of Grades II-IV and III-IV

Acute GVHD is graded according to the BMT CTN MOP. The first day of acute GVHD onset at a certain grade will be used to calculate cumulative incidence curves for that GVHD grade (e.g., if the onset of grade I acute GVHD is on Day 19 post-transplant and onset of grade III is on Day 70 post-transplant, time to grade III is Day 70). This endpoint will be evaluated through 100 days.

3.2.7. Chronic GVHD

Chronic GVHD is scored according to the BMT CTN MOP. The first day of chronic GVHD onset will be used to calculate cumulative incidence curves.

3.2.8. Current Immunosuppressive (IS) Free Survival

This function is an estimate of the chance that a patient is alive and not receiving immunosuppressive therapy at a given point in time for any reason. This outcome measure takes into account subsequent immunosuppressive therapy that may occur following discontinuation of initial immunosuppressive therapy. Patients will be censored for this endpoint at the time of relapse. A similar approach has been used in analyzing the role of DLI following allogeneic transplants for CML where relapse is expected to be frequent but subsequent disease control is also expected after treatment of relapse with DLI (59). A multi-state model will estimate this with inputs being the patient's immunosuppressive therapy and survival status at each potential examination time. Immunosuppressive drugs include cyclosporine, tacrolimus, prednisone, methotrexate, azathioprine, mycophenolate mofetil, sirolimus, clofazimine, PUVA, anti-thymocyte globulin, OKT3, daclizumab, basilixumab, visilizumab, infliximab and alemtuzumab.

3.2.9. Relapse of the Original Malignancy

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 AML, ALL, CML, MDS, CMML, Myelofibrosis or JMML 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, even if transplant physicians will utilize the information to alter therapy. Data on tapering immunosuppression, infusing donor T cells, 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. The appearance of new dysplastic changes within the bone marrow, or
4. No circulating blasts, but the marrow contains 5-20% blasts, a repeat bone marrow \geq one week later with > 5% blasts is necessary to meet the criteria for relapse, or
5. The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

Chronic Myelogenous Leukemia (CML) -

Hematologic relapse will be diagnosed when:

1. Immature hematopoietic cells are persistently documented in the peripheral blood, or
2. There is myeloid hyperplasia in the bone marrow in the presence of cytogenetics relapse.

Cytogenetic relapse will be diagnosed when:

1. 50% of the metaphases exhibit the characteristic 9;22 translocation with at least ten metaphases analyzed, or
2. At least one metaphase exhibits the 9;22 translocation on each of two separate consecutive examinations at least one month apart, regardless of number of metaphases analyzed.

Myelodysplastic (MDS) and Myeloproliferative Syndromes (include CMML, AMM or Idiopathic Myelofibrosis, and JMML) - Relapse will be diagnosed when there is:

1. Reappearance of pre-transplant morphologic abnormalities, detected in two consecutive bone marrow specimens taken at least one month apart, or
2. Satisfying above criteria for evolution into acute leukemia, or
3. Reappearance of pre-transplant cytogenetic abnormalities in at least 50% of metaphases with at least ten metaphases examined, or
4. Reappearance of pre-transplant cytogenetic abnormality in at least one metaphase on each of two separate consecutive examinations at least one month apart, regardless of the number of metaphases analyzed.

Relapse will be defined to occur in the absence of the evidence above if specific therapy, such as infusion of donor lymphocytes, use of interferon, or second transplant, is initiated for relapse reversal.

3.2.10. Donor Lymphocyte Infusion (DLI)

The indication for DLI will be collected, i.e., treatment of relapse of the original malignancy, treatment of a new malignancy, boost for immune reconstitution, reversal of graft failure, or others. Pretreatment of the recipient with chemotherapy or irradiation will be recorded. Pretreatment of the donor with G-CSF will be recorded.

3.2.11. Infections

Microbiologically documented infections will be reported by site of disease, date of onset, severity and resolution, if any. For definitions, see Chapter 6 and the BMT CTN MOP.

3.2.12. Immune Reconstitution

This will be measured in all patients by:

1. The rate of peripheral blood repopulation by CD3, CD4, CD8 and $\gamma\delta$ T cells, NK cells, DC1, DC2, monocytes and B cells.
2. The rate of blood repopulation by EBV or CMV-specific T cells measured by tetramer staining, and response to CMV, tetanus and aspergillus antigens ex vivo.
3. The rate of blood repopulation with recent thymus emigrants measured by T cell receptor excision circle-positive T cells.
4. The serum levels of immunoglobulin G, A, and M and plasma levels of IL-2 and IL-7.
5. Hepatitis B, Tetanus, Diphtheria and Pneumococcus antibody titers in response to immunization.

3.2.13. Patient and Donor Quality of Life

Details about these endpoints are given in Chapters 7 and 8.

3.2.14. Three-year Survival

The endpoint is three-year survival. Two separate analyses will be conducted, one from time of randomization and one from time of transplant.

3.2.15. Donor Recovery to Baseline Toxicity Scores

Appropriate statistical methods to detect trends over the available spectrum of donor follow-up times will be employed for baseline toxicity recovery to baseline endpoints.

3.2.16. Donor Recovery to Baseline CBC and WBC Differential Values

Appropriate statistical methods to detect trends over the available spectrum of donor follow-up time will be employed for baseline CBC recovery to baseline endpoints.

CHAPTER 4

4. PATIENT AND DONOR REGISTRATION, ENROLLMENT AND EVALUATION

4.1. Donor Search Initiation

Transplant centers will initiate the donor search by submitting patient demographics, HLA, and disease information to the NMDP coordinating center, using standard NMDP forms and additional data entry mechanisms developed for this trial. It is anticipated that 50-90% of the patients will have suitable donors identified as defined by HLA type, transplant center donor matching preferences, patient age, disease risk, and financial coverage (see *step (1)* in Figure 4.1). It is anticipated that the duration of the search will vary between two months and more than one year with a median time of approximately four months.

Figure 4.1 below highlights the event flow for recipients and donors in the trial. The time scale is arbitrary beginning at the top and flowing downward. Critical steps described in this Section are numbered (1) through (10).

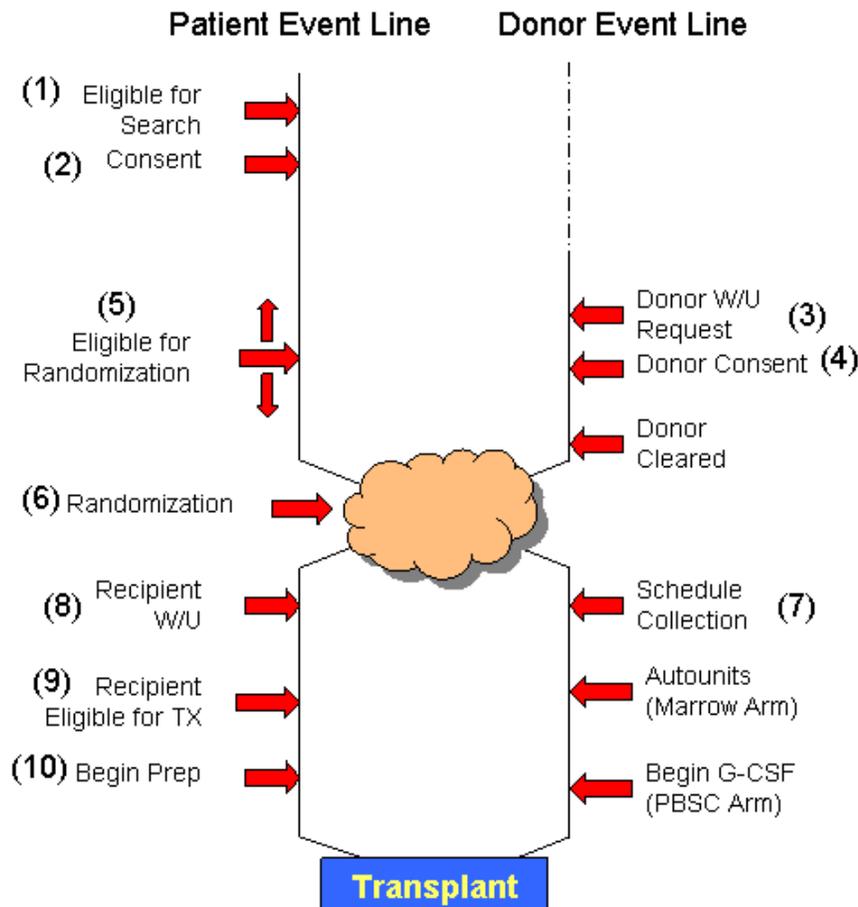


Figure 4.1 – Study Treatment

4.2. Approaching Patients About the Study

Typically, transplant physicians first interact with the patient in a consultation session either before or, more likely, after initiation of the donor search, and in rare cases after a suitable donor has been identified. During the initial consultation session, physicians explain the risks and benefits of transplant approaches and alternative therapies. They also explain transplant modalities including the potential sources of hematopoietic cells for transplantation. In such a setting, it will be appropriate for transplant physicians to approach eligible patients about their potential interest in the randomized trial of PBSC versus marrow transplantation. Since most patients are affected by serious, rapidly progressing diseases and must proceed to transplantation as soon as possible, approaching patients for study participation at this stage will avoid ‘last minute’ pressure to obtain patient informed consent, and allow the required donor and patient procedures to be scheduled as soon as a suitable donor is identified.

4.3. Screening for Patient Eligibility

Transplant center physicians will evaluate the patient eligibility for randomization onto this study (Section 2.3). For patients who cannot be seen at the transplant center, data to satisfy eligibility criteria will be obtained through direct communication with the patient and the patient's physician. Patients that are not eligible will proceed off study and no further follow-up will be obtained.

4.4. Patient Consent to Randomization

Eligible patients who would like to participate in the trial will sign the appropriate Institutional Review Board (IRB) approved form, providing evidence of informed consent to proceed to randomization to PBSC or marrow, contingent upon finding a suitable donor willing to participate in the trial (see *step (2)* in Figure 4.1). Patients will be informed that participation is dependent upon donor willingness to be randomized and upon the patient meeting specified eligibility criteria immediately prior to start of conditioning. Alternate approaches in the event that either of these criteria is not met will be explained. Patients who cannot travel to the transplant center because of medical contraindications or other reasons will be counseled by phone and will be allowed to mail the signed consent form.

4.5. Patient Refusal

Patients who decline randomization on this study will proceed towards transplant off study.

4.6. Donor Selection and Work-Up

As suitably matched donors are identified, the transplant center is notified. The transplant physician selects the best donor for the patient and requests donor ‘work-up’. Donor ‘work-up’ consists of a physical evaluation and an information session (see *step (3)* in Figure 4.1). Selection of the best donor occurs **before** the donor is approached for participation in this study.

4.7. Donor Deferral

If a candidate donor is found unsuitable to donate, an alternative donor will be sought.

4.8. Donor Consent

During the donor information session, the donor center physician explains the cell harvest procedures to the candidate donor. Donors for patients who have consented to this study will be asked to participate in the study at this time (see *step (4)* in Figure 4.1). Donors will express their consent to participate by signing an IRB-approved consent form. Documentation of donor consent, as well as documentation of donor eligibility, will be recorded on the Donor Form in AdvantageEDC by NMDP staff.

4.9. Donor Refusal

If a donor refuses to participate in the study, the patient will be off study. The donor will be asked to donate either marrow or PBSC, according to transplant physician preference and standard NMDP policies.

4.10. Transplant Protocol Registration

Before randomization occurs, the transplant center must state through AdvantageEDC which conditioning regimen and GVHD prophylaxis regimen will be used (see *step (5)* in Figure 4.1). Such a registration step will avoid potential biases that preferential association of a certain regimen with one treatment arm could confer to the study. At this stage, the transplant center will also verify that the patient is still a candidate for transplantation, is eligible for the trial and has consented to participate in the trial. This data will be entered on the Enrollment Form in AdvantageEDC.

4.11. Randomization

Once both patient and donor are deemed eligible and have given written informed consent, and the transplant center has confirmed patient eligibility and registered the patient's conditioning and GVHD prophylaxis regimens, randomization occurs (see *step (6)* in Figure 4.1).

4.12. Treatment Scheduling

Once the randomization arm is known, a transplant calendar is negotiated between the search-coordinating unit, donor center and transplant center, and the transplant date is scheduled (see *step (7)* in Figure 4.1). It is anticipated that 2-3 weeks will elapse between the randomization and the day of cell harvest and transplant. This period is necessary to schedule the marrow or PBSC harvest. During this period, donors may donate and store up to 3 autologous red cell units, if randomized to marrow, or receive G-CSF injections, if randomized to PBSC. During this period, transplant center physicians will complete the patient evaluation.

4.13. Patient Evaluation

The patient pre-transplant evaluation will be completed within four weeks of initiation of conditioning (see *steps (8) and (9)* in Figure 4.1). This step is necessary because patient organ function, infection status and status of malignancy may vary over time. This evaluation will protect patients with a new contraindication to transplant from initiating transplant therapy at an unsafe time. Results of the pre-transplant evaluations as outlined in Section 4.15.4.1 will be entered on the Baseline Form in AdvantageEDC.

4.14. Patient Deferral

Patients who meet exclusion criteria will be deferred. One option is remaining on study and rescheduling the transplant when eligibility criteria are again met, for example after clearance of a serious infection. Another option is proceeding to transplant or other treatment off study, if that is the best treatment option determined by the transplant physician for the patient. Patients deferred will continue to be followed for the primary endpoint.

4.15. Study Monitoring

A visit schedule based on transplant date is displayed for printing in AdvantageEDC and is referred to as ‘Follow-up Schedule.’

Table 4.15: 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
60 days	60 ± 2 days
9 week	63 ± 2 days
10 week	70 ± 2 days
11 week	77 ± 2 days
12 week	84 ± 2 days
13 week	91 ± 2 days
14 week	98 ± 2 days
100 day	100 ± 2 days
4 month	120 ± 28 days
6 month	180 ± 28 days
7 month	210 ± 28 days
9 month	270 ± 28 days
11 month	330 ± 28 days
12 month	365 ± 28 days
24 month	730 ± 28 days
36 month	1095 ± 28 days

4.15.1. Case Report Forms

A description of the forms, the procedures required for forms completion and timeliness of submission can be found in the Data Management Handbook and User’s Guide. Forms that are not received within the specified time are considered delinquent. Transplant Centers can view submitted, past due, and expected forms via AdvantageEDC. A missing form will continue to be requested either until the form is reported, or until an exception is granted.

4.15.2. Reporting Patient Deaths

Recipient death while at the transplant center must be reported to the BMT CTN Data Coordinating Center (DCC) within 24 hours of the event. Death after the patient has left the transplant center must be reported within 24 hours of the event notification but no more than 30 days after the event. If the cause of death is unknown, it need not be recorded at the time of initial reporting. However, once the cause of death is determined, the form must be updated.

4.15.3. Reporting Serious Adverse Events

4.15.3.1. Patient SAEs

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system. 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. All grade 3-5 adverse reactions to vaccines should be reported within three working days. 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.

4.15.3.2. Donor SAEs

Marrow Donors - Reporting of SAEs following marrow donation will be consistent with standard BMT CTN procedures. Serious and unexpected adverse events should be reported within three working days, and will include unexpected or life-threatening complications of anesthesia, and severe pain, debility, or incapacitation related to mechanical injury during marrow harvest. Other SAEs, including prolonged hospitalization or hospital readmission, will be tracked, staged according to CTCAE, and reported on appropriate systems.

PBSC Donors - Reporting of SAEs following G-CSF administration and apheresis donation will be consistent with NMDP policies and procedures. Serious and unexpected adverse events should be reported within three working days, and will include complications of central line placement, and severe or life-threatening reactions to G-CSF administration or apheresis. The Data and Safety Monitoring Board will receive summary reports of all adverse donor experiences on at least an annual basis.

4.15.4. Patient Assessments

Table 4.15.4 summarizes patient clinical assessments over the course of the study.

Table 4.15.4: Summary of Patient Clinical Assessments

Study Assessments/ Testing	Baseline	Days Post-Transplant																						
		7	14	21	28	35	42	49	56	63	70	77	84	91	98	180	210	270	330	365	730	1095	1825	
History, physical exam, weight, height, and Karnofsky/Lansky performance status	X	X	X	X	X	X	X	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	X			X					X	X	X	
Infectious disease titers ³	X																							
EKG	X																							
DLCO, FEV1 and FVC	X																							
Bone marrow aspirate for pathology and cytogenetics	X												X								X	X	X	
Bone marrow biopsy for pathology													X								X	X	X	
Patient anti-donor lymphocyte cross match (in mismatched transplants only)	X																							
Chest X-ray	X																							
β-HCG serum pregnancy test (females only)	X																							
GVHD and other morbidity assessments ⁴		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X	
5 mL sample from allograft for graft characterization	X																							
5 mL heparinized blood for HLA typing	X																							
Blood samples for immune reconstitution assays ⁵					0								0			0					0	0		
Plasma samples for IL-7 and IL-2 levels													0			0					0	0		
dT vaccination ⁶																X				X				
PCV7 vaccination ⁶																	X	X						

Study Assessments/ Testing	Baseline	Days Post-Transplant																							
		7	14	21	28	35	42	49	56	63	70	77	84	91	98	180	210	270	330	365	730	1095	1825		
PPV23 vaccination ⁶																				X					
Hepatitis B vaccination ⁶																X	X			X					
Serum sample for immunoglobulin and antibody titers ^{7, 8}	0															0				0	0	0			
Blood sample for natural killer cell receptors acquisition ancillary study	0												0			0					0				
Peripheral blood T-cell chimerism ⁹	X				X								X								X	X			
Patient quality of life interviews	0															0					0	0		0 ¹⁰	

- ¹ CBC performed three times weekly 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: creatinine, bilirubin, alkaline phosphatase, AST, and ALT. 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 (HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, varicella zoster virus, syphilis, HIV and HTLV 1/2 antibody.
- ⁴ GVHD and other morbidity assessments performed weekly until Day 100 post-transplant.
- ⁵ Immune reconstitution assays include: FACS analysis, tetramer assay, TREC analysis, and T-cell responses to tetanus, CMV, and Aspergillus antigens, and CBC with differential.
- ⁶ Vaccinations should be given ± 1 week of the scheduled date.
- ⁷ Sample for antibody titers should be drawn just before vaccination. Includes dT antibody titer, S. pneumoniae antibody and opsynphagoctytic titer, Hepatitis B antibody titer, and H. influenzae antibody titer.
- ⁸ Quantitative Ig to include IgG, IgM, and IgA.
- ⁹ Recommended, but not mandatory.
- ¹⁰ Will not be analyzed as part of the randomized trial.

X = Generally performed for transplant patients.
0 = Required for this study.

4.15.4.1. Pre-Transplant Evaluations

The following evaluations, which are generally performed for transplant eligibility, should be determined < 4 weeks before initiation of conditioning therapy:

1. History, physical examination, height and weight.
2. Karnofsky or Lansky performance status.
3. CBC with differential and platelet count, creatinine, bilirubin, alkaline phosphatase, AST, ALT.
4. CMV antibody test, Hepatitis panel (HepB SAb, HepB SA_g, HepB Core Ab, HepC Ab), herpes simplex virus, varicella zoster virus, syphilis, HIV and HTLV1/2 antibody.
5. EKG.
6. DLCO, FEV₁, and FVC.
7. Bone marrow aspirates for pathology and cytogenetics.
8. If the donor is HLA mismatched, patient anti-donor lymphocyte cross match must be performed to rule out donor-directed sensitization (60, 61).
9. Chest X-ray.
10. β-HCG for serum pregnancy test (for women of childbearing potential).
11. Heparinized blood sample for post-transplant chimerism assay (recommended but not mandatory).
12. Heparinized blood sample for retrospective HLA typing to the NMDP repository. A separate NMDP consent form is used for blood sample acquisition for the NMDP repository and HLA typing.
13. Sample from the marrow or PBSC allograft for graft characterization.

The following evaluations, which are required for this study, should be determined < 4 weeks before initiation of conditioning therapy:

1. Serum for quantification of IgG, IgM and IgA, and antibody titers to diphtheria and tetanus.
2. Blood sample for natural killer cell receptors acquisition ancillary study.
3. Quality of life survey.

4.15.4.2. Post-Transplant Evaluations

The following evaluations are generally performed for transplant recipients:

1. History and physical exam to assess GVHD and other morbidity weekly until Day 100 post-transplant, then at six months, one year and then yearly until three years post-transplant. GVHD evaluation and grading to be in keeping with BMT CTN MOP.
2. Data on occurrence of infections will be collected as specified in Chapter 6.

3. CBC at least three times a week from Day 0 until ANC > 500 mcL for 3 days after nadir reached. Thereafter CBC twice per week until Day 28, then weekly until 12 weeks, then six months, one year and then yearly until three years post-transplant.
4. Creatinine, bilirubin, alkaline phosphatase, ALT, AST, twice a week until Day 28 (or four weeks) and then weekly until 12 weeks, six months, one year and then yearly until three years post-transplant.
5. Bone marrow aspirate and biopsy to pathology, aspirate to cytogenetics at 12 weeks, one year and then yearly until three years post transplant.
6. dT vaccine at 6 and 11 months post-transplant, Hepatitis B vaccine at 6, 7, and 11 months post transplant, PCV7 vaccine at 7 and 9 months post-transplant, and PPV23 vaccine at 11 months post-transplant. Vaccinations should be given ± 1 week of scheduled date.
7. Quantification of peripheral blood T cell chimerism at 1, 3, 12, and 24 months post-transplant (recommended but not mandatory – see Appendix C).

The following evaluations are required for this study:

1. Heparinized blood for quantification of peripheral blood immune reconstitution at 1, 3, 6, 12, and 24 months post-transplant.
2. Serum for quantification of IgG, IgM and IgA, and antibody titers to diphtheria, tetanus, and pneumococcus at 6, 11, 12 and 24 months post-transplant. Serum for antibody titers to *H. influenzae* type B and Hepatitis B at 6, 12, and 24 months post-transplant. Antibody titers should be drawn just before vaccination.
3. Blood sample for natural killer cell receptors acquisition ancillary study at 3, 6, and 12 months post-transplant.
4. Quality of life surveys at 6 months, 1 year and 2 years.

4.15.5. Required Observations for Donor

Routine pre-allografting work-up in keeping with NMDP guidelines (see Donor Companion Manual for this protocol). Work-up to include the following evaluations, which are generally performed for transplant donors:

Pre-collection Evaluations:

1. Complete history and physical examination.
2. HLA typing of heparinized peripheral blood sample to determine compatibility.
3. Serologic testing for Hepatitis B and C (HBsAg, anti-HBc, anti-HCV), CMV, syphilis, HIV1/2 and HTLV I/II. Molecular testing for HIV, HCV, and West Nile virus as recommended by the FDA.
4. Sickle cell trait testing.
5. ABO Rh blood typing. In the case of donor-recipient ABO incompatibility, the graft should be manipulated according to institutional practices.

6. Heparinized blood samples for HLA typing to NMDP repository. A separate NMDP consent form is used.
7. Heparinized blood sample for Chimerism assays, if requested by the transplant center (not mandatory but recommended).
8. Baseline toxicity scores, and CBC and WBC differential.
9. Toxicity scores on each day of G-CSF administration.
10. Number of autologous units collected prior to marrow donation.

Collection Day Evaluations:

11. Type and duration of anesthesia, volume of marrow collected, pre- and post-marrow donation CBC and WBC differential, and number of autologous units infused.
12. Pre- and post-leukapheresis CBC and WBC differential and volume of whole blood processed.
13. Toxicity scores on day of collection.
14. Product CBC.

Post-collection Evaluations:

15. Toxicity scores post-donation at two days, weekly until donor reports recovery from donation, one month, six month, and annually for a minimum of three years.
16. CBC post-donation at one month, six months, and annually for a minimum of three years.

The following evaluations are required for this study:

1. Serum for Hepatitis B antibody titer.
2. Quality of life assessments as specified in Chapter 8.
3. Blood sample for natural killer cell receptors acquisition ancillary study pre-donation (prior to G-CSF if PBSC).
4. Product sample for cellular composition testing.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

The study is designed as a Phase III, randomized, multicenter, prospective comparative study of G-CSF mobilized PBSC versus marrow transplantation in HLA compatible unrelated donors. The target enrollment is initially 550 patients, with a provision to increase enrollment to 652 patients depending on the observed rate of patients dropping out without receiving a transplant.

5.1.1. Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Both Core and non-Core Centers will enroll patients on this study. Details of accrual estimates follow in the sample size section.

5.1.2. Randomization

All patient-donor pairs who have consented to the randomization as detailed earlier will be randomized once the donor has been cleared for donation. Randomization will be performed in a 1:1 ratio using random block sizes for the PBSC and marrow arms. Randomization will be stratified by transplant center and by disease risk (see Table 5.4).

5.1.3. Primary Endpoint

The primary endpoint is the two-year survival probability.

5.1.4. Primary Hypothesis

The primary comparison of interest in this study is the two-year survival with PBSC transplantation as compared to marrow transplantation. However, because this is a long-term endpoint, a monitoring rule comparing six-month survival between the two arms was put into place, to protect patients against unexpected (>10%) differences in six month mortality. Therefore, the primary hypothesis, accounting for both the primary comparison of two-year mortality as well as the stopping rule for six-month mortality, is a composite hypothesis which can be formally stated as:

There will not be a difference in two-year survival with PBSC transplantation as compared to marrow transplantation AND the difference in six-month survival between PBSC transplantation and marrow transplantation will be $\leq 10\%$.

The alternative statistical hypothesis is that two-year survival after PBSC versus marrow transplantation will differ OR six-month survival after PBSC versus marrow transplantation will differ by more than 10%.

5.2. Analysis of the Primary Hypothesis

Because the primary hypothesis is a composite hypothesis, the analysis will split the overall type I error rate of 5% into 4.5% for the comparison of two-year survival and 0.5% for the comparison of six-month mortality. This weighting reflects the primary interest on the two-year comparison. The resulting procedure will control the overall type I error rate at 5% when there is no difference in two-year mortality and the true difference in six-month mortality is $\leq 10\%$.

5.2.1. Comparison of Two-year Survival

The standard and experimental therapy arms will be compared using the stratified binomial comparison (Mantel-Haenszel test). All patients who are randomized will be included in the analysis based on an intention to treat. Survival times will be based on time since randomization, so that those patients who drop out of the study after randomization but before transplant can still be included. The final analysis will be performed after all patients have been followed for a minimum of two years post-transplant. In addition to this pointwise comparison, Kaplan-Meier survival curves will be constructed for each group. Estimates of the difference between these survival curves and confidence bands for these differences will be constructed using the method of Zhang and Klein (62). In the event that there are no significant differences between the two arms, a post hoc power analysis will be performed.

5.2.2. Comparison and Interim Monitoring of Six-month Mortality

There will be periodic interim analyses approximately every six months beginning nine months after the study opens to test whether the difference in six-month mortality rates is $\leq 10\%$ against the alternative that the difference is $> 10\%$. An allowable difference, for which we would not stop early, of 10% is used because NMDP Phase II data indicates a potential for early survival differences between PBSC and marrow to dissipate by two years. For example, Table 1.6.2 gives an estimated relative risk of PB relative to marrow of 0.6 for the first 100 days followed by an estimated relative risk of 1.2 after 100 days. This would result in a difference of 6.5% at six months, which is approximately 0% at two years; the allowable difference of 10% is chosen to reflect uncertainty in the Phase II data.

A significance level of 0.5% is allocated to these interim analyses. The stopping rule will only be applied to the estimated 495 patients who actually receive the randomized transplant, rather than the intent-to-treat population. Because there are multiple looks at the data, a Pocock stopping boundary will be applied to control the type I error rate. Therefore, at each interim analysis the hypothesis that the difference in six-month mortality rates is less than or equal to 10% will be tested against the alternative that it is greater than 10%, using a two-sided $\alpha=0.005$ level Pocock critical value with interim analysis schedule given in Table 5.2. This test will be done by comparing the Kaplan-Meier estimates of six-month mortality, and using Greenwood's formula for the variance in each group.

The final interim analysis procedure is to stop if

$$Z_1 = \frac{|\hat{p}_1(6mo) - \hat{p}_2(6mo) - 0.10|}{SE(\hat{p}_1 - \hat{p}_2)} > c_{0.005} \approx 3.222.$$

where $c_{0.005} = 3.222$ is the Pocock two-sided stopping boundary with significance level 0.005 and stopping points given in Table 5.2.

If this hypothesis is rejected, all analyses will be sent to the DSMB for expedited review. Operating characteristics of this interim analysis for safety are given below, as a function of the true difference in six-month survival (Delta), assuming an exponential survival curve with 55% or 55% + Delta survival at six months in the marrow or PB arms, respectively, and assuming uniform accrual over three years. All estimates are based on 10,000 simulations. As shown, this stopping rule will have good power to detect a large difference of 25-30% in six-month mortality, but will not stop often for smaller differences that may dissipate by two years.

Table 5.2: Probability of Stopping

Interim Analysis	1	2	3	4	5	
Accrual Month	9	15	21	27	33	
Patients Enrolled	124	206	289	371	454	
Delta	Probabilities of Stopping					Total
15%	0.6%	0.5%	0.8%	0.8%	0.9%	3.6%
20%	1.5%	3.0%	4.4%	4.9%	5.7%	19.5%
25%	4.2%	11.1%	14.4%	15.5%	14.6%	59.8%
30%	10.7%	28.1%	26.8%	17.9%	9.5%	93.0%

5.3. Sample Size and Power Considerations

Sample size calculations are based on the analysis of the primary endpoint of two-year survival, conducted at the 4.5% significance level. Based on the eligibility criteria, the estimated survival for the marrow transplant arm at two years is 35% as detailed in Table 5.3 below. The study is powered to detect a 12.5% difference in the two-year survival of 35% among patients who actually receive a transplant. Because randomization takes place prior to determination of a patient’s eligibility for transplant, NMDP experience indicates that between 5-15% of the randomized patients in each arm will never receive a transplant. These patients are typically high risk and are assumed to all die within six months. Therefore, the intent-to-treat populations to be compared in the primary analysis are assumed to be a mixture of 85-95% who receive the randomized stem cell source, and 5-15% who never receive a transplant. The resulting two-year survival rates for the intent-to-treat populations are given in the table below, as well as the powers to detect these differences, for sample sizes of 275 per group (550 total) and 326 per group (652 total), and for differences of Delta=10%, 12.5%, and 15%. A total sample size of

550 patients will have 80% power to detect the targeted difference of 12.5% in two-year survival rates for a 5% dropout rate using a two-sided binomial comparison with $\alpha=0.045$.

Table 5.3: Power to Reject the Null Hypothesis under Various Scenarios¹

Delta	Source		Transplanted	Intention to Treat Population		
			Population	5% Dropout	10% Dropout	15% Dropout
12.5%	Marrow	2 Yr. Survival	35.0%	33.3%	31.5%	29.7%
		Power (N=550)		80%	76%	72%
	PB	2 Yr. Survival	47.5%	45.1%	42.8%	40.4%
		Power (N=652)		86%	83%	80%
10%	PB	2 Yr. Survival	45.0%	42.8%	40.5%	38.3%
		Power (N=550)		61%	57%	53%
	PB	2 Yr. Survival	45.0%	42.8%	40.5%	38.3%
		Power (N=652)		69%	65%	61%
15%	PB	2 Yr. Survival	50.0%	47.5%	45.0%	42.5%
		Power (N=550)		92%	89%	86%
	PB	2 Yr. Survival	50.0%	47.5%	45.0%	42.5%
		Power (N=652)		95%	94%	91%

¹The table has been simplified for interpretability. Power calculations are based on a two-sided test.

5.4. Accrual

This study will accrue patients from U.S. and Canadian Transplant Centers and donors from U.S., Canadian, and German Donor Centers, according to the eligibility criteria described in Chapter 2. According to data from NMDP (based on 2002 numbers), there are approximately 350 patients who would be potentially eligible for this protocol transplanted in 14 non-Pediatric Blood and Marrow Transplant Consortium (PBMTTC) Core Centers per year. Assuming an enrollment rate of 40%, the Network plans to accrue 140 patients annually from these Core Centers. Among the PBMTTC Centers doing at least 6 pediatric or at least 15 total unrelated donor peripheral blood or bone marrow transplants a year (N=9 centers), NMDP data indicate that there are about 125 potentially eligible for this study a year (70 under the age of 20 years). Assuming an enrollment rate of 40%, the Network plans to accrue an additional 50 patients annually. The Network plans to accrue an additional 40 patients a year from non-Core NMDP Centers. In summary, we estimate accruing 190 patients annually from 23 Core Centers and 40 from 5-8 non-Core centers. These estimates were corroborated by surveys of Core Centers and non-Core Centers asking for the number of unrelated donor transplants done in the 12-month period from March 2001-March 2002. Although, this survey indicated a somewhat higher anticipated accrual, we chose to plan the study based on the conservative estimates given above because: 1) they are based on real data on actual numbers of NMDP-facilitated transplants in these centers; 2) participants may be lost based on either patient unwillingness to participate or donor unwillingness to participate; and, 3) about 20% of NMDP-facilitated transplants in the U.S. use donors from non-U.S. donor centers.

Given these conservative estimates, it is anticipated that the accrual goal of 550 patients will be met in three years (see Figure 5.4 below). Accrual will be closely monitored. If necessary, the

DCC will identify additional U.S. and Canadian non-Core NMDP Centers that can contribute a minimum of three patients per year to the study. Accrual will also be monitored to ascertain that enrolled patients reflect women, minorities and children in proportion to the numbers expected based on available NMDP data regarding general unrelated donor transplant recipients. In addition, the rate of patients enrolling in the study and not receiving a transplant will be closely monitored and compared with our target rate of 5%. If the observed rate appears to be as high as 15%, increasing accrual to up to 652 patients will be considered.

Table 5.4: Outcome of U.S. Unrelated Donor Blood or Marrow Transplants – 1996-2001

Risk Stratum	Disease / Stage [^]	N	100-day survival	1-year survival	2-year survival	3-year survival	4-year survival	5-year survival	# Tx's 2001* NMDP
Good	CML-CP	1097	75±3	59±3	53±3	50±3	47±3	42±4	61 (10%)
	CML-AP/CP2+	401	67±5	41±5	31±5	28±5	26±5	22±6	44 (7%)
	AML-CR1	357	67±5	43±5	36±6	32±6	32±6	32±6	83 (13%)
	AML-CR2	381	74±4	47±5	40±5	38±6	34±6	33±7	67 (11%)
	ALL-CR1	287	73±5	54±6	44±6	41±6	38±7	38±7	42 (7%)
	ALL-CR2	431	74±4	46±5	37±5	34±5	33±5	31±5	77 (12%)
	ALL-CR3	125	70±8	43±9	33±9	29±9	29±9	25±11	15 (2%)
	MDS-RA	121	69±8	45±9	42±9	36±10	25±11	25±11	17 (3%)
	MDS-RAEB	143	60±8	36±8	30±8	29±8	27±8	27±8	30 (5%)
	JCML (JMML)	25	68±18	48±20	43±20	43±20	34±22	34±22	0 (0%)
	MFMM	37	59±16	45±16	41±17	41±17	41±17	41±17	7 (1%)
	Total Good Risk	3405	72±2	50±2	42±2	39±2	37±2	34±2	443 (70%)
	Poor	CML-BP	72	56±12	25±10	15±9	13±8	13±8	9±9
AML-CR>2		38	45±16	26±14	18±12	18±12	18±12	18±12	6 (1%)
AML-Not in CR		648	57±4	23±3	15±3	14±3	12±3	11±4	100 (16%)
ALL-Not in CR		275	48±6	18±5	10±4	9±4	7±3	6±3	50 (7%)
MDS-RAEBT		114	69±9	39±9	24±8	23±8	21±8	17±10	18 (3%)
CMML		34	73±15	25±18	25±18	25±18	25±18	25±18	9 (1%)
Total Poor Risk		1199	56±3	24±3	15±2	14±2	12±2	11±3	193 (30%)
TOTAL		4604	68±1	43±1	35±1	33±1	31±2	28±2	636 (100%)

* Includes all NMDP centers, U.S. and non-U.S., core and non-core centers.

[^] Abbreviations: CP = chronic phase; AP = accelerated phase; CR = complete remission; RA = refractory anemia; RAEB = refractory anemia with excess blasts; BP = blast phase; RAEBT = refractory anemia with excess blast in transformation.

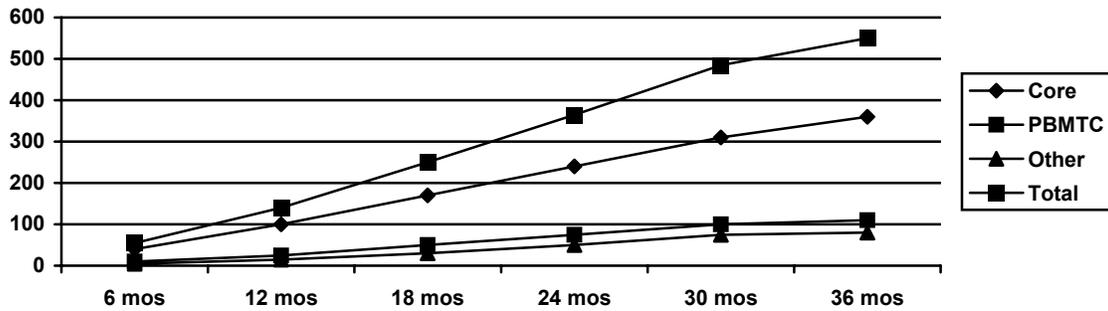


Figure 5.4 – Anticipated Patient Accrual

5.5. Interim Analyses

Interim analyses will be conducted for safety at times coincident with regularly scheduled meetings of the National Heart, Lung, and Blood Institute (NHLBI)-appointed Data and Safety Monitoring Board (DSMB). Policies and composition of the DSMB are described in the BMT CTN MOP.

Toxicity, adverse experiences, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis. Treatment will be coded for all analyses unless the DSMB requests that the code be revealed.

5.6. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients, and for all patients who actually receive a transplant. Between group comparisons will be performed for continuous variables via a t-test and for categorical variables, via the chi-square test.

5.7. Analysis of Secondary Endpoints

Transplant-related event data will only be collected on patients who actually receive a transplant and will use event times calculated from the time of transplantation. Therefore, these comparisons will be made using the actually transplanted populations. Because of the potential for unequal drop out between the two arms, adjustment for covariates will be used to make these groups comparable, if necessary. Covariates to be considered are transplant center, year of transplant, preparative regimen, GVHD prophylaxis, recipient characteristics (age, sex, body mass index [BMI], race, performance status, diagnosis, disease stage, time from diagnosis to transplant, CMV status, comorbid diseases) and donor characteristics (age, sex, BMI, race, CMV status and parity), and HLA match.

5.7.1. Two-year Survival among Transplanted Patients

The two-year survival will be compared between patients actually receiving the randomized transplant stem cell source, using a stratified Mantel-Haenzel test. In addition, logistic regression may be used to adjust for patient characteristics, which are unbalanced in the actually transplanted arms.

5.7.2. Neutrophil Engraftment > 500/mcL

Rates of neutrophil engraftment over time, treating death prior to engraftment as a competing risk, will be compared between the two groups using a stratified log-rank test, and the cumulative incidence curves will be estimated for each group. Cox regression will be performed to compare the groups after adjusting for covariates, which may be imbalanced due to patient dropout.

5.7.3. Platelet Engraftment > 20,000 and 50,000/mcL Transfusion Independent

Rates of platelet engraftment over time, treating death prior to engraftment as a competing risk, will be compared between the two groups using a stratified log-rank test, and the cumulative incidence curves will be estimated for each group. Cox regression will be performed to compare the groups after adjusting for covariates that may be imbalanced due to patient dropout.

5.7.4. Acute GVHD of Grades II-IV and III-IV

The stratified log-rank test will be used to compare the cumulative incidence of acute GVHD of grades II-IV or III-IV by Day 100 between the treatment groups considering death as a competing risk. Cox regression will be performed to compare the groups after adjusting for covariates, which may be imbalanced due to patient dropout.

5.7.5. Chronic GVHD

Rates of chronic GVHD, treating death prior to occurrence of chronic GVHD as a competing risk, will be compared between the two groups using a stratified log-rank test, and the cumulative incidence curves will be estimated for each group. Cox regression will be performed to compare the groups after adjusting for covariates, which may be imbalanced due to patient dropout.

5.7.6. Current Immunosuppressive (IS) Free Survival

Patients on either arm may go off IS therapy, and then need to subsequently reinstate therapy. The current immunosuppressive free survival is an estimate of the likelihood that a patient will be alive and not on immunosuppressive therapy at any given point in time. Patients will be censored for this endpoint at the time of relapse.

These survival curves will be compared between the two arms of the study across all time points using a technique found in Klein et al (63).

The probability that a patient is alive and off IS therapy at 2, 6, 9, 12, 15, 18, 21, 24, 30 and 36 months will be estimated. In the analysis at K months, the numerator for this estimate counts patients alive and off IS therapy, and the denominator counts all patients followed to K months, regardless of survival status. These probabilities will be compared using standard tests for binomial proportions.

5.7.7. Relapse of the Original Malignancy

Rates of relapse, treating death prior to relapse as a competing risk, will be compared between the two groups using a stratified log-rank test, and the cumulative incidence curves will be estimated for each group. Cox regression will be performed to compare the groups after adjusting for covariates that may be imbalanced due to patient dropout.

5.7.8. Donor Lymphocyte Infusion

The use of DLI will be recorded and analyzed as a secondary endpoint. DLI will be a competing risk for evaluation of acute and chronic GVHD.

5.7.9. Bacterial, Viral and Invasive Fungal Infection

Infectious complications will be analyzed in relation to patients' clinical risk with comparison of the two treatment cohorts (PBSC versus marrow) and adjusted by other relevant clinical risk factors. These may include, but will not be limited to: pre-transplant infectious history and serostatus, time to neutrophil engraftment, and acute and chronic GVHD. Analysis of infection incidence (by cumulative incidence) and infection density (number of infections over time for patients with repeated infections), especially during later time periods, will be performed. Multivariate regression analysis will be performed to test for the contribution of stem cell source (PBSC versus marrow) and other relevant covariates to the incidence of infections. Specific analyses using these techniques will be performed for bloodstream infections (bacteremia), systemic fungal infections, and viral infections (CMV, HSV, respiratory viruses), and infections that lead to added isolation precautions in the hospital setting (e.g., resistant enterococcus, *Clostridium difficile*, varicella zoster, adenovirus, rotavirus, respiratory viruses).

5.7.10. Patient and Donor Quality of Life

Details about these analyses will be given in the separate sections on quality of life.

5.7.11. Three-Year Survival

Same as for the primary and secondary two-year endpoints.

5.8. Safety Analysis

All entered patients will be included in the safety analysis.

5.8.1. Adverse Events

All reported serious treatment related adverse events will be carefully examined with respect to the severity and relationship to study treatment. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 3.0. The incidence for each reported study group associated adverse experience delineated in Section 4.15 will be presented for each group.

5.9. Laboratory Tests

Graft Characterization - Descriptive statistics will be computed on the cellular constituents of the graft, separately for each graft type. These will be compared between graft types using nonparametric Wilcoxon rank sum tests. Counts of the immune cells of different types in the graft (including donor CD34 and dendritic cells) as well as the graft type will be used to model post-transplant GVHD, relapse, and various measures of immune reconstitution through Cox regression, treating death prior to immune reconstitution, GVHD, or relapse as a competing risk.

Immune Reconstitution - Descriptive statistics will be computed on the cellular constituents and Ig types separately by treatment arm. These will be compared between treatment arms using nonparametric Wilcoxon rank sum tests. Levels of IL-2 and IL-7 will be correlated using nonparametric measures with the levels of T cells in the blood. Response to vaccinations will be compared between treatment arms using the binomial comparison of proportions.

Chimerism - Chimerism results will be compared between the treatment arms using nonparametric Wilcoxon rank sum tests.

5.10. Donor Recovery

Donor Recovery to Baseline Toxicity Scores - Appropriate statistical methods to detect trends over the available spectrum of donor follow-up time will be employed for baseline toxicity recovery to baseline endpoints. Such methods may include, but not necessarily be limited to: analysis of variance with repeated measures techniques, non-parametric paired comparisons, or other methods suitable for comparisons of correlated data.

Donor Recovery to Baseline CBC and WBC Differential Values - Appropriate statistical methods to detect trends over the available spectrum of donor follow-up time will be employed for baseline CBC recovery to baseline endpoints. Such methods may include, but not necessarily be limited to: analysis of variance with repeated measures techniques, non-parametric paired comparisons, or other methods suitable for comparisons of correlated data.

5.11. Subgroup Analyses

Subgroup analyses will be performed on the following subgroups: pediatric patients (<16), disease risk (High vs. low, as defined in Table 5.4), and HLA matching status (matched on HLA-A, B, C, DRB1 vs. mismatched). First the direction and magnitude of the treatment effect in the subgroup will be compared with the rest of the sample to look for qualitative differences. In addition, statistical hypothesis testing will be performed on endpoints of interest to look for significant interactions between the treatment and each subgroup of interest. However, because of the greatly reduced sample sizes in such subgroups, these tests are underpowered and not anticipated to reach statistical significance in most cases. They will be used only to note very strong interactions and to generate hypotheses.

CHAPTER 6

6. INFECTIOUS COMPLICATIONS OF TRANSPLANTATION

The early neutropenia, mucocutaneous barrier disruption and extended period of immunodeficiency after allogeneic transplantation leave patients vulnerable to serious and life-threatening infections. Because engraftment as well as immune reconstitution rates may differ following PBSC versus marrow transplantation, in this trial individual infectious complications will be prospectively monitored and compared. The primary question asked in this protocol component is whether there will be a significant difference in the incidence, severity and case-fatality rate of microbiologically documented infections between the PBSC and the marrow arms of the trial.

Regimens to prevent and treat infectious complications of transplantation have evolved over the last three decades and continue to evolve, as have diagnostic and monitoring tools. Specific prophylactic, monitoring and therapeutic regimens also vary from center to center. While the study randomization will be stratified by center, in part for this reason, knowledge of prevention regimens used at each center will assist with the interpretation of putative relationships between study arm and infectious complications on this trial.

Infection prophylaxis and complication monitoring forms and instructions for completion of the forms are included in the Data Management Handbook and User's Guide.

6.1. Required Data Elements for Collection

6.1.1. Pre-transplant Infections that may have an Impact on the Transplant by Recurrence

Information regarding clinically significant fungal infections that occurred before transplant will be obtained based on the expected possibility of their reactivation during transplantation. In addition, cytomegalovirus (CMV) serostatus of the donor and recipient, and herpes simplex (HSV) and varicella zoster virus (VZV) serostatus of the recipient will be collected. The presence of fungal, bacterial and viral infections requiring treatment will also be captured as part of the pre-treatment eligibility screening form, as these infections are grounds for delaying or deferring the transplant.

6.1.2. Infectious Disease Prophylaxis

To determine what infection preventive measures were used, centers will be surveyed annually to report their infection prophylaxis protocols applicable to patients enrolled on this trial. These center-defined, rather than patient-specific, data will be compiled for analysis. The survey will include questions on: systemic bacterial, viral, fungal and pneumocystis prophylaxis, pre-emptive therapy for positive CMV pp65 antigen or PCR tests. Infection prophylaxis varies by time period post-transplant.

The center infection prophylaxis survey will include the following periods:

1. Early neutropenia combined with mucocutaneous barrier disruption, weeks –1 through week + 4 post-transplant;
2. Resolution of early neutropenia combined with continuing recovery from mucocutaneous barrier disruption, from 4-12 weeks post-transplant;
3. Extended period of immunodeficiency from 12-26 weeks post-transplant; and
4. Extended period of immunodeficiency from 26-52 weeks post-transplant.

Centers should indicate varying practices over time in their survey responses.

6.1.3. Specific Reporting of Individual Infections

6.1.3.1. Data of interest

The objective of this protocol component is to capture microbiologically defined opportunistic infections. These will include the following etiologies:

1. Viruses
2. Fungi
3. Bacteria
4. Protozoa
5. Others

For the case definition for each infectious syndrome please refer to the BMT CTN Infectious Diseases MOP. Case definitions specify clinical manifestations of disease and microbiological data. Microbiological data will be captured from evidence of microbiology isolates, as well as genetic or antibody probes tested on fluid or tissue samples. Clinical manifestations specific for each infectious disease syndrome will be captured by the case report forms using data from clinical source documents.

Specific microbiology information about *Candida* and *Aspergillus* species will be included in the MOP, as this emerging and serious infection class is now being managed with multiple alternate antifungal agents.

6.1.3.2. Tempo of data acquisition and reporting

To enhance the reporting of all individual infections, infections forms should be filed as soon as possible after diagnosis. Patient charts should be reviewed on Days 28, 100, 180, 365 and 730 to ensure that all clinically significant infections were captured between these reporting time periods. If no clinically significant infections have occurred, that negative information will be reported.

CHAPTER 7

7. PATIENT QUALITY OF LIFE

7.1. Background and Significance

7.2. Overview and Rationale

Quality of life (QOL) refers to every dimension of life except for its length, and includes physical abilities, symptoms, social well-being, psycho-emotional status, and spiritual/existential qualities. It reflects how well people feel, what they can accomplish, how satisfied they are with their lives, and whether their lives have meaning and purpose. Within this broad concept, health-related quality of life (HRQOL) refers to aspects of QOL that are attributable to health, disease or medical treatment (for simplicity, the abbreviation QOL will be used in this protocol). Following hematopoietic stem cell transplantation (HSCT), QOL can range from perfect, with no physical, emotional or social sequelae and a greater appreciation for life, to severely compromised with physical disability, pain and psychological despair. Of course, most patients who have undergone HSCT fall within this spectrum.

The figure below shows an example of QOL taxonomy. Global QOL (“Overall, how is your quality of life?”) is made up of several domains such as physical symptoms and functioning, emotional well-being, social relationships etc. HSCT survivors generally report high global quality of life following HSCT, but many specific symptoms (64, 65, 66, 67, 68, 69, 70) and limitations on their daily activities (71). However, despite many problematic long-term complications, almost all patients indicate they would undergo the procedure again given similar circumstances (72, 73, 74, 75). In addition, for some common problems after HSCT such as fatigue, sleep and sexual functioning, documented dissatisfaction is also high in the general population and chemotherapy-treated patients (76, 77).



The purpose of the QOL component of this trial comparing unrelated PBSC versus marrow as a stem cell source is to understand the long-term QOL implications of one graft source versus another. While the trial is powered with survival as the primary endpoint, QOL will be an especially important secondary endpoint if survival is not statistically different, or if the incidence of chronic GVHD is higher in one group. It is also possible that immunologic recovery, peri-transplant experiences and complications, speed of physical recovery, and expectations may influence ultimate QOL.

It is very important that data collection is centralized, patients' response burden is minimized and QOL assessments are fully integrated into the trial to maximize the chance of complete data collection. With this goal in mind, the number of data instruments will be minimized and focused on answering the research question, assuming that other psychological, social etc. factors are balanced by the randomization process. Specifically, associations between QOL and specific clinical events or patient characteristics will not be investigated. Other ongoing studies fully address those issues.

7.3. Preliminary Work

NHLBI has sponsored a randomized trial of T cell depletion vs. immunosuppressive medications for acute GVHD prophylaxis in unrelated donor marrow transplantation (TCD). Accrual and follow-up are complete. Dr. John Wingard and the International Bone Marrow Transplant Registry (IBMTR) have concluded a large, cross-sectional study of QOL and relationships incorporating patients, spouses and controls. Both these studies have shown the feasibility of a centralized, telephone data collection strategy using mailed surveys followed by phone interviews. Overall and item completion rates were excellent, and anecdotally, the personal contact was much appreciated by the patients. Results are not yet available from these studies, but completion rates in the NHLBI trials were excellent (baseline – 91%, 100 days – 59%, 6 months – 64%, one year – 73%, 3 years – 84%). However, compliance varied and improved as the study progressed. In addition, a pediatric component was planned but closed early due to poor compliance. In order to facilitate comparison of the current study with the NHLBI and IBMTR studies, every effort has been made to include similar instruments and assessment times.

7.4. Specific Aims

The overall aim is to compare the QOL of patients undergoing unrelated donor marrow transplantation with that of patients undergoing unrelated donor PBSC transplantation. Other aims include:

1. To compare chronic GVHD symptom burden (as measured by the chronic GVHD symptom scale) between the two treatment groups.
2. To compare physical, functional, and transplant-specific QOL modules (as measured by the Trial Outcome Index [TOI] of the Functional Assessment of Chronic Illness Therapy [FACT-BMT] and the rate of return to work) between the two groups.
3. To compare the positive and negative psycho-emotional aspects of transplantation (as measured by the Mental Health Inventory) between the two groups.

7.5. Hypotheses

1. There will be greater chronic GVHD symptom burden in recipients of PBSC transplants at one-year post-transplantation.
2. There will be no difference in the physical, functional, and transplant-specific QOL between the two groups over time through two years post-transplantation.
3. There will be no difference in rate of return to work at two years.

4. There will be no difference in the positive and negative psycho-emotional aspects of transplantation, as measured by the Mental Health Inventory.

7.6. Eligibility and Exclusion Criteria

7.6.1. Inclusion Criteria

1. Enrollment in the randomized clinical trial.
2. At least 16 years of age.
3. Signed informed consent.

7.6.2. Exclusion Criteria

1. Inability to communicate in English or Spanish.
2. Inability to participate in interviews due to cognitive, linguistic or emotional difficulties.
3. Current uncontrolled psychiatric illness.
4. No telephone or access to a telephone.
5. This study will not be offered to children and their parents based on the experience with the NHLBI TCD study. In addition, QOL considerations and instruments differ between adult and pediatric patients necessitating a separate analysis. It is anticipated that minority representation will mirror that in the randomized study.

7.7. Study Procedures

7.7.1. Study Design

Patients will be enrolled in the QOL study at the time they provide first consent for the randomized trial. Once a donor is confirmed, the patient will be sent a QOL study packet including a cover letter, copy of the QOL interview, and information to schedule the time for a pre-transplant interview. Interviews will be conducted in either English or Spanish.

Interviewers will read the verbatim questions to the subject, who will indicate their answers. Interviewers will record those answers. If a patient wishes to stop and continue later or another day, that is permissible. Three contacts with the patient will be allowed with his/her permission to obtain complete data at each time point. In addition, a toll-free line will be established for patient questions or in case it is easier for the patient to complete the surveys at another phone (e.g., at a clinic appointment or a friend's house).

Patients will be surveyed prior to transplantation (within 1 month of admission), and at 6 months, 1 year and 2 years. Post-transplant interviews may occur +/- 1 month from the scheduled time point. Permission will also be sought for QOL assessment at 5 years post-transplantation, although these data will not be analyzed as part of the randomized controlled trial.

7.7.2. Study Endpoints

The four study endpoints of the QOL component will be:

1. The chronic GVHD symptom scale.
2. The Trial Outcome Index of the FACT-BMT.
3. Occupational functioning.
4. The Psychological Distress and Psychological Well-Being Subscales of the Mental Health Inventory.

7.7.3. Instruments

Table 7.7.3: Description of Instruments

Instrument	Domains	Rationale
Sociodemographics	Race/ethnicity, Age, Gender, Education, Income	
Global quality of life	Karnofsky performance status Perception of overall health, Perception of overall QOL, Rating scale	Assesses patient self-perceived global quality of life and functioning.
FACT-BMT	Physical, Emotional, Social Functional, Transplant-specific	Collected in NHLBI TCD and IBMTR QOL study. Allows comparison with other cancer populations.
Mental Health Inventory (MHI)	MHI Index, Psychological distress, Psychological well-being	Measures depression, anxiety, positive affect, emotional ties and loss of behavioral and emotional control. Includes the mental subscale from the SF36.
Occupational functioning	Occupational functioning	Only about 75% of surviving patients return to work, and return to work is associated with better QOL. This instrument was used in NHLBI study.
Chronic GVHD module	Chronic GVHD summary score	Anticipated rates of cGVHD are 50-90%. Measures cGVHD problems with skin, energy, lung, nutrition, psychological, eye, and mouth.
Alternative contacts		Contact information for two alternative individuals.
Distress assessment		Measures distress caused by survey administration.

Sociodemographics: Eight standardized questions will assess ethnicity (Hispanic/Non-Hispanic), race (White, Black, Asian, American Indian/Alaskan Native, Native Hawaiian or other Pacific Islander, Multiracial), age, sex, education, work status and occupation, and family income.

Global Quality of Life: Four standard questions will assess patient self-assessed Karnofsky performance status, overall health and overall quality of life (excellent, very good, good, fair, poor), and a rating scale for overall quality of life (where 0 equals death and 100 equals perfect quality of life).

FACT-BMT: The FACT-BMT is a 37-item instrument composed of the FACT-G and transplant-specific subscale. The FACT-G is comprised of 4 domains, physical (7 items), social (7 items, including sexual satisfaction), emotional (6 items) and functional (7 items, including work, sleep and leisure activities). The transplant-specific module (10 scored items) includes appetite, appearance, mobility and fatigue (78,79). Higher scores indicate better functioning. The Trial Outcome Index (TOI) is composed of the physical, functional, and transplant-specific modules (80). Data from 132 observations in unrelated donor recipients post-transplantation (6-60 months) showed a mean of 66.76, SD 19.53, range 11.8-96.0.

Mental Health Inventory (MHI): Thirty-eight items divided into two summary scores and five subscales measure anxiety, depression, positive affect, emotional ties, and loss of behavioral and emotional control (this instrument includes the entire mental subscale of the SF36). As transplantation has been associated with both positive and negative psycho-emotional sequelae, it is important that the instrument detects both. Psychological well-being is measured by 14 items with a reported mean of 59.16 and SD 12.16 in a general population sample of 5,000 individuals. Cronbach's alpha is 0.92, one year test-retest 0.63, and higher scores indicate better functioning. On the 24 item psychological distress scale, mean is 47.54, SD 15.39, Cronbach's alpha 0.94, one-year test-retest 0.62, and higher scores indicate more distress (81, 82). The MHI was sensitive to changes associated with azacytidine treatment in MDS patients, and baseline scores were very similar to that of the general population.

Occupational Functioning: Occupational functioning was measured in the NHLBI TCD trial using 6 items that assess current job status, type of work (will be captured using Hollingshead categories), number of hours of paid and unpaid work, school, importance of work and change in work goals.

Chronic GVHD Symptom Scale: The 30 item cGVHD symptom scale measures degree of bother of cGVHD manifestations in skin, energy, lung, nutrition, psychological, eye and mouth. Responses are captured on a five-point Likert scale ("no symptoms, or not bothered at all", "slightly bothered," "moderately bothered," "bothered quite a bit," or "extremely bothered"). Scores for each domain are converted to a 0-100 scale where higher scores indicate more bother. Mean (SD) was 12 (9) for patients with mild (N=55), 18 (13) for patients with moderate (N=39), and 34 (13) for patients with severe (N=13) disease. Although the SF-36 and FACT-BMT were sensitive to changes in overall health, only the chronic GVHD symptom scale was sensitive to changes in patient-perceived chronic GVHD severity (83).

Alternative Contact Information: The names of two people who do not live with the subject, but would be able to locate the patient in case of phone number change, move etc. will be obtained. Names, addresses and phone numbers of these alternative contacts will be collected.

Distress Assessment: Two items will assess distress at the conclusion of each survey administration. One question measures level of comfort with the questions (very comfortable, comfortable, a little uncomfortable, very uncomfortable) and degree of stress caused by the questions (a great deal, a lot, some, a little, none). These questions were modified from studies of bereaved family members. Responses of “very uncomfortable” with questions or “a great deal” or “a lot” of stress caused by the survey leads to follow-up questions and an offer of referral. Actual referral or the need to notify the transplant center Principal Investigator due to distress caused by the survey administration will constitute an unexpected serious adverse event.

7.7.4. Required Data

Table 7.7.4: Required Data

Instrument	N items	1 & 2			
		Pre	6 mos	yrs	5 years
Sociodemographics	8	X			
Global quality of life	4	X	X	X	X
FACT-BMT	37	X	X	X	X
Mental Health Inventory (MHI)	38	X	X	X	X
Occupational functioning	6	X		X	X
Chronic GVHD module	30		X	X	
Alternative contacts	2	X	X	X	
Distress assessment	2	X	X	X	X
TOTAL N ITEMS		97	114	120	87
ANTICIPATED TIME		20 min	20 min	25 min	15 min

7.8. Description of Study Process

7.8.1. Identification of Eligible Patients

Upon provision of informed consent for participation in the randomized clinical trial, patients will also complete a Patient Contact Form to allow the QOL interviewer to reach them. This form will capture name, address, home phone number, email address, alternative contact information, preferred language, and preferred time to be contacted. Site coordinators will provide transplant center name, type of transplant, date of admission, date of transplant, transplant center and patient NMDP identification numbers and patient’s study number. This information will be faxed to the QOL coordinating center and entered into a password-protected database. Upon receipt of this information, patients will be mailed a packet of information including a cover letter explaining more about the QOL survey procedures, the first survey for their review, and contact information for more questions.

7.8.2. Informed Consent

Consent for QOL data collection is contained in the informed consent document for the trial. Procedures between the QOL coordinating center and the BMT CTN Data Coordinating Center (DCC) will ensure that a copy of the informed consent is on file before collection of the QOL data.

7.8.3. Collection of QOL Data

QOL interviewers will call the patient at a day and time that is convenient for them, or patients may call a toll-free number at a predetermined time. Baseline data will be collected within one month prior to graft infusion and after an admission date is scheduled. For each subsequent contact, the QOL coordinator will call or email the clinical contact person associated with the patient within a month of contact in order to prevent contact attempts with deceased patients. Once confirmation of survival is obtained, the QOL coordinator will mail the patient a packet of information, and call the patient to schedule the QOL interview. The post-transplant interviews may occur +/- 1 month from the scheduled time. At the conclusion of each survey administration, patients will be reminded of the next date of contact and the procedures that will be followed.

7.8.4. Location of Missing Patients

If patients cannot be located through the contact information provided, or through the transplant center, then the alternative contacts will be used to locate the patient. With the patient's permission, updated contact information will be forwarded to the transplant center for their records.

7.8.5. Withdrawal of Consent for QOL Data Collection

If patients wish to discontinue participation in the QOL study, the QOL interviewer will notify the Principal Investigator at the transplant center immediately. In approximately one week, the Principal Investigator will call the patient back to make an attempt to keep the patient in the study by explaining the goals of the study and the required data needs. Should the patient still wish to drop out of the QOL study, no further contact will be attempted. However, QOL data will be removed from the database only when specifically requested by the patient.

7.8.6. Fifth Year Contact

Although the fifth year will not be officially part of the randomized controlled study or the analysis, consenting patients for long-term follow-up allows important long-term data to be collected. Similar procedures as for the two-year survey will be followed.

7.8.7. Letter of Appreciation and Communication of Findings

At the conclusion of the study, a letter of appreciation will be sent to all surviving patients thanking them for their participation. If a patient dies, a letter will NOT be sent to the next of kin.

7.8.8. Management of Adverse Reactions

Patients enrolled in this study will undergo up to five interviews. At the start of each interview, patients will be told clearly that they may skip over any interview questions they wish and may withdraw from the study at any time. Despite our best efforts, it is conceivable that some patients may find the process upsetting. Names and phone numbers of local people to contact will be listed in the consent form and provided at the end of each interview. Notification of the transplant center Principal Investigator based on distress caused by participation in the study will be considered an unexpected, serious adverse event and will be reported to the Principal Investigator, the IRB and the DCC. However, distress incidentally detected will be reported to physicians and noted in the research file, but will not be considered an adverse event. Section 7.11.1 details study procedures in case distress is detected with potential to cause injury to self or others.

7.9. Statistical Considerations

7.9.1. Sample Size

As quality of life is a secondary endpoint for the randomized clinical trial, the available sample size is predetermined by the primary endpoint of survival. Thus, statistical considerations will focus on the power to detect differences given the enrollment and likely survival of the treatment arms.

The available sample size at two years will be 60 for marrow and 81 for PBSC, based on expected accrual and the following additional assumptions:

1. 90% of patients are adults (age > 18 years) who communicate in English or Spanish.
2. Compliance with QOL assessments is 80%.
3. Survival is 45% in the PBSC and 35% in the marrow group at two years.

The hypothesis related to chronic GVHD symptoms pertains only to the one-year time point, and return to work applies to the two-year assessment. All other hypotheses address differences between the two groups (marrow versus PBSC) over four potential time points: pre-transplant, six months, one year and two years. For illustrative purposes, there is 64% power to detect a 0.5 SD difference in the scores of interest at the two year time point (assuming 81 PBSC and 60 marrow eligible survivors) and with a Bonferroni correction $p=0.01$ and two-sided testing. These detectable differences are presented in Table 7.9.1.

Table 7.9.1: Detectable Differences

Outcome	Raw scores	0.5 SD
CGVHD Symptoms	12 vs. 18.5	6.5
Trial Outcome Index	60 vs. 70	10
Psychological Well-Being	56 vs. 62	6
Psychological Distress	44 vs. 52	8

Differences in QOL between the two groups will be assessed in two main ways. First, the marginal QOL scores given that a patient is alive will be compared at the specific time points described above using simple t-tests/confidence intervals. Each of these time point comparisons will be done using the patients alive at that time. Additionally, a second analysis will be done using the Integrated Quality Adjusted Survival to compare the two treatments on an aggregated assessment of QOL over the entire period of observation. This second analysis will account for potential differences in the survival rates between the two groups.

7.9.2. Missing Data

Missing data is a common problem in survey and/or longitudinal studies. Reasons of missing data are multifold: death, relapse, drop-out, early termination, or missing assessments. Death rates are expected to be substantial based on the underlying disease states and the nature of unrelated donor transplantation, and will be accounted for by the Quality Adjusted Survival, as discussed above. For comparison of QOL among survivors, every effort will be made to collect all measurements from all eligible patients to minimize missing data from survivors. However, as experience with the TCD trial suggests, there appear to be fewer problems with missing data at later time points because initial toxicity has diminished. If missing data occur, we will diagnose the mechanism and pattern of missing data based on information provided by the site and we will perform missing data analysis. Since prior studies suggest that missing data in HSCT studies is associated with poor QOL (84) (i.e., informative right censoring, non-ignorable missing), we will explore the generalized Schlucter model (85), which is a joint model for longitudinal and survival data, where the survival component of the model acts as a missing data mechanism using software developed at the Dana-Farber Cancer Institute (86). This model essentially allows missing QOL measurements at a specific time point of interest to be imputed based on how soon after that time the patient dies. Note that use of subsequent survival information to input the QOL scores is primarily useful when comparing QOL at earlier time points, because the survival times will be observed until two years for each patient, while at later time points there may be less additional time for which the patient's survival status is recorded. Therefore this should be a reasonable approach to dealing with the missing data related to QOL.

7.9.3. Modified Intent-to-Treat

A modified intent-to-treat analysis is planned using all randomized patients who are transplanted according to their randomization assignment.

7.10. Risks and Discomforts

No medical treatment will be delivered as part of the QOL component. Participation is limited to completion of the surveys. It is possible that some of the questions may be upsetting, although they are all validated instruments used on thousands of patients. Patients will be reminded before every survey administration that they may skip items if they wish. Distress will be assessed at the completion of each survey, and distress attributable to participation in the study (as opposed to distress detected incidentally) will be considered a severe adverse event reportable to the IRB.

7.10.1. Potential Risks to Research Subjects

As this is an observational study, there are no associated physical risks. It is possible that the survey questions could cause emotional distress, but the risk is likely to be minimal. Distress will be assessed after every contact with patients, and if we detect a high level of distress, the transplant center Principal Investigator will be notified.

7.10.2. Adequacy of Protection Against Risks

The informed consent document clearly outlines the QOL procedures, assessment points, time commitment and goals of this portion of the trial and must be signed by the patient. Study participants may withdraw their consent to participate at any time or may refuse to participate in any aspect of the study. This withdrawal will not compromise their medical care in any way.

Confidential and emotionally sensitive material will be collected from the patients. These data will be kept in locked research areas. Access to all data will be limited to study personnel.

7.10.3. Sources of Research Materials

For the QOL component, potentially identifiable information on patients will consist of completed surveys. Patient sociodemographics, quality of life, functional status, employment status, mental health and chronic GVHD symptoms will be measured. Permission to collect all data will be obtained through the informed consent document, and will be obtained specifically for research purposes. However, if a high level of emotional distress is detected, the transplant center Principal Investigator will be notified.

7.10.4. Potential Benefits

Patients participating in this study are not expected to obtain any direct benefit although some patients do report feeling better after participation in other QOL studies.

7.10.5. Potential Benefits of the Proposed Research to the Subjects and Others

This study will involve minimal risk to participants. No benefits to the patients, as a result of participation in the study, are anticipated. However it is hoped that future patients will benefit.

The risks of the study to participants are minimal whether measured absolutely or relative to what will be learned to benefit future patients.

7.11. Monitoring and Quality Assurance

7.11.1. Patient Tracking

Patient tracking will be accomplished through a master file maintained by the QOL interviewers. Every four months, a progress report with total number of contacts attempted, total number of surveys successfully collected, and barriers to complete data collection will be produced. In this way, response rates will be constantly monitored with the ability to enhance data collection procedures if inadequate QOL participation is detected.

If serious distress is detected (suicidal, homicidal or psychotic features), the Principal Investigator at the patient's transplant center will be notified for the patient's own protection. This safeguard will be clearly outlined in the patient consent form, "Your answers to the quality of life interviews will be kept private and not included in your medical records nor shared with your physicians or other caregivers. Your answers will be coded with a study number only and kept in password-protected electronic files or locked in file cabinets. Only study personnel will have access to your information. However, if any of your answers lead us to believe you are seriously depressed or in danger of hurting yourself, your physician will be notified."

7.11.2. Oversight of Project Staff

Prior to patient contact, all study staff will be able to:

1. Administer QOL surveys over the phone under appropriate supervision
2. Demonstrate basic knowledge about the medical procedures under study and know where to refer patients who have questions about their medical conditions
3. Explain and answer questions about the standardized instruments
4. Know how to recognize and refer patients experiencing distress to the study investigators

Ongoing quality will be maintained through random monitoring of interviews and additional training provided as necessary.

CHAPTER 8

8. DONOR QUALITY OF LIFE

8.1. Background and Significance

Although both bone marrow harvest and PBSC collection are fairly well tolerated by donors (see Chapter 1), there may be significant differences between the procedures in terms of their impact on donor quality of life (QOL). In a French study (87), researchers performed a prospective evaluation of anxiety, pain, and inconvenience. Patients were randomly assigned to apheresis or bone marrow harvest for collection of stem cells in preparation for an autologous hematopoietic cell transplant. Marrow donor patients experienced more anxiety and pain than PBSC patients. Patients undergoing PBSC collection experienced more positive judgments toward the collection procedure than bone marrow donor patients. Patients who had a venous catheter placed for collection of stem cells experienced more pain than those from whom stem cells were collected by peripheral venous access.

A group in Norway (88) also conducted a randomized study of safety and complaints of PBSC or marrow donation of stem cells. They found a striking difference in the total burden of complaints, duration of hospital stay, and sick leave in the two groups of donors, favoring PBSC donors. Interestingly, they found that PBSC donors used more analgesics than marrow donors. They hypothesized that these differences may have been due to the nature of the discomfort and the expectation that PBSC donors would continue to work during their daily injections of growth factor. They indicated that the method used for informing donors may have influenced expectations, possibly impacting the post-procedure assessment. However, they do not elaborate this point.

Switzer et al., (89) compared the physical and psychosocial experiences of marrow and PBSC donors donating cells a second time. Although the study was cross-sectional and retrospective, examination of quality of life outcomes from donors who have experienced both procedures makes this study unique. Results were similar to the aforementioned studies; a greater proportion of marrow donors reported post-donation physical side effects as compared to PBSC donors. A greater proportion of marrow donors reported using pain medications. Individuals who donated marrow for their first donation and PBSCs for their second reported PBSC donation as less physically difficult, time-consuming, and inconvenient as compared to marrow donation.

Rowley et al., (90) compared the experiences of marrow and PBSC donors participating in a randomized trial, and did not find significant differences in symptom burden or emotional status between collection methods. They found that pain levels and duration were similar for the two groups, although they peaked at different times. Both marrow and PBSC donors reported minimal fluctuations in emotional status. However, as emotional status was measured with only a single, global item, these results should be interpreted with caution. The most significant difference between the groups was that recovery time was shorter for PBSC donors.

Given the few studies conducted and their somewhat contradictory results, further investigation is warranted to better describe the potential differences in quality of life following marrow versus PBSC donation.

8.2. Specific Aims and Hypotheses

Our overall goal is compare the QOL of marrow donors with PBSC donors. We are interested in knowing if the physical and psychosocial symptom burdens, recovery time, inconvenience, concerns, and satisfaction levels of marrow and PBSC donors differ depending on the donation method. Specific aims include:

1. To compare the physical side effects, functional ability, and recovery time of donors randomized to PBSC or marrow donation.
2. To compare the psychosocial side effects between the two donation methods.
3. To compare the inconvenience and restriction of activities between the two groups.
4. To compare the level of concern about donation of each group.
5. To compare levels of satisfaction reported by each type of donor.

8.2.1. Hypotheses

1. PBSC donors will report fewer numbers of side effects and greater functional ability overall, but a greater degree of bone pain, than marrow donors. PBSC donors will recover to baseline functioning faster than marrow donors.
2. PBSC donors will report less anxiety about donation than marrow donors.
3. PBSC donors will report lower levels of inconvenience and restriction of daily activities than marrow donors.
4. PBSC donors will report fewer concerns about donation than marrow donors.
5. PBSC donors will report greater satisfaction levels than marrow donors.

8.3. Eligibility and Exclusionary Criteria

Potential study participants will be the 550 donors (~275 each of PBSC and marrow) recruited to participate in the randomized clinical trial (RCT). Donors must (a) meet the standard NMDP requirement for donor eligibility, (b) be selected for participation in the RCT, (c) meet the inclusion and exclusion criteria listed below, and (d) give signed informed consent to participate in both the RCT and the Donor Quality of Life study.

8.3.1. Inclusion criteria

1. Enrollment in the parent randomized clinical trial.
2. Signed informed consent.

8.3.2. Exclusion Criteria

1. Inability to read and speak in English, because the instruments to be used in the Quality of Life study have not all been validated in other languages.
2. Inability to complete telephone interview due to cognitive or linguistic difficulties.
3. Lack of telephone access.
4. Age less than 18 years.

8.4. Study Procedures

8.4.1. Study Design

Pre-donation. Donors will be enrolled upon completion of their evaluations and agreement to the study randomization.

Within four weeks prior to marrow donation or initiation of G-CSF administration for PBSC donors, participants will complete the baseline interview. Every attempt will be made to administer the baseline interview as close to donation or G-CSF administration. PBSC donors will have an additional assessment at Day 4 of G-CSF administration, since the preparatory procedures for PBSC donation are considered part of the donation process and include experiences that likely affect QOL.

Post-donation. Donors will be surveyed within 48 hours after donation, then weekly until they indicate normal functioning for a period of three consecutive weeks. Long-term assessment will occur at 6 and 12 months. All questionnaires will be administered by telephone by an independent interviewer. Basic medical information will be obtained directly from donors by the donor center following standard NMDP procedures and forms. Information will include the need for central venous catheter placement, hospitalization and reason, and any serious adverse event.

Permission will be sought for repeated QOL and satisfaction assessment yearly for five years. These data will not be included as part of this randomized trial.

8.4.2. Study Endpoints

Study endpoints include physical recovery, including symptoms, functioning, and recovery time, psychological and social functioning, degree of inconvenience experienced, concerns about donation, and satisfaction with donation.

8.4.3. Measures

Sociodemographic Questions: Age, sex, marital status, education level, and work status will be assessed. Race/ethnicity will be identified using NIH categories.

Physical Recovery: Physical side effects will be measured by a series of questions used by Switzer et al., in their 2001 study of second-time donors. These questions include assessment of fever, overall pain, and specific side effects. These questions will be supplemented with similar

questions contained on the standard NMDP forms, which assess side effects, complications, medication use, and discomfort in specific parts of the body, as well as evaluation of return to baseline functioning. Four additional items will assess highest pain intensity, average pain, amount of pain, and pain's effect on sleep using visual analog scales used previously by Rowley et al., (90). Functional status will be measured by toxicity criteria, which is standard on the NMDP forms.

General Physical, Social, and Emotional Functioning: Global physical, social, and emotional functioning will be assessed with the 12-item Medical Outcomes Survey Short-Form 12v2 (91). The SF-12v2 is widely used, reliable and a well-validated instrument that is appropriate for individuals with a broad range of functional limitations. It has the advantage of being linked to a substantial body of normative data.

Psychological Functioning: Psychological status will be measured by the Profile of Mood States-Short Form (92). This is a 30-item measure that produces an overall distress score, as well as scores on six subscales: depression, anxiety, anger, confusion, fatigue, and vigor. This scale has been shown to have good reliability and validity (92) and has been used extensively in the assessment of psychological aspects of quality of life.

Convenience: The degree to which the procedure interferes with daily activities, and requires that special arrangements be made for coverage of work or domestic responsibilities, the number of days off from work, and the restriction of leisure activities will be assessed with items from the standard NMDP forms and items used in previous studies (89).

Concerns about Donation: The degree to which donors are concerned about short- and long-term health effects of donation will be assessed with questions used in previous studies (89).

Satisfaction with Donation: Donors' level of satisfaction with their donation experience will be assessed with questions used in previous studies (89).

Clinical Data: Number of blood transfusions given, requirement for a central line and the number and duration of leukapheresis procedures will also be assessed via NMDP forms.

Table 8.4.3: Data Collection Timeline

Measures	N items	Pre	Day 4- PBSC only	Within 48 hours donation	Weekly until 3 weeks after full recovery	Final weekly assessment after full recovery	6 & 12 mos
Sociodemographics and Background Information	13	X					
Influence of Others	4	X				X	
Concerns about Donation	5	X (7 items)	X	X		X	X
Preparedness	5	X				X	
Physical Symptom Scale	12	X	X	X	X	X	X
Physical/Emotional Function: SF-12	12	X		X		X	X
Pain	4	X	X	X	X	X	X
Profile of Mood States	30	X		X		X	X
Satisfaction and Feelings about Donation	9			X		X	X
Response of Others	3			X		X	X
Side Effects	7		X (6 items)	X	X	X	X
Inconvenience	5		X (4 items)			X	X
Concerns about the Recipient	5			X	X	X	X
TOTAL N ITEMS	105	87	35	87	28	92	88
ANTICIPATED TIME		20 min	10 min	20 min	5 min	25 min	20 min

8.5. Description of Study Process

8.5.1. Contact Information

Refer to Donor Center Companion Manual.

8.5.2. Informed Consent

A copy of the signed informed consent will be kept in a secure location to ensure confidentiality.

8.5.3. Collection of QOL Data

All interviews will be administered by telephone by a trained interviewer. If donors wish, they can receive a mailed copy of the interviewer's questionnaire to review before the telephone interview. Medical information will be obtained by the donor center following standard NMDP procedures and forms.

8.5.4. Withdrawal of Consent for QOL Data Collection

If a donor wishes to discontinue participation, every attempt will be made to ascertain the reason for discontinuation. In general, the project coordinator or the study Principal Investigator will briefly review the procedures to make certain that the cause of withdrawal is not misunderstanding of study procedures.

8.5.5. Letter of Appreciation and Summary of Results

At the close of the study, thank you letters will be sent to each participant. A summary of study results will be made available upon request.

8.6. Statistical Considerations

8.6.1. Sample Size

As donor quality of life is a secondary endpoint for this randomized trial, the sample size is predetermined by the primary endpoint of patient survival. A total sample size of 550 will provide more than adequate power to examine group-level differences between PSBC and marrow donors.

8.6.2. Group Comparisons

All demographic variables will be summarized and the PBSC and marrow groups will be compared with chi-squared tests as appropriate. All outcome variables will be compared between the two groups at each time point using t-tests for continuous outcomes, nonparametric Wilcoxon tests for ordinal outcomes, chi-square tests for nominal categorical variables, and chi-square trend tests for ordinal categorical variables, as appropriate. A significance level of 0.01 will be used as protection against multiplicity due to a large number of outcome variables and time points examined. In addition, because physical recovery and psychological functioning are assessed both at baseline and subsequent times, adjustment for baseline measurements will be considered. Symptom reporting (three categories) will be compared between the two groups at each time point using chi-squared tests, and may be adjusted for baseline symptom levels by treating them as strata variables. Pain and psychological functioning will be compared between the two groups using mixed models for repeated measures data. Clinical data will be compared between the two groups using nonparametric Wilcoxon tests or chi-squared tests as appropriate.

8.6.3. Missing Data

Missing data will initially be assumed to be missing at random, requiring no adjustment to the mixed models analysis across time. If this is the case, separate tests performed at each time point will be done with the complete data at that time. However, missing cases will be examined to determine whether data are missing systematically by key sociodemographic indicators.

8.7. Risks and Discomforts

QOL data collection involves non-invasive survey procedures that pose no risk to the participants. It is possible, although highly improbable, that completion of the survey items could elicit distress. However, participants are instructed not to answer any questions that make them uncomfortable. Donors also are informed that they may withdraw from study participation at any time without penalty. Should high levels of distress be detected during donor contacts, the interviewer will attempt to determine the nature and intensity of the distress, and will ask the donor if they wish to receive a follow up call from their local donor coordinator, Principal Investigator of the RCT, or from a member of the Donor Services Staff at the NMDP. If the donor says yes, the interviewer will contact the appropriate individual within 12 hours. That individual, in turn, will make every attempt to contact the donor by telephone within 24 hours.

8.8. Potential Benefits

There are no direct benefits to participating in this study. However, participants may experience positive feelings associated with sharing their experiences and/or contributing to research that may help others in the future.

8.9. Monitoring and Quality Assurance

The QOL data is confidential and will be kept in secure areas accessible only to study personnel. The study will be approved by the IRBs of all participating centers. Standard operating procedures to respond to any adverse event are delineated above.

APPENDIX A

RATIONALE FOR THE STUDY DESIGN

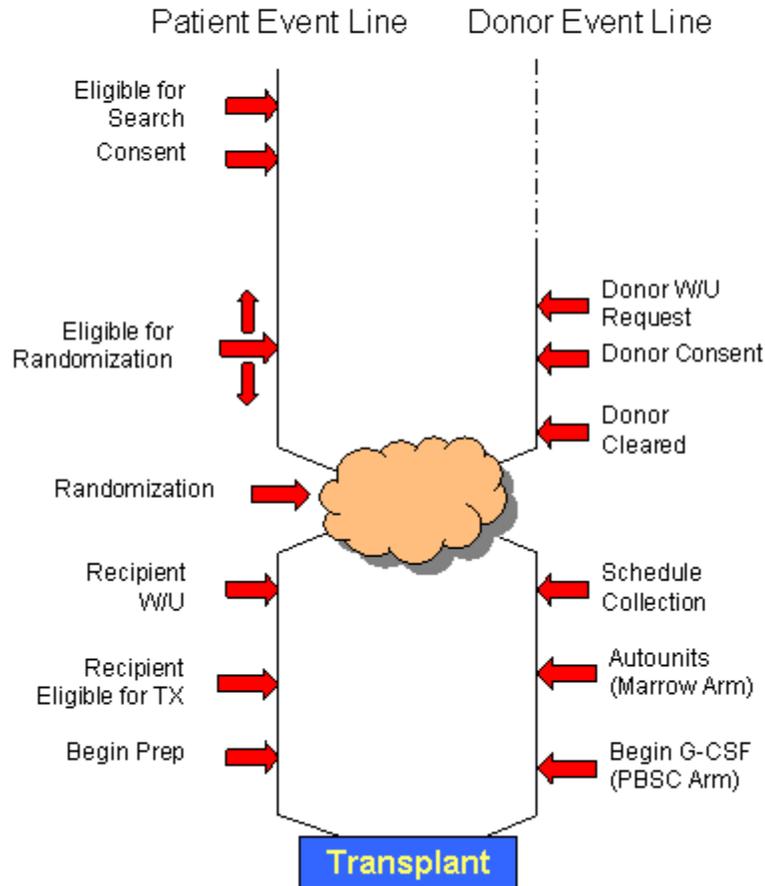
APPENDIX A – RATIONALE FOR THE STUDY DESIGN

In creating this study, the protocol team held extensive discussions about the proper approach to donor and recipient enrollment. The study is complicated because two research subjects, the hematopoietic stem cell (HSC) donor and the HSC recipient, must be managed contemporaneously. Between these two, the recipients are inherently more unstable and more likely to shift in their eligibility status over short periods of time.

The selected management schema is depicted in Figure 1. Here the recipient eligibility is divided into two components, eligibility for randomization and eligibility for transplantation. The donor will be selected, enrolled and cleared for donation prior to randomization. The recipient should be confirmed eligible for randomization prior to donor work-up (using the somewhat abbreviated criteria described in Section 2.3, with information that can be obtained by phone or mail for patients remote from the transplant center), but must be confirmed eligible on full evaluation at the transplant center after randomization but before conditioning therapy is initiated.

Once the pair is randomized, the recipient will undergo work-up to determine final eligibility for transplantation. Simultaneously, the donor will be prepared for the assigned donation, bone marrow or mobilized peripheral blood. The donor's preparation will require 2 – 3 weeks, during which time the recipient will be confirmed eligible for transplantation (Figure 1).

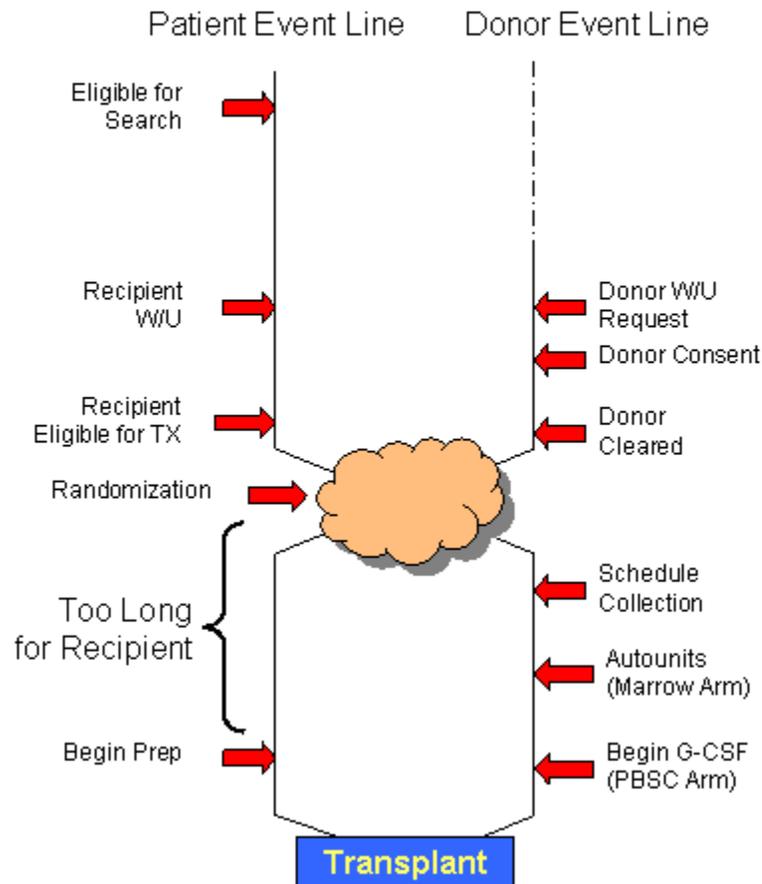
Fig. 1, Event Flow for Blood Versus Marrow, Selected Schema



The major disadvantage of this approach is that a certain proportion of recipients will be found ineligible for transplant after randomization. Based upon NMDP data, this is expected to be 15% or less, and has led to appropriate adjustment in the sample size (see Section 5.3). The intent to treat analysis is discussed in the protocol.

Several alternative approaches were considered. The first of these involved performing work-up of both the donor and recipient prior to randomization (Figure 2).

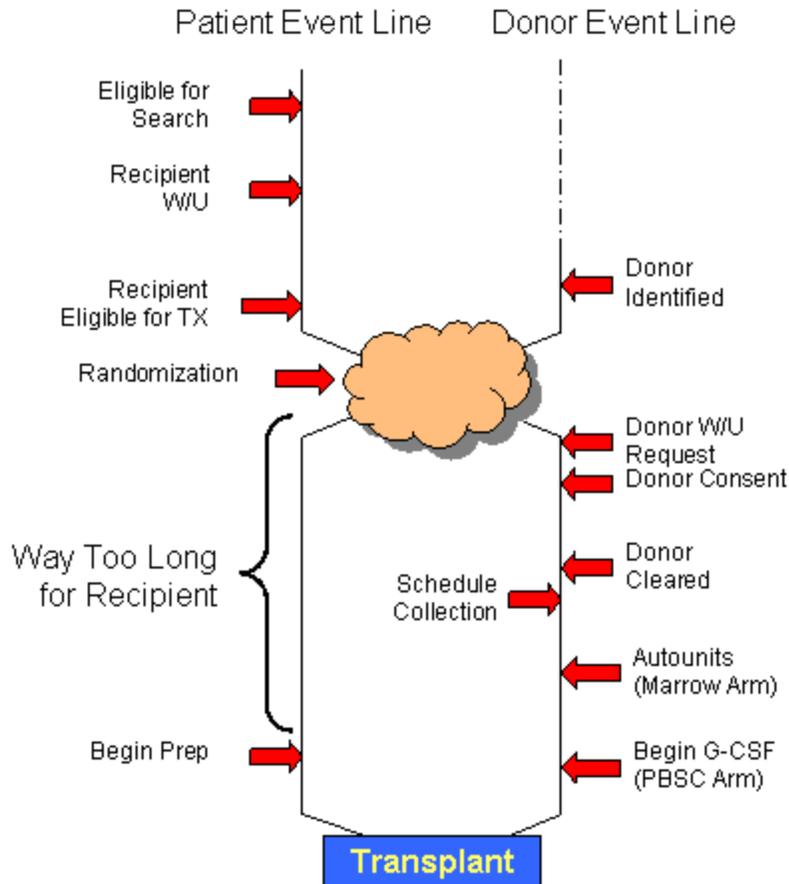
Fig 2. Event Flow for Blood Versus Marrow, Discarded Schema I



This schema has the advantage of ensuring that the recipient is fully eligible for the study and transplantation prior to randomization. The problem here is that following randomization the donor must still be prepared for donation. During this 2 - 3 week preparation, the recipient will have ample time to change in status. Complete or partial rework-ups would be needed for some recipients. Also a consideration, long-distance recipients, i.e., those living far from the transplant center, would need to travel back and forth or stay in the transplant center city for several weeks before transplant.

A modified version of schema II was also considered at the request of some donor center medical directors (Figure 3). It was reasoned that donor enrollment would be greatly simplified if the randomization assignment was known at the time of donor work-up request.

Fig 3. Event Flow for Blood Versus Marrow, Discarded Schema 1a

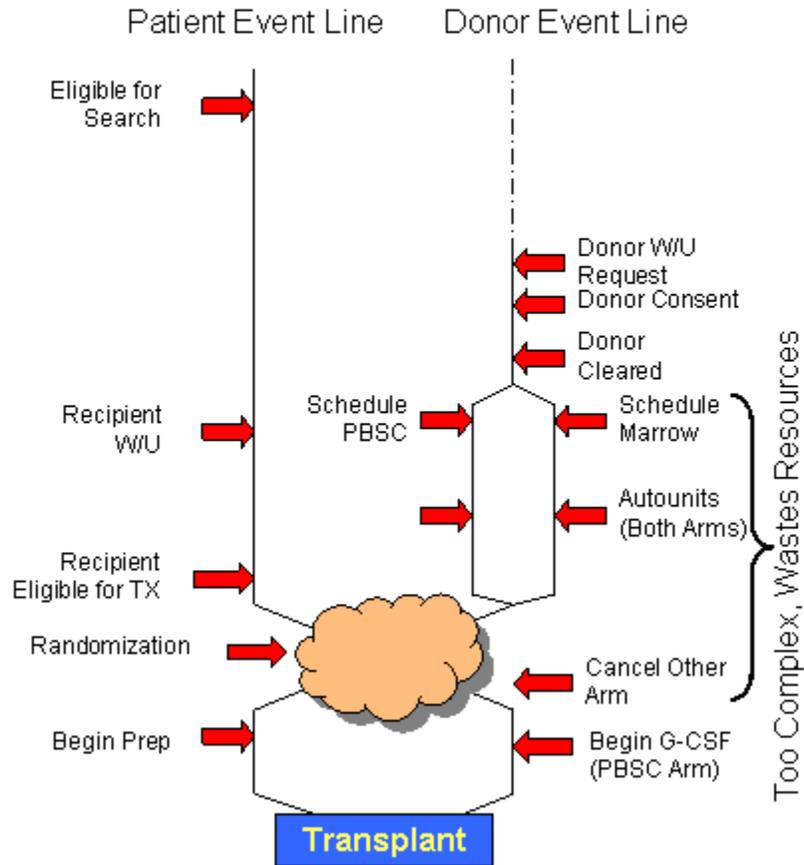


Thus, the recipient would be randomized to a treatment arm and the donor invited to participate in the study by agreeing to provide the assigned product. This model was discarded because it further aggravated the time delay for recipients between randomization and transplantation. In addition, there were concerns because it could be argued (strongly) that donors were being randomized prior to their enrollment.

The ideal randomization schema would place randomization as close as possible to the start of therapy. This model is shown in Figure 4. This model, unfortunately, would require that donors be prepared for both PBSC and marrow donation during the days prior to randomization. Thus it would be necessary to schedule collection time in both the operating room and apheresis center. In all likelihood, donors eventually randomized to PBSC would still need to provide autologous blood before the randomization. This model was rejected because it is too complex, it ties up

resources that do not belong to the donor centers (operating room and apheresis time) and it would be prohibitively costly (Figure 4).

Fig. 4 Event Flow for Blood Versus Marrow, Discarded Schema II



APPENDIX B-1

RECIPIENT CONSENT FORM and ATTACHMENTS

Informed Consent to Participate in Research



1. Title of Research Study

A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors

2. Principal Investigator Contact Information at Your Institution

Name/Title/Phone number/

3. Contact information for Emergencies after Hours or on Weekends or Holidays

Name/Phone number/

4. Sponsors and Source of Funding or Other Material Support

The research in this study is paid for by the National Institutes of Health (NIH) and the National Marrow Donor Program[®] (NMDP). The NMDP and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) will direct the research study. This study will be done at many different medical centers, including [Center Name/Location].

5. Introduction

This is a consent form for a research study. You are being invited to participate in this study because you have a disease that may be treated with a transplant of either bone marrow or peripheral blood stem cells (PBSC). This form is intended to give you information to help you decide if you want to participate in this study. You should read this form and ask any questions you may have before agreeing to be in the study.

Doctors have been successfully treating blood disorders such as leukemia and myelodysplasia with a transplant of blood stem cells from either the bone marrow or the peripheral blood. The goal of this study is to see if patients receiving a transplant from an unrelated donor have better results using blood stem cells from: 1) bone marrow or 2) peripheral blood. The study may find that patients have similar results with either type of transplant.

Important results of this study will include:

- Survival
- Quality of life
- Blood counts after transplant
- Number and severity of infections
- Graft-versus-host disease (GVHD)
- Relapse of disease (return of disease)

Other information about the study:

- You will not be paid to be in this study.
- You or your insurance company will pay the bills for your medical treatment.
- You will not be charged for research tests.
- You will face the same risks and benefits as any other bone marrow or peripheral blood stem cell (PBSC) transplant patient.

It is your choice whether or not to participate in this study. You and the medical staff at your transplant center will discuss other treatment options before you make your decision about participating in this study.

6. Purpose of the Study

This study will look at two kinds of blood stem cell transplants, bone marrow and peripheral blood stem cell (PBSC), and their side effects. At this time, doctors use both types of blood stem cells for transplant. Previous studies have compared the survival of patients who received an unrelated donor transplant from bone marrow with patients who received an unrelated donor transplant from PBSCs. In these studies there was no difference in survival between the bone marrow transplant patients and PBSC transplant patients. This may have been because the patients in each group did not have the same characteristics (for example, different diseases, different ages).

In this study, the patient and donor will be randomly assigned (much like the toss of a coin) to either the bone marrow or the PBSC transplant study group. By randomly assigning the patients to receive either a bone marrow or PBSC transplant, the characteristics of each study group should be similar. The primary goal is to see which type of blood stem cell transplant (bone marrow or PBSC) has better survival results. With similar patient characteristics in each study group, researchers should be able to find out if one type of blood stem cell transplant (bone marrow or PBSC) has better survival results for patients, or if both types of blood stem cell transplants have similar survival results.

An important part of this study will look at how well you feel after your transplant. Researchers want to know the effects from each type of stem cell used for the transplant and how long they last.

Good effects might include:

- Quick recovery of blood counts after transplant
- No relapse of disease
- High cure rates
- Few infections
- Able to return to important activities in life

Bad effects might include:

- Slow recovery or no recovery of blood counts after transplant
- Relapse of disease
- Severe graft-versus-host disease (GVHD)
- Serious infections
- Not able to return to important activities in life

The information collected from this study will help doctors and future patients make better treatment choices. About 550 patients will take part in this study at many centers around the country.

7. Study Procedures

If you agree to participate in the study, the transplant process has many steps. A matched donor must be found. Both you and the donor will need to give permission to participate in this study. A donor could refuse to participate in this study, but continue to be available for your transplant. In that case, you may decide to have a transplant using this donor, but not participate in this study or another donor may be found who does want to participate in this study.

Since this study looks at the results of two different kinds of transplants, bone marrow and peripheral blood stem cell (PBSC), the kind of transplant you will receive will be decided randomly, like a coin toss. Neither you nor your doctor chooses the type of transplant; the type of transplant you will receive is determined by a computer program. Half of the patients in the study will have a bone marrow transplant. The other half will receive a PBSC transplant. Participation in the study means that you are willing to accept either type of transplant.

One part of the study will involve collecting your medical information. Your medical information will be collected for three years. The study coordinators at your center will collect information from your medical record chart every week for 100 days, then at 6 months, 1 year, 2 years, and 3 years.

Another part of the study will ask questions about your physical and emotional health. This information will be collected for five years. A trained interviewer will contact you by telephone before your transplant, then 6 months, 1 year, 2 years and 5 years after your transplant. These interviews will last approximately 15-25 minutes and will be done at a convenient time for you. They will include questions about side effects, health problems and how well you can do things that are important to you. When you are contacted, you may skip any questions you don't want to answer.

As part of the standard transplant procedure, you will need to take many medications and have other medical treatments. The medical staff will explain these during discussion of your medical care.

8. Possible Discomforts and Risks

You will face risks from the transplant itself, and from treatments given before and after the transplant. Your doctor thinks these risks are less than the risk from the disease for which you are receiving a transplant.

The bone marrow and PBSCs from the donor contain blood stem cells, which allow your blood counts (red blood cells, white blood cells, and platelets) to recover. Blood stem cells make all the blood cells in the bone marrow and serve the entire body. It is possible that even after the transplant your bone marrow will not work well enough, and you will be at an increased risk of infections and even death. Infections after transplant can be from bacteria, viruses, parasites, or fungi. Early after transplant, the risk of getting an infection might be less after a PBSC transplant, because the blood counts return faster than with bone marrow. Later, the risk of infections might be increased in PBSC transplants, because graft-versus-host disease (GVHD) might be worse and last longer. Blood counts will be done often to track recovery of the bone marrow. You will get platelets and red cells as needed to keep your counts at a healthy level.

There is a risk that stem cells may not grow after being given to you. This is called graft failure. Graft failure can be fatal unless you have a second transplant. Failure of the donor cells to grow (graft failure) may result from a mismatch with the donor, infection, a reduced effect of pre-transplant drugs on your body, or not enough cells in the product. This risk may be less with PBSCs, since PBSCs contain more blood stem cells than bone marrow.

Graft-versus-host disease (GVHD) is a frequent problem after unrelated donor transplantation. After the cells in the product begin to grow, there is a risk that the donor cells may react against your body. GVHD may show up as a skin rash, or liver or stomach problems. GVHD may cause nausea (feeling sick to your stomach), vomiting (throwing up), lack of appetite, stomach cramps, diarrhea (loose stools), and bleeding of the gut. Chronic GVHD may occur later after transplantation and may involve problems with the eyes, mouth, lips, throat and liver. Early (acute) or late (chronic) GVHD may be bad enough to cause death. GVHD is treated with drugs that weaken the body's defense

system, and thus make you more likely to get an infection. The chance of getting GVHD may be increased with PBSCs, since PBSC transplants contain more donor cells.

Relapse of your disease might occur after transplant, especially in patients with advanced disease. This risk may be decreased by PBSC transplantation.

If one type of transplant does have better results, and you are not randomly assigned to that study group, you may not receive the same benefits as those in the study group with overall better results.

Completion of the quality of life interviews will not cause you any physical discomfort, although it is possible that you will find some of the questions or topics upsetting. If you do, there will be someone available to speak with you. They will be able to refer you to appropriate counselors or other support people.

Refer to Appendix A, B, C or D for additional risks and toxicities related to the specific transplant conditioning regimen you will receive, the drugs you will receive to help prevent graft-versus-host disease (GVHD) and risks and toxicities related to the transplant procedure itself.

9. Unknown or Unexpected Side Effects

As with any treatment, there may be unknown and/or unexpected side effects from a bone marrow or PBSC transplant. We may learn new things about bone marrow or PBSC 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.

10. Alternative Treatments Available if You Don't Want to be in the 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:

- No treatment
- Chemotherapy
- A transplant using your own bone marrow or PBSCs
- A transplant of bone marrow or PBSCs from a relative
- A transplant of cord blood cells
- A bone marrow or PBSC transplant from an unrelated donor without participation in this study

11. Possible Benefits to Participating in the Study

This research study is comparing the treatment results of bone marrow and PBSC transplants. At this time doctors do not know if one type of transplant has better results than the other, or if they both have the same results. If one type of transplant does have better results, and you are randomly assigned to that study group, you may benefit from participating in the study. The knowledge gained from this study may help future patients who need a blood stem cell transplant, but there is no expectation that you will benefit from participating in the study.

As a result of the bone marrow or PBSC transplant your disease may be put in remission or continue in remission.

12. Cost of Participating in the Study

You and/or your insurance company will pay all medical expenses relating to, or arising from transplantation of either bone marrow or PBSC. Research tests described in Section 20 will be paid by the NIH and the NMDP.

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/.

13. Reimbursement for Participating in the Study

You will not be paid for participating in this study.

14. In the Event of Injury While Participating in the Study

If you are injured or become ill while taking part in this study, medical care will be provided at this center. No funds have been set aside to pay you if you are injured. You or your insurance company will be charged for ongoing medical care and/or hospitalization.

Contact your doctor or one of the people listed at the start of this form if you are concerned about a research-related injury.

15. Withdrawing from the Study

You may decide to withdraw at any time, for any reason, without notice from this study that compares bone marrow transplant with PBSC transplant. If you wish, you may withdraw from the study but still receive a blood stem cell 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 [the Principal Investigator] in writing (his/her address is on the front page of this form). 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.

If you withdraw from the study, 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) office at /number/.

16. Reasons Your Doctor May Take You off the Study

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

- You would be harmed by staying in the study.
- You need treatment not allowed in this study.
- You do not follow directions that are important to participating in the study.
- The study is cancelled.

17. Protection of your Privacy and Confidentiality of Your Research Records

Your participation in this research study will be kept private and confidential. All your medical, demographic (such as race and ethnicity, gender and household income) and quality of life 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 for inspections or audits. In agreeing to participate, you consent to such inspections and to the copying of excerpts from these records, if required by these authorized representatives.

Organizations with access to your research and medical information:

- /Institution/
- The National Institutes of Health (NIH)
- 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/
- The National Marrow Donor Program (NMDP)
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Quality of Life staff at Center on Outcomes, Research, and Education at Evanston Northwestern Healthcare
- Laboratory staff at Dr. Edmund Waller’s laboratory at Emory University, Esoterix, Inc., Dr. Jeffrey Miller’s laboratory at the University of Minnesota

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

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

18. Expiration Date for Keeping Your 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/.

19. Benefit to Doctors for Your Participation in this Study

Your doctors have no money invested in 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. In addition, the hospital where you will receive your transplant is paid for participating in the study.

20. Blood Samples for Research Purposes

You will be asked to provide blood samples to see if infection-fighting cells are working and to help better understand tissue matching between donors and recipients in this study. You do not have to participate in this part of the study.

If you agree, you will provide blood samples up to 7 times (10-100 mL each time or approximately 1-7 tablespoons) between the time transplant is initiated and two years after (up to a total for all 7 blood draws of 430 mL or approximately 2 cups). The samples will be saved for future testing. The blood

can usually be drawn from your central line at the time of other blood collections. If this is not possible, then it will be drawn directly from a vein.

As a standard part of the transplant procedure you will receive vaccinations for diphtheria, tetanus, Hepatitis B and pneumococcus. The research studies on infection-fighting cells will include studies to look at how well these vaccinations are working. You may still receive the vaccinations as part of your standard medical care even if you decide not to participate in the research on infection-fighting cells.

The doctors conducting this study may choose to do some additional research tests on the blood samples. These tests would only be done if the groups overseeing the safety and protection of subjects participating in this study approved these additional tests. These tests would only be performed on blood samples that were left-over after the tests on infection-fighting cells, vaccinations, and tissue matching were done; no additional blood would be drawn for these tests. This research may include tests to determine and evaluate other factors that affect transplant outcome in this study.

Any of your blood samples drawn for research purposes will be sent to laboratories that have a contract with the NMDP to conduct these research tests. Your blood will be labeled with a unique code that contains no information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratory where your blood is being tested does not have a link to this code. Your blood will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study.

If any of your blood samples are left over after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung and Blood Institute (NHLBI) sample repository in Maryland. If your left-over blood samples are sent to the repository, they will be given an anonymous code. These left-over blood samples stored at the repository can never be linked to you. Any research performed on these left-over blood samples must first be approved by an advisory panel at the NHLBI.

You are free to not take part in this research and still participate in the other parts of the study. There will be no change in your care if you choose not to give blood samples for research purposes. Please mark your choice below (check only one box):

- I agree to have blood drawn for research purposes.
- I do not agree to have blood drawn for research purposes.

Signature

Date

21. Subject’s Consent

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

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.

Attachment A

Additional Risks and Toxicities Related to the Standard Transplant Procedure Total Body Irradiation and Cyclophosphamide Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications and irradiation therapy you will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your doctor may give you medications to lessen some of the side-effects.

Risks Related to the Transplant Conditioning Regimen

Cyclophosphamide (Cytoxan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder. A few patients may have bladder damage and bleeding for a longer time. You will be given large amounts of a sterile solution through your central line to protect your bladder. A bladder catheter (thin plastic tube) may be inserted into your bladder, if your physician thinks that it can help you. Cyclophosphamide slows the making of new red blood cells, white blood cells, and platelets. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. Cyclophosphamide also lowers your defense system. As a result, you may have more infections for several months after transplant. In a small number of patients, cyclophosphamide can damage the heart muscle causing heart failure. Sometimes cyclophosphamide causes abnormal heart function. If this occurs you may have shortness of breath and have fluids build-up in your body. This medication can also cause the lungs to become scarred. If scarring of the lungs occurs it will usually happen three to six months after you receive the medication. Scarring of the lungs can cause you to die. Cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced but you would still be able to have intercourse. Women who are still menstruating may have irregular periods or may no longer have any periods. Whether you are a man or woman, this medication will likely greatly decrease your chances of being able to have a child. It is not known whether the use of cyclophosphamide will cause more side effects or problems with your health in the future.

Total Body Irradiation (TBI): TBI may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), and painful swelling of the saliva gland for a few days. You may also experience short-term hair loss. TBI kills both sick and normal marrow, leading to a lack of red blood cells, white blood cells, and platelets. The short-term loss of these blood cells could cause you to become anemic, develop an infection, and/or bleeding. This will continue until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. There is a risk that cataracts (cloudiness) may develop in your eyes. This may mean partial loss of vision, and you may need contact lenses or surgery to remove the cataracts. The TBI dose used will probably result in sterility (not being able to have children.) It is not known whether the use of TBI will cause more side effects or problems with your health in the future.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cell (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-versus-host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects you may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects, they generally go away when the dose of the medication is decreased. A few patients have had a seizure while on these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate and Steroids: These medications interfere with the body's defense system (the immune system). This may cause you to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but

more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy, irradiation therapy, or both. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines and irradiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores you will be given medicine to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and irradiation therapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy and radiation cause severe lung damage that cannot always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. As a result of irradiation, cataracts may occur earlier in life compared to a person who had not had a transplant. If you develop cataracts (cloudiness in the eyes) they may require treatment. It is rare, but your kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk you may develop a second cancer as a result of the chemotherapy, irradiation and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment B

Additional Risks and Toxicities Related to the Standard Transplant Procedure Busulfan and Cyclophosphamide Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications you will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your doctor may give you medications to lessen some of the side-effects.

Risks Related to the Transplant Conditioning Regimen

Cyclophosphamide (Cytoxan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause you to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder. A few patients may have bladder damage and bleeding for a longer time. You will be given large amounts of a sterile solution through your central line to protect your bladder. A bladder catheter (thin plastic tube) may be inserted into your bladder, if your physician thinks that it can help you. Cyclophosphamide slows the making of new red blood cells, white blood cells, and platelets. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in you. You will get blood transfusions as needed. Cyclophosphamide also lowers your defense system. As a result you may have more infections for several months after transplant. In a small number of patients, cyclophosphamide can damage the heart muscle causing heart failure. Sometimes cyclophosphamide causes abnormal heart function. If this occurs you may have shortness of breath and have fluids build-up in your body. This medication can also cause the lungs to become scarred. If scarring of the lungs occurs it will usually happen three to six months after you receive the medication. Scarring of the lungs can cause you to die. Cyclophosphamide can damage the male (testes) or female (ovaries) sex glands. In men, the number of sperm may be reduced but you would still be able to have intercourse. Women who are still menstruating may have irregular periods or may no longer have any periods. Whether you are a man or woman, this medication will likely greatly decrease your chances of being able to have a child. It is not known whether the use of cyclophosphamide will cause more side effects or problems with your health in the future.

Busulfan: This medication disrupts the growth of cancer cells and destroys them. While taking busulfan you most likely will have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), lower white blood cell count that increases your risk of infection, lower platelet count that increases your risk of bleeding, hair loss, stopping of menstrual periods in women, temporary reduced or no sperm production in men. Less likely side effects that you may experience are fatigue, sores in the mouth or on the lips, fever, rash, loss of appetite, changes in color of the skin, seizure. Rare side effects that you may experience are damage to your lungs, which may cause you to cough, be short of breath and have trouble breathing. It is rare, but busulfan can also cause changes in your liver function.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cell (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause

an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects you may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate and Steroids: These medications interfere with the body's defense system (the immune system). This may cause you to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores you will be given medicine to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy. The blood vessels may become ‘leaky’ and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that can not always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. It is rare, but your kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk you may develop a second cancer as a result of the chemotherapy and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment C

Additional Risks and Toxicities Related to the Standard Transplant Procedure Fludarabine and Melphalan Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications you will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your doctor may give you medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Fludarabine: This is a medication used to treat cancer. It is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells. Likely side effects you may experience are low white blood cell count with increased risk of infection, low platelet count with increased risk of bleeding, feeling tired or sleepy, and anemia (low red blood cell count). Rare side effects you may experience include confusion or coma, trouble seeing or problems with your eyes, trouble breathing, diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), pneumonia, agitation, numbness and tingling of the fingertips and toes, and kidney problems.

Melphalan: This medication disrupts the growth of cancer cells and destroys them. Side effects you most likely will experience include nausea (feeling sick to your stomach), hair loss, and low white blood cell count, which may lead to infection. Less likely side effects you may experience include diarrhea (loose stools), mouth ulcers, and low platelet count with increased risk of bleeding. It is rare, but you may experience a severe allergic reaction. Symptoms of a severe allergic reaction include itching, hives (bumps on your skin), flushing (redness), wheezing, chest tightness, skin rashes, fever, chills, muscle stiffening, severe breathing problems, and loss of appetite.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cell (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects you may experience may include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects they generally go away when the dose of the medication decreased. A few patients have had a seizure while taking these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly withheld. The effect on kidneys seems to increase when other medications that might cause kidney problems are given at the same time, especially antibiotics.

Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by-mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause you to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and as a result bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets, and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It may often be managed successfully, and completely resolve. However, complications can arise that can be fatal.

Mouth Sores and Diarrhea: The large doses of medicines cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores you will be given medicine to help control the pain. If your mouth sores are severe you may not be able to eat normally until they are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage

if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of this the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that can not always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. It is rare, but your kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk you may develop a second cancer as a result of the chemotherapy and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating all of this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment D

Additional Risks and Toxicities Related to the Standard Transplant Procedure Fludarabine and Busulfan Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications you will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your doctor may give you medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Fludarabine: This is a medication used to treat cancer. It is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells. Likely side effects you may experience are low white blood cell count with increased risk of infection, low platelet count with increased risk of bleeding, feeling tired or sleepy, and anemia (low red blood cell count). Rare side effects you may experience include confusion or coma, trouble seeing or problems with your eyes, trouble breathing, diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), pneumonia, agitation, numbness and tingling of the fingertips and toes, and kidney problems.

Busulfan: This medication disrupts the growth of cancer cells and destroys them. While taking busulfan you most likely will have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), lower white blood cell count that increases your risk of infection, lower platelet count that increases your risk of bleeding, hair loss, stopping of menstrual periods in women, temporary reduced or no sperm production in men. Less likely side effects that you may experience are fatigue, sores in the mouth or on the lips, fever, rash, loss of appetite, changes in color of the skin, seizure. Rare side effects that you may experience are damage to your lungs, which may cause you to cough, be short of breath and have trouble breathing. It is rare, but busulfan can also cause changes in your liver function.

Antithymocyte Globulin (ATG): This medication is given pre-transplant with the conditioning regimen medications to try and prevent both acute and chronic graft-versus-host disease. While taking ATG you most likely will have, a fever and chills, a lower white blood cell count that increases your risk of infection, a lower platelet count that increases your risk of bleeding, and a skin rash. Less likely side effects you may experience are fatigue, diarrhea, vomiting, muscle aches and headaches. Rare side effects that you may experience are changes in your blood pressures (either higher or lower blood pressure), rapid heart beat, be short of breath and have trouble breathing, chest pain and retention of fluids.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft versus Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects you may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects you may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If you experience these effects, they generally go away when the dose of the medication is decreased. A few patients have had a seizure while on these medications. You may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which you may have already developed from the procedures and medications used to prepare you for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate and Steroids: These medications interfere with the body's defense system (the immune system). This may cause you to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help your blood to clot. Your platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy, irradiation therapy, or both. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body.

It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines and irradiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If you have severe mouth sores you will be given medicine to help control the pain. If your mouth sores are severe you may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and irradiation therapy. The blood vessels may become ‘leaky’ and fluid enters the abdominal cavity, lungs, and other tissues. You may gain water weight and not go to the bathroom as often as you normally do. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. You may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible you may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy and radiation cause severe lung damage that cannot always be treated. If this happens, you may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: You may experience side effects that occur several months to many years after your transplant. You may experience poor function of the thyroid gland, requiring you to take thyroid medication. It is rare, but your kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk you may develop a second cancer as a result of the chemotherapy, irradiation and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: You will receive intravenous fluids during the transplant process and you may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Legal Guardian Informed Consent to Participate in Research



1. Title of Research Study

A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors

2. Principal Investigator Contact Information at Your Child’s Institution

Name/Title/Phone number/

3. Contact Information for Emergencies after Hours or on Weekends or Holidays:

Name/Phone number/

4. Sponsors and Source of Funding or Other Material Support

The research in this study is paid for by the National Institutes of Health (NIH) and the National Marrow Donor Program[®] (NMDP). The NMDP and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) will direct the research study. This study will be done at many different medical centers, including [Center Name/Location].

5. Introduction

This is a consent form for a research study. Your child is being invited to participate in this study because he/she has a disease that may be treated with a transplant of either bone marrow or peripheral blood stem cells (PBSC). This form is intended to give you information to help you decide if you want your child to participate in this study. You should read this form and ask any questions you may have before allowing your child to participate in the study.

Doctors have been successfully treating blood disorders such as leukemia and myelodysplasia with a transplant of blood stem cells from either the bone marrow or the peripheral blood. The goal of this study is to see if patients receiving a transplant from an unrelated donor have better results using blood stem cells from: 1) bone marrow or 2) peripheral blood. The study may find that patients have similar results with either type of transplant.

Important results of this study will include:

- Survival
- Quality of life
- Blood counts after transplant
- Number and severity of infections
- Graft-versus-host disease (GVHD)
- Relapse of disease (return of disease)

Other information about the study:

- Your child will not be paid to be in this study.
- You or your child's insurance company will pay the bills for your child's medical treatment.
- You will not be charged for research tests.
- Your child will face the same risks and benefits as any other bone marrow or peripheral blood stem cell (PBSC) transplant patient.

You and your child have a choice whether or not to participate in this study. The medical staff at your child's transplant center will discuss other treatment options before you make a decision about allowing your child to participate in this study.

6. Purpose of the Study

This study will look at two kinds of blood stem cell transplants, bone marrow and peripheral blood stem cell (PBSC), and their side effects. At this time, doctors use both types of blood stem cells for transplant. Previous studies have compared the survival of patients who received an unrelated donor transplant from bone marrow with patients who received an unrelated donor transplant from PBSCs. In these studies there was no difference in survival between the bone marrow transplant patients and PBSC transplant patients. This may have been because the patients in each group did not have the same characteristics (for example, different diseases and different ages).

In this study, the patient and donor will be randomly assigned (much like the toss of a coin) to either the bone marrow or the PBSC transplant study group. By randomly assigning the patients to receive either a bone marrow or PBSC transplant, the characteristics of each study group should be similar. The primary goal is to see which type of blood stem cell transplant (bone marrow or PBSC) has better survival results. With similar patient characteristics in each study group, researchers should be able to find out if one type of blood stem cell transplant (bone marrow or PBSC) has better survival results for patients, or if both types of blood stem cell transplants have similar survival results.

An important part of this study will look at how patients recover after transplant. Researchers want to know what the effects are from each type of blood stem cells used for the transplant and how long they last.

Good effects might include:

- Quick recovery of blood counts after transplant
- No relapse of disease
- High cure rates
- Few infections
- Able to return to important activities in life

Bad effects might include:

- Slow recovery or no recovery of blood counts after transplant
- Relapse of disease
- Severe graft-versus-host disease (GVHD)
- Serious infections
- Not able to return to important activities in life

The information collected from this study will help doctors and future patients make better treatment choices. About 550 patients will take part in this study at many centers around the country.

7. Study Procedures

If you allow your child to participate in this study, the transplant process has many steps. A matched donor must be found. You will need to give permission for your child to participate in the study and the donor will also need to give permission to participate in this study. A donor could refuse to participate in this study, but continue to be available for your child's transplant. In that case, you may

decide that your child will have a transplant using this donor, but not participate in this study, or another donor who does want to participate in this study may be found.

Since this study looks at the results of two different kinds of transplants, bone marrow and peripheral blood stem cell (PBSC), the kind of transplant your child will receive will be decided randomly, like a coin toss. Neither you, nor your child's doctor, choose the type of transplant; the type of transplant your child will receive is determined by a computer program. Half of the patients in the study will have a bone marrow transplant. The other half will receive a PBSC transplant. Participation in the study means that you are willing to accept either type of transplant for your child.

One part of the study will involve collecting your child's medical information. Your child's medical information will be collected for three years. The study coordinators at your child's center will collect information from your child's medical record chart every week for 100 days, then at 6 months, 1 year, 2 years and 3 years.

If your child is 16 or 17 years old, another part of the study will ask questions about his/her physical and emotional health. This information will be collected for five years. A trained interviewer will contact your child by telephone before his/her transplant, then 6 months, 1 year, 2 years and 5 years after the transplant. These interviews will last approximately 15-25 minutes and will be done at a convenient time for your child. They will include questions about side effects, health problems and how well your child can do things that are important to him/her. When your child is contacted, your child may skip any questions he/she doesn't want to answer.

As part of the standard transplant procedure, your child will need to take many medications and have other medical treatments as part of the transplant. The medical staff will explain these during discussion of your child's medical care.

8. Possible Discomforts and Risks

Your child will face risks from the transplant itself and from treatments given before and after the transplant. Your child's doctor thinks these risks are less than the risk from the disease for which your child is receiving a transplant.

The bone marrow and PBSCs from the donor contain blood stem cells, which allow your child's blood counts (red blood cells, white blood cells, and platelets) to recover. Blood stem cells make all the blood cells in the bone marrow and serve the entire body. It is possible that even after the transplant your child's bone marrow will not work well enough and he/she will be at an increased risk of infections and even death. Infections after transplant can be from bacteria, viruses, parasites, or fungi. Early after transplant, the risk of getting an infection might be less after a PBSC transplant, because the blood counts return faster than with bone marrow. Later, the risk of infections might be increased in PBSC transplants, because graft-versus-host disease (GVHD) might be worse and last longer. Blood counts will be done often to track recovery of the bone marrow. Your child will get platelets and red cells as needed to keep his/her counts at a healthy level.

There is a risk that stem cells may not grow after being given to your child. This is called graft failure. Graft failure can be fatal unless your child has a second transplant. Failure of the donor cells to grow (graft failure) may result from a mismatch with the donor, infections, a reduced effect of pre-transplant medications on your child's body, or not enough cells in the product. This risk may be less with PBSCs, since PBSCs contain more blood stem cells than bone marrow.

Graft-versus-host disease (GVHD) is a frequent problem after unrelated donor transplantation. After the cells in the product begin to grow, there is a risk that the donor cells may react against your

child's body. GVHD may show up as a skin rash, or liver or stomach problems. GVHD may cause nausea (feeling sick to your stomach), vomiting (throwing up), lack of appetite, stomach cramps, diarrhea (loose stools), and bleeding of the gut. Chronic GVHD may occur later after transplantation and may involve problems with the eyes, mouth, lips, throat and liver. Early (acute) or late (chronic) GVHD may be bad enough to cause death. GVHD is treated with drugs that weaken the body's defense system, and thus makes your child more likely to get an infection. The chance of getting GVHD may be increased with PBSCs, since PBSC transplants contain more donor cells.

Relapse of your child's disease might occur after transplant, especially in patients with advanced disease. This risk may be decreased by PBSC transplantation.

If one type of transplant does have better results, and your child is not randomly assigned to that study group, your child may not receive the same benefits as those children in the study group with overall better results.

Completion of the quality of life interviews will not cause your child any physical discomfort, although it is possible that your child will find some of the questions or topics upsetting. If this occurs, there will be someone available to speak with your child. They will be able to refer your child to appropriate counselors or other support people.

Refer to Appendix A, B, C or D for additional risks and toxicities related to the specific transplant conditioning regimen your child will receive and the specific drugs your child will receive to help prevent graft-versus-host disease (GVHD).

9. Unknown or Unexpected Side Effects

As with any treatment, there may be unknown and/or unexpected side effects from a bone marrow or PBSC transplant. We may learn new things about bone marrow or PBSC transplants that might make you or your child want to stop being in the study. We will let you know if this happens and you can decide if you want to continue to allow your child to be in the study.

10. Alternative Treatments Available if You Don't Want Your Child to be in the Study

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

- No treatment
- Chemotherapy
- A transplant using your child's own bone marrow or PBSCs
- A transplant of bone marrow or PBSCs from a relative
- A transplant of cord blood cells
- A bone marrow or PBSC transplant from an unrelated donor without participation in this study

11. Possible Benefits to Participating in the Study

This research study is comparing the treatment results of bone marrow and PBSC transplants. At this time doctors do not know if one type of transplant has better results than the other, or if they both have the same results. If one type of transplant does have better results, and your child is randomly assigned to that study group, he/she may benefit from participating in the study. The knowledge gained from this study may help future patients who need a blood stem cell transplant, but there is no expectation that your child will benefit from participating in this study.

As a result of the bone marrow or PBSC transplant your child's disease may be put in remission or continue in remission.

12. Cost of Participating in the Study

You and/or your child's insurance company will pay all medical expenses relating to, or arising from transplantation of either bone marrow or PBSC. Research tests described in Section 20 will be paid by the NIH and the NMDP.

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

13. Reimbursement for Participating in the Study

You or your child will not be paid for participating in this study.

14. In the Event of Injury While Participating in the Study

If your child is injured or becomes ill while taking part in this study, medical care will be provided at this center. No funds have been set aside to pay you or your child if injury occurs. You or your insurance company will be charged for ongoing medical care and/or hospitalization.

Contact your child's doctor or one of the people listed at the start of this form if you are concerned about a research-related injury.

15. Withdrawing from the Study

You may decide to withdraw your child at any time, for any reason, without notice, from this study that compares bone marrow transplant with PBSC transplant. If you wish, you may withdraw your child from the study but he/she may still receive a blood stem cell transplant. If you decide to withdraw your child from the study after your child has had some or all of the pre-transplant treatments and decide to have no transplant at all, then your child's blood counts may not return and he/she could die.

If you decide to withdraw your child from the study, we ask that you tell [the Principal Investigator] in writing (his/her address is on the front page of this form). If you withdraw your child, there will be no penalty or loss of benefit to which your child is entitled, and he/she will continue to receive medical care.

If you withdraw your child from the study, the medical staff will continue to tell us about your child's progress for three years after his/her transplant. If you do not want this, you must specifically tell your child's doctor.

If you have any questions about your child's rights as a study subject, you may phone the Institutional Review Board (IRB) office at /number/.

16. Reasons Your Child's Doctor May Take Your Child off the Study

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

- Your child would be harmed by staying in the study.
- Your child needs treatment not allowed in this study.
- Your child does not follow directions that are important to participating in the study.
- The study is cancelled.

17. Protection of Your Child’s Privacy and Confidentiality of Your Child’s Research Records

Your child’s participation in this research study will be kept private and confidential. All your child’s medical, demographic (such as race and ethnicity, gender and household income) and quality of life information will be kept private and confidential. (*Name of Transplant Center*) and the organizations listed below will not disclose your child’s 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 child’s research and medical information for inspections or audits. In allowing your child to participate, you consent to such inspections and to the copying of excerpts from your child’s records, if required by these authorized representatives.

Organizations with access to your child’s research and medical information:

- /Institution/
- The National Institutes of Health (NIH)
- 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/
- The National Marrow Donor Program (NMDP)
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Quality of Life staff at Center on Outcomes, Research, and Education at Evanston Northwestern Healthcare
- Laboratory staff at Dr. Edmund Waller’s laboratory at Emory University, Esoterix, Inc., and Dr. Jeffrey Miller’s laboratory at the University of Minnesota

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

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

18. Expiration Date for Keeping Your Child’s 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 child’s research records or access to your child’s files, please call /name/ at /number/.

19. Benefit to Doctors for Your Child’s Participation in the Study

Your child’s doctors have no money invested in 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. In addition, the hospital where your child will receive his/her transplant is paid for participating in the study.

20. Blood Samples for Research Purposes

You will be asked to allow your child to provide blood samples to see if infection-fighting cells are working and to help better understand tissue matching between donors and recipients in this study. You do not have to allow your child to participate in this part of the study.

If you agree, your child will provide blood samples up to 7 times (10-100 mL each time or approximately 1-7 tablespoons) between the time transplant is initiated and two years after (up to a total for all 7 blood draws of 430 mL or approximately 2 cups). The samples will be saved for future testing. The amount of blood drawn will never be more than what is safe for your child to provide. The blood can usually be drawn from your child's central line at the time of other blood collections. If this is not possible, then it will be drawn directly from a vein.

As a standard part of the transplant procedure your child will receive vaccinations for diphtheria, tetanus, Hepatitis B and pneumococcus. The research studies on infection fighting-cells will include studies to look at how well these vaccinations are working. Your child may still receive the vaccinations as part of his/her standard medical care even if your child does not participate in the research on infection-fighting cells.

The doctors conducting this study may choose to do some additional research tests on the blood samples. These tests would only be done if the groups overseeing the safety and protection of subjects participating in this study approved these additional tests. These tests would only be performed on blood samples that were left over after the tests on infection-fighting cells, vaccinations, and tissue matching were done; no additional blood would be drawn for these tests. This research may include tests to determine and evaluate other factors that affect transplant outcome in this study.

Any of your child's blood samples drawn for research purposes will be sent to laboratories that have a contract with the NMDP to conduct these research tests. Your child's blood will be labeled with a unique code that contains no information that could identify him/her. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratory where your child's blood is being tested does not have a link to this code. Your child's blood will be stored at these laboratories until all the sample has been used for the research tests or until the end of the study.

If any of your child's blood samples are left over after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung, and Blood Institute (NHLBI) sample repository in Maryland. If your child's left-over blood samples are sent to the repository, they will be given an anonymous code. These left-over blood samples stored at the repository can never be linked to your child. Any research performed on these left-over blood samples must first be approved by an advisory panel at the NHLBI.

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.

Attachment A

Additional Risks and Toxicities Related to the Standard Transplant Procedure Total Body Radiation and Cyclophosphamide Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications and irradiation therapy your child will receive as part of the conditioning for the transplant and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your child's doctor may give your child medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Cyclophosphamide (Cytoxan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause your child to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder. A few patients may have bladder damage and bleeding for a longer time. Your child will be given large amounts of a sterile solution through his/her central line to protect the bladder. A bladder catheter (thin plastic tube) may be inserted into your child's bladder, if your child's physician thinks that it can help him/her. Cyclophosphamide slows the making of new red blood cells, white blood cells, and platelets. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in your child. Your child will get blood transfusions as needed. Cyclophosphamide also lowers the defense system. As a result your child may have more infections for several months after transplant. In a small number of patients, cyclophosphamide can damage the heart muscle causing heart failure. Sometimes cyclophosphamide causes abnormal heart function. If this occurs your child may have shortness of breath and have fluids build-up in his/her body. This medication can also cause the lungs to become scarred. If scarring of the lungs occurs it will usually happen three to six months after your child receives the medication. Scarring of the lungs can cause your child to die. Cyclophosphamide can adversely affect the production of hormones responsible for the onset and completion of puberty and the number and function of eggs (girls) and sperm (boys) leading to decreased fertility and even sterility. The onset of puberty can be delayed in your child and your child's ultimate height can be decreased. Since it is not possible to predict in a specific child the extent of these effects, it is important that your child has continuing, careful follow-up after the transplant. It is not known whether the use of cyclophosphamide will cause more side effects or problems with your child's health in the future.

Total Body Irradiation (TBI): TBI may cause your child to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), and painful swelling of the saliva glands for a few days. Your child may also experience short-term hair loss. TBI kills both sick and normal marrow, leading to a lack of red blood cells, white blood cells, and platelets. The short-term loss of these blood cells could cause your child to become anemic, develop an infection, and/or bleeding. This will continue until the transplanted donor cells begin to work in your child. Your child will get blood transfusions as needed. There is a risk that cataracts (cloudiness) may develop in your child's eyes. This may mean partial loss of vision, and your child may need contact lenses or surgery to remove the cataracts. TBI can adversely affect the production of hormones responsible for the onset and completion of puberty and the number and function of eggs (girls) and sperm (boys) leading to decreased fertility and even sterility. The onset of puberty can be delayed in your child and your child's ultimate height can be decreased. Since it is not possible to predict in a specific child the extent of these effects, it is important that your child has

continuing, careful follow-up after the transplant. It is not known whether the use of TBI will cause more side effects or problems with your child's health in the future.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects your child may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects your child may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If your child experiences these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. Your child may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD, experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your child's body. It may cause or can worsen the mouth sores or inflammation of the mouth which your child may have already developed from the procedures and medications used to prepare him/her for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your child's kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause your child to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help the blood to clot. Your child's platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy, irradiation therapy, or both. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines and irradiation cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If your child has severe mouth sores he/she will be given medicine to help control the pain. If your child's mouth sores are severe, he/she may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy and irradiation therapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. Your child may gain water weight and not go to the bathroom as often as he/she normally does. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. Your child may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible your child may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy and irradiation cause severe lung damage that cannot always be treated. If this happens, your child may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: Your child may experience side effects that occur several months to many years after the transplant. Your child may experience poor function of the thyroid gland, requiring him/her to take thyroid medication. As a result of irradiation, cataracts (cloudiness of the eyes) may occur earlier in life as compared to a person who had not had a transplant. If your child develops cataracts they may require treatment. It is rare, but your child's kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk your child may develop a second cancer as a result of the chemotherapy, irradiation and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: Your child will receive intravenous fluids during the transplant process and he/she may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment B

Additional Risks and Toxicities Related to the Standard Transplant Procedure Busulfan and Cyclophosphamide Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications your child will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your child's doctor may give your child medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Cyclophosphamide (Cytosan): This is a common medication used to treat cancer. This medication kills cancer cells by stopping them from growing. Cyclophosphamide may cause your child to have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), short-term hair loss, short-term bladder problems, and, at times, bleeding from the bladder. A few patients may have bladder damage and bleeding for a longer time. Your child will be given large amounts of a sterile solution through the central line to protect his/her bladder. A bladder catheter (thin plastic tube) may be inserted into your child's bladder, if your child's physician thinks that it can help him/her. Cyclophosphamide slows the making of new red blood cells, white blood cells, and platelets. This causes a risk of infection and/or severe bleeding until the transplanted donor cells begin to work in your child. Your child will get blood transfusions as needed. Cyclophosphamide also lowers the defense system. As a result your child may have more infections for several months after transplant. In a small number of patients, cyclophosphamide can damage the heart muscle causing heart failure. Sometimes cyclophosphamide causes abnormal heart function. If this occurs your child may have shortness of breath and have fluids build-up in his/her body. This medication can also cause the lungs to become scarred. If scarring of the lungs occurs it will usually happen three to six months after your child receives the medication. Scarring of the lungs can cause your child to die. Cyclophosphamide can adversely affect the production of hormones responsible for the onset and completion of puberty and the number and function of eggs (girls) and sperm (boys) leading to decreased fertility and even sterility. The onset of puberty can be delayed in your child and your child's ultimate height can be decreased. Since it is not possible to predict in a specific child the extent of these effects, it is important that your child has continuing careful follow-up after the transplant. It is not known whether the use of cyclophosphamide will cause more side effects or problems with your child's health in the future.

Busulfan: This medication disrupts the growth of cancer cells and destroys them. While taking busulfan your child most likely will have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), lower white blood cell count that increases the risk of infection, lower platelet count that increases the risk of bleeding, hair loss, stopping of menstrual periods in girls who have reached puberty, temporary reduced or no sperm production in boys who have reached puberty. Less likely side effects that your child may experience are fatigue, sores in the mouth or on the lips, fever, rash, loss of appetite, changes in color of the skin, seizure. Rare side effects that your child may experience are damage to the lungs, which may cause him/her to cough, be short of breath, and have trouble breathing. It is rare, but busulfan can also cause changes in your child's liver function.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects your child may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects your child may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If your child experiences these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. Your child may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD, experience a painful sensation in their hands or feet or both. The pain decreases or goes when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your child's body. It may cause or can worsen the mouth sores or inflammation of the mouth which your child may have already developed from the procedures and medications used to prepare him/her for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your child's kidney is already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause your child to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one drug or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help the blood to clot. Your child's platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising,

but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If your child has severe mouth sores he/she will be given medicine to help control the pain. If your child's mouth sores are severe, he/she may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. Your child may gain water weight and not go to the bathroom as often as she/she normally does. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. Your child may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible your child may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that can not always be treated. If this happens, your child may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: Your child may experience side effects that occur several months to many years after the transplant. Your child may experience poor function of the thyroid gland, requiring him/her to take thyroid medication. It is rare, but your child's kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk your child may develop a second cancer as a result of the chemotherapy and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: Your child will receive intravenous fluids during the transplant process and he/she may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment C

Additional Risks and Toxicities Related to the Standard Transplant Procedure Fludarabine and Melphalan Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications your child will receive as part of the conditioning for the transplant and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your child's doctor may give your child medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Fludarabine: This is a medication used to treat cancer. It is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells. Likely side effects your child may experience are low white blood cell count with increased risk of infection, low platelet count with increased risk of bleeding, feeling tired or sleepy, and anemia (low red blood cell count). Rare side effects your child may experience include confusion or coma, trouble seeing or problems with your child's eyes, trouble breathing, diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), pneumonia, agitation, numbness and tingling of the fingertips and toes, and kidney problems.

Melphalan: This medication disrupts the growth of cancer cells and destroys them. Side effects your child most likely will experience include nausea (feeling sick to stomach), hair loss, and low white blood cell count, which may lead to infection. Less likely side effects your child may experience include diarrhea (loose stools), mouth ulcers, and low platelet count with increased risk of bleeding. It is rare, but your child may experience a severe allergic reaction. Symptoms of a severe allergic reaction include itching, hives (bumps on the skin), flushing (redness), wheezing, chest tightness, skin rashes, fever, chills, muscle stiffening, severe breathing problems, and loss of appetite.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects your child may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects your child may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If your child experiences these effects, they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. Your child may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are

given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD, experience a painful sensation in their hands or feet or both. The pain decreases or goes away when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your body. It may cause or can worsen the mouth sores or inflammation of the mouth which your child may have already developed from the procedures and medications used to prepare him/her for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your child's kidneys are already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause your child to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one medication or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help the blood to clot. Your child's platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If your child has severe mouth sores he/she will be given medicine to help control the pain. If your child's mouth sores are severe, he/she may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. Your child may gain water weight and not go to the bathroom as often as he/she normally does. Capillary leak syndrome can be difficult to

manage if extra fluid enters the lungs and causes difficulty breathing. Your child may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible your child may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that can not always be treated. If this happens, your child may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: Your child may experience side effects that occur several months to many years after the transplant. Your child may experience poor function of the thyroid gland, requiring him/her to take thyroid medication. It is rare, but your child's kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk your child may develop a second cancer as a result of the chemotherapy and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: Your child will receive intravenous fluids during the transplant process and he/she may have difficulty eliminating all of this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

Attachment D

Additional Risks and Toxicities Related to the Standard Transplant Procedure Fludarabine and Busulfan Conditioning Regimen

There are certain risks related to a bone marrow or peripheral blood stem cell (PBSC) transplant. There are risks from the medications your child will receive as part of the conditioning for the transplant, and risks related to the transplant itself. Most of these risks and side effects are listed below, but they will vary from person to person. There may be more risks involved with transplantation, and there may be more side effects. Your child's doctor may give your child medications to lessen some of the side effects.

Risks Related to the Transplant Conditioning Regimen

Fludarabine: This is a medication used to treat cancer. It is used in stem cell transplants to reduce the risk of rejecting the donor's transplanted cells. Likely side effects your child may experience are low white blood cell count with increased risk of infection, low platelet count with increased risk of bleeding, feeling tired or sleepy, and anemia (low red blood cell count). Rare side effects your child may experience include confusion or coma, trouble seeing or problems with your child's eyes, trouble breathing, diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), pneumonia, agitation, numbness and tingling of the fingertips and toes, and kidney problems.

Busulfan: This medication disrupts the growth of cancer cells and destroys them. While taking busulfan your child most likely will have diarrhea (loose stools), nausea (feeling sick to your stomach), vomiting (throwing up), lower white blood cell count that increases the risk of infection, lower platelet count that increases the risk of bleeding, hair loss, stopping of menstrual periods in girls who have reached puberty, temporary reduced or no sperm production in boys who have reached puberty. Less likely side effects that your child may experience are fatigue, sores in the mouth or on the lips, fever, rash, loss of appetite, changes in color of the skin, seizure. Rare side effects that your child may experience are damage to the lungs, which may cause him/her to cough, be short of breath, and have trouble breathing. It is rare, but busulfan can also cause changes in your child's liver function.

Antithymocyte Globulin (ATG): This medication is given pre-transplant with the conditioning regimen medications to try and prevent both acute and chronic graft-versus-host disease. While taking ATG your child will most likely will have, a fever and chills, a lower white blood cell count that increases your child's risk of infection, a lower platelet count that increases your child's risk of bleeding, and a skin rash. Less likely side effects your child may experience are fatigue, diarrhea, vomiting, muscle aches and headaches. Rare side effects that your child may experience are changes in your blood pressures (either higher or lower blood pressure), rapid heart beat, be short of breath and have trouble breathing, chest pain and retention of fluids.

Risks Related to the Infusion of Bone Marrow or Peripheral Blood Stem Cells (PBSC)

The infusion of bone marrow or PBSC usually has few side effects. Rarely the infusion may cause a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction (which shows up as a severe drop in blood pressure and may cause loss of consciousness).

Risks Related to the Medications Used to Help Prevent Graft-Versus-Host Disease (GVHD)

Cyclosporine or Tacrolimus: These medications are used to try to prevent GVHD. These two medications have similar side effects. The immediate side effects your child may experience include nausea (feeling sick to your stomach) or vomiting (throwing up) when the medications are given orally. Other side effects your child may experience include high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. If your child experiences these effects they generally go away when the dose of the medication is decreased. A few patients have had a seizure while taking these medications. Your child may experience a change of liver or kidney function, in which case the medication dose will be reduced or possibly even withheld. The effect on kidneys seems to increase when other medications, which might cause kidney problems, are given at the same time, especially antibiotics. Occasionally, the kidney damage caused may require the use of an artificial kidney machine (hemodialysis).

Some patients when given cyclosporine through a vein to treat GVHD, experience a painful sensation in their hands or feet or both. The pain decreases or goes when the GVHD improves or when the cyclosporine is given by mouth instead of through a vein.

Some patients given tacrolimus develop diabetes and must take insulin while taking tacrolimus.

Methotrexate: This is also a medication used to try to prevent GVHD. Methotrexate causes damage to cells, and therefore can affect many different tissues of your child's body. It may cause or can worsen the mouth sores or inflammation of the mouth which your child may have already developed from the procedures and medications used to prepare him/her for the transplant. Methotrexate may slow down the recovery of blood cells after transplantation. Methotrexate can cause kidney damage. If your child's kidney is already damaged for other reasons, it can worsen kidney function. If kidney damage does occur, the methotrexate dose may be reduced or the medication may not be given at all.

Cyclosporine, Tacrolimus, Methotrexate, and Steroids: These medications interfere with the body's defense system (the immune system). This may cause your child to have more infections (especially viral infections and pneumonia) for several months after transplant.

If other agents are used for GVHD prophylaxis, then analogous paragraphs describing risk of those agents must be added to your version of the consent form.

Risks Related to the Transplant Procedure

The following risks are not specifically related to any one drug or the transplanted donor cells, but they are risks that are a part of the transplant procedure.

Bleeding: Platelets help the blood to clot. Your child's platelets will be low until the new bone marrow grows and, as a result, bleeding may occur. This can be minor bleeding, such as nosebleeds or bruising, but more serious, life-threatening bleeding in the lungs and brain can occur if the platelet count remains low. Usually, there is success in preventing major bleeding problems with transfusions of platelets. However, some patients may not respond well to transfused platelets and may be at serious risk for bleeding.

Veno-Occlusive Disease (VOD): This can occur as a result of high dose chemotherapy. VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain,

and extra fluid build-up in the abdominal cavity and other parts of the body. It can often be managed successfully, and completely resolve. However, complications can arise that may be fatal.

Mouth Sores and Diarrhea: The large doses of medicines cause irritation in the lining of the mouth and intestines. This can result in painful mouth sores and diarrhea. If your child has severe mouth sores he/she will be given medicine to help control the pain. If your child's mouth sores are severe, he/she may not be able to eat normally until the sores are healed. Mouth sores get better when the white blood count starts to rise, and engraftment occurs.

Capillary Leak Syndrome: This may occur as a result of chemotherapy. The blood vessels may become 'leaky' and fluid enters the abdominal cavity, lungs, and other tissues. Your child may gain water weight and not go to the bathroom as often as she/she normally does. Capillary leak syndrome can be difficult to manage if extra fluid enters the lungs and causes difficulty breathing. Your child may die if there is continued fluid collection in the lungs.

Unexpected Organ Damage and Other Side Effects: It is possible your child may experience unexpected, life-threatening heart, lung, kidney, or liver damage as a result of the transplant. Occasionally, the high doses of chemotherapy cause severe lung damage that cannot always be treated. If this happens, your child may need to use oxygen or even a respirator. The lung damage may get worse and be life-threatening. Rarely, multi-organ failure (such as lung and kidney failure) may occur, which is often fatal.

Late Effects: Your child may experience side effects that occur several months to many years after the transplant. Your child may experience poor function of the thyroid gland, requiring him/her to take thyroid medication. It is rare, but your child's kidneys could be affected, causing anemia (low red blood cell count) or high blood pressure. There is also a risk your child may develop a second cancer as a result of the chemotherapy and/or underlying disease. If secondary cancers occur they generally do not occur until 10 to 15 years after the transplant. The long-term effects upon heart, lung, and brain are unknown.

Fluid Build-up: Your child will receive intravenous fluids during the transplant process and he/she may have difficulty eliminating this fluid. Furosemide is a medication that is often given to help eliminate this excess fluid. This medication may cause hearing loss and loss of body chemicals such as potassium and sodium.

APPENDIX B-2
DONOR CONSENT FORM

NATIONAL MARROW DONOR PROGRAM® (NMDP)
A PHASE III RANDOMIZED, MULTICENTER TRIAL COMPARING G-CSF MOBILIZED
PERIPHERAL BLOOD STEM CELLS WITH MARROW TRANSPLANTATION FROM HLA
COMPATIBLE UNRELATED DONORS

DONOR/SUBJECT RESEARCH CONSENT FORM

Would you be willing to take part in a research study?

Because you have been matched with a recipient in seeking a blood stem cell transplant, you are being asked to take part in a clinical trial (a type of research study). This research study is sponsored by the NMDP and the Blood and Marrow Clinical Trials Network (BMT CTN). In this clinical trial the blood-forming cells will be collected from either the donor's bone marrow or the donor's bloodstream. This research study will only include people who choose to be in it.

This form contains key facts about the study and what you will be asked to do if you take part. Please read it in detail and take your time to decide. You might want to view the PBSC vs. Marrow Randomized Clinical Trial Donor Consent video as well (also offered as a CD-ROM). If you do not want to take part in this study, you may still be asked to donate for this recipient.

If you have any questions, please ask your Donor Center Coordinator or the Donor Center Medical Director before you make your final choice. If you agree to take part, you will be given a copy of this consent form for your records.

1. Why is this study being done?

The National Marrow Donor Program® (NMDP) uses bone marrow and blood-forming cells from the bloodstream for transplantation. In the past, blood-forming cells were always taken from the bone marrow. Now we know that a drug called "filgrastim" can increase the number of blood-forming cells in the bloodstream so much that these cells can be collected from the bloodstream of donors and used for transplant. When these blood-forming cells are collected from the bloodstream they are called peripheral blood stem cells (PBSC).

When the NMDP compared recipients who received bone marrow with recipients who received PBSCs, there was no difference in survival between the two groups. But because the recipients in each group did not have the same characteristics (age, disease type and so on) more research is needed.

This study will randomly assign recipients and donors into the two groups (bone marrow or PBSC). This makes it fairer to compare the two groups.

The NMDP and the BMT CTN hope what they learn from this study will help doctors and future recipients and donors make the best choice for the type of blood-forming cells to use for transplant; bone marrow or PBSC. If you would like to know more about why this study is needed, read Attachment A.

This study has two main goals:

1. To see if recipients given blood-forming cells from a donor's bone marrow do better or worse than recipients given PBSCs.
2. To compare three things about donors who donate bone marrow to those who donate PBSCs:
 - What differences (if any) are there in physical side effects that donors feel?
 - What differences are there in the time it takes donors to recover?
 - How does the quality of life differ for the two types of donors? For instance: how does a donor feel emotionally, how does donation affect a donor's daily life, and what does the donor feel about the donation process?

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

If you agree to take part in this research study, your donation will be different in these three ways:

1. How you donate – from your bone marrow or your bloodstream – will be chosen at random. A computer will make this choice.
2. You will be asked to give four extra blood samples for research purposes.
3. You will be asked to answer questions about how you feel emotionally after the donation.

Your safety is important. After you join the study, your health will be checked just like any donor. To protect both you and the recipient, you will have:

- A complete check-up.
- Standard blood tests.
- Blood tests for diseases like hepatitis, West Nile virus and HIV.
- A check for sickle hemoglobin (hemoglobin S).
- If you are a woman, a test to see if you are pregnant.

These tests will help to make sure that donating is safe for both you and the recipient getting the donation. (If you have more questions about why the blood tests are needed, see Attachment B.) All donors will have these tests. You will have these tests before you know if you will donate bone marrow or PBSCs. You must be able to donate both ways – from your bone marrow or your bloodstream – to go forward in this study. If you are able to donate only one way and cannot go forward in this study, you may still be asked to donate for this recipient.

Either as part of your complete check-up or as part of some other scheduled blood draw, 9 teaspoons of blood will be drawn from a vein in your arm for research studies. Your blood will be tested for antibodies specific to germs that cause infection, for example, Hepatitis B. The antibody levels in your blood may be compared against the antibody levels in the recipient's blood after the transplant. These samples will also be used to better understand tissue matching between donors and recipients.

If you are able to go forward in the study, you will be chosen at random to donate either from your bone marrow or your bloodstream. This means that the way you donate will be picked by chance. A computer program will make the choice. You cannot choose how you will donate. You will have an equal chance of giving blood-forming cells from bone marrow or from your bloodstream. Your donation itself will be just the same as if you were not taking part in the study.

If you are chosen to donate bone marrow:**1. Getting Ready to Donate Bone Marrow**

You may be asked to donate blood for your own use (this is called “autologous” blood donation). Depending on how much bone marrow you are asked to donate, you may need to have one to three units (each unit is about a pint or about two cups) of your blood drawn and stored before the donation. You will be asked to sign a separate consent form each time you give a unit of blood. If your blood counts are low after your marrow donation, your stored blood will be given back to you by transfusion.

The doctors at the transplant center where the recipient is being treated may also ask for a sample of your blood before the transplant. The blood will be used at the transplant center for tests needed in treating the recipient. For instance, DNA from your blood may be stored to help see which blood cells growing in the recipient after the transplant come from your cells and which come from the recipient's cells. You will not be asked to give more than about 20 teaspoons of blood. The blood will be drawn from a vein in your arm. This blood cannot be used for research studies without further consent from you.

2. Donating Bone Marrow

Bone marrow is collected in an operating room in a hospital. You will be given either general anesthesia or spinal anesthesia. Before the bone marrow donation, you will meet with a doctor to discuss the type of anesthesia that will be used. (This consent form is not for the anesthesia or the actual bone marrow donation. At the hospital you will be asked to sign another consent form for the anesthesia and the bone marrow donation.)

The amount of bone marrow you will be asked to donate depends on the size of the recipient. For safety reasons, no more than two teaspoons of bone marrow per pound of your body weight will be removed. For instance: if you weigh 150 pounds, no more than 6 cups of bone marrow would be taken.

You will lie on your stomach for the donation. Your bone marrow will be taken out of your pelvic bone (iliac crest). The doctor taking the bone marrow will make at least two, and maybe more, very small cuts in the skin of your back that covers the pelvic bones. Hollow needles will be placed through these cuts and into the bone. After a needle is put in the marrow space of the bone, a syringe will be attached to the needle and the marrow will be drawn out. Once the bone marrow is taken, the anesthetic will be allowed to wear off and you will be returned to your hospital room.

Your donated bone marrow may be tested to find out the number and types of cells, to make sure that it is sterile, and to learn other things that may be important to the transplant.

How much time will it take to donate bone marrow?

A list of visits and calls is given in the following table (an X marks what will happen on each visit/call):

Visit/Call	Risks Assessed	Unit of Blood Drawn and Stored	Bone Marrow Donated	Blood Drawn	Quality of Life Assessed by Phone
Screening check-up	X			X	
1 st Quality of Life contact					X
Pre-donation appointment 1 ^a		X		X	
Pre-donation appointment 2 ^a		X			
Pre-donation appointment 3 ^a		X			
Bone marrow donation	X		X	X	
2 days after donation (call)	X				X
1 week after donation ^b (call)	X				X
1 month after donation	X			X	
6 months after donation	X			X	X
1 year after donation	X			X	X
2 years after donation	X			X	
3 years after donation (study ends)	X			X	
Yearly visits after donation as part of the NMDP's routine donor follow up	X			X	

^a The number of autologous blood units you give depends on how much bone marrow will be taken.

^b Calls will continue weekly until complete healing from donation is reported.

What are the possible risks of donating bone marrow?

Caution: You should not take aspirin or aspirin-containing drugs for two weeks before your donation, or for soreness after it, without a doctor’s approval.

GIVING A SAMPLE OF BLOOD	
Risks	<p><i>Very small, may include:</i></p> <ul style="list-style-type: none"> • Bruising where the needle was put in. • Fainting. • More rarely, infection where the needle was put in.
DONATING BONE MARROW	
Risks	<p><i>From the anesthetic:</i> For a few hours after your bone marrow has been taken, you may feel groggy and sick from the anesthetic. You will not be allowed to eat food or to get out of bed until you are wide awake and all the anesthetic has worn off. Even after the anesthetic has worn off, you may still be sick and faint for a period of time.</p> <p><i>From the collection:</i> You should expect to feel some pain from the collection of the bone marrow. Most donors go through soreness in their lower back, like a back strain, that lasts for a few weeks. You may find it hard to sit in a chair for long periods of time or to climb stairs. You will most likely be less active than normal for the first two weeks after your donation.</p> <p>There are certain risks with donating bone marrow.</p> <p>Serious problems from bone marrow collection are rare but could occur due to an unexpected reaction to the anesthetic or trouble with the process of taking the bone marrow.</p> <p><i>Possible risks with anesthetics include:</i></p> <ul style="list-style-type: none"> • High fever. • Allergic reaction. • Low blood pressure and a slowed heart rate. • Not able to pass urine for a brief time (spinal anesthesia). • Headache (spinal anesthesia). <p><i>Possible risks from donation include:</i></p> <ul style="list-style-type: none"> • Infection where the skin was cut to collect your bone marrow (requires antibiotic treatment). • Pain or numbness in a leg. • Bleeding where the skin was cut. • More severe pain than normal. • Bone, nerve or other tissue damage (requires more medical treatment or physical therapy). <p>Life-threatening problems are extremely rare. But you should know, that as with any surgery, there is a risk of death.</p>

Additional Risks

Donating can cause intense feelings, especially if the transplant does not succeed. These feelings may range from stress during the process to great joy or the blues after the donation. By donating for this recipient, you are doing all you can to help them. You cannot control the success of the transplant, or whether the recipient lives or dies. You should not feel personally responsible for the outcome.

You may be asked to donate again for the recipient if the donated cells do not grow in the recipient or if the recipient's disease is not cured. If you are asked to donate again, you are free to say no.

If you are chosen to donate PBSCs:

1. Getting Ready to Donate PBSCs

The drug filgrastim has been shown to increase the number of blood-forming cells in the bloodstream. You will get a shot of filgrastim under your skin once a day for five days. Before each shot, you will be asked about any symptoms you may have. You will have blood samples (1½ to 3 teaspoons) taken from a vein in your arm before your shots on Day 1 and on Day 5. These samples are used to see how the drug affects your blood cell counts.

The doctors at the transplant center where the recipient is being treated may also ask for a sample of your blood before the transplant. The blood will be used at the transplant center for tests needed in treating the recipient. For instance, DNA from your blood may be stored to help see which blood cells growing in the recipient after the transplant come from your cells and which come from the recipient's cells. You will not be asked to give more than about 20 teaspoons of blood. The blood will be drawn from a vein in your arm. This blood cannot be used for research studies without further consent from you.

2. Donating PBSCs

PBSCs are donated in a hospital or blood center. Before you donate, a needle will be placed in a vein in each of your arms. Blood is removed through the needle in one arm and passed through a special machine called a blood cell separator. This process is called "apheresis." The machine collects your PBSCs, and the rest of your blood is given back through the needle in your other arm. You will make one or two PBSC donations, depending on the size of the recipient. During each donation you will need to lie fairly still in a recliner chair for four to six hours.

With each donation, 2 teaspoons of blood will be taken at the start and at the end of the process to measure your blood cell counts. Your donation may be tested to find out the number and types of cells, to make sure that it is sterile, and to learn other things that may be important to the transplant.

Needing a Central Line

Sometimes, a donor's arm veins are not big enough for the needles used in the apheresis process. In the NMDP's experience, this happens in about 18% of women and 3% of men. If your veins are too small, you may be asked to have a special blood-drawing tube called a "central line" placed in a larger vein in your body. The choice to use a central line may be made at your complete check-up (when your veins will be checked) or it could be made on the day you donate.

Placing a central line requires a surgical procedure under local anesthesia. A doctor does this in a hospital. In this case, your collection will also take place in the hospital and, if you donate over two days, you will need to stay in the hospital the night between donations.

If a central line is recommended in your case, you will be asked to sign a separate consent form that explains the risks of central line placement. You are free to say no to having a central line placed. If you choose to not have the central line placement, you may be asked to donate bone marrow instead.

How much time will it take to donate PBSCs?

A list of visits and calls is given in the following table (an X marks what will happen on each visit/call):

Visit/Call	Risks Assessed	Filgrastim Shot Given	PBSCs Donated	Blood Drawn	Quality of Life Assessed by Phone
Screening check-up	X			X	
1 st Quality of Life contact					X
Preparation, Day 1	X	X		X	
Preparation, Day 2	X	X			
Preparation, Day 3	X	X			
Preparation, Day 4	X	X			X
First donation, Day 5	X	X	X	X	
Second donation ^a	X		X	X	
2 days after donation (call)	X				X
1 week after donation ^b (call)	X				X
1 month after donation	X			X	
6 months after donation	X			X	X
1 year after donation	X			X	X
2 years after donation	X			X	
3 years after donation (study ends)	X			X	
Yearly visits after donation as part of the NMDP’s routine donor follow up	X			X	

^a If needed, based on size of the recipient.

^b Calls will continue weekly until complete healing from donation is reported.

What are the possible risks of donating PBSCs?

Cautions: You should not take aspirin or drugs with aspirin in them while getting filgrastim and for two weeks after PBSC donation without a doctor’s approval. During the PBSC donation, your platelet count may be lower because platelets are collected with the PBSCs. Taking aspirin when your platelet count is lower may increase your chance of bleeding.

You should not take filgrastim if you are pregnant. You should not become pregnant while taking filgrastim and for 48 hours after the last shot. This drug could cause serious problems for an unborn child.

The following table lists side effects and risks for receiving filgrastim and donating PBSCs.

GIVING A SAMPLE OF BLOOD	
Risks	<p><i>Some people have:</i></p> <ul style="list-style-type: none"> • Bruising where the needle was put in. • Fainting. <p><i>Very few people have:</i></p> <ul style="list-style-type: none"> • An infection where the needle was put in.

GETTING SHOTS OF FILGRASTIM	
Risks	<p><i>Most people have:</i></p> <ul style="list-style-type: none"> • Pain from the shot. • High white blood cell count. White blood cell counts usually return to normal levels within a few days to a few weeks after you stop receiving filgrastim. • Aching pain in bones while getting the filgrastim. The aching bone pain is usually relieved by acetaminophen (Tylenol™) or ibuprofen (Motrin™, Advil™). If you have pain that is not relieved by these drugs, you should contact the Donor Center Coordinator, _____ at () _____, and the dose of filgrastim may be reduced. <p><i>Some people have:</i></p> <ul style="list-style-type: none"> • Headaches. • Muscle aches. • Being tired. • Nausea and vomiting. • Trouble sleeping. <p><i>Very few people have:</i></p> <ul style="list-style-type: none"> • Allergy symptoms: <ul style="list-style-type: none"> – rapid heart rate. – Dizziness. – shortness of breath. – itching or rash. <p>All symptoms usually go away within two or three days after stopping filgrastim.</p> <ul style="list-style-type: none"> • Lowered platelet count. Filgrastim may cause your platelet count to be lower than normal. Platelets help stop bleeding. Two out of 1400 NMDP donors had very low platelet counts that needed to be watched closely. Although one donor went into the hospital for this, neither had symptoms from the low platelet count and both got well.

GETTING SHOTS OF FILGRASTIM (cont'd)	
	<p>Your platelet count will be measured on Day 5, before the first PBSC donation. You will be told if your platelet count is less than 80% of the lower limit of normal. In this case, depending on the true value of your platelet count, a doctor will talk with you about other options, such as to:</p> <ul style="list-style-type: none"> – Monitor your platelet count during the PBSCs donation. – Shorten the donation process. – Delay the donation for a day. – Cancel the PBSCs donation. – Ask you to consider a bone marrow donation. – Ask you to consider some other course of action that is okay with you. <ul style="list-style-type: none"> • There is a small (about 1 in 1,200) risk of being hospitalized for observation of side effects from the filgrastim (for example bone pain, nausea). • There is a small (about 1 in 10,000) risk of pain and bleeding from the spleen. <p>The NMDP is aware of four non-NMDP donors who had pain and bleeding from the spleen while getting filgrastim. In two cases the spleen was taken out by surgery. All four got well. Symptoms of bleeding from the spleen are pain in the upper left side just below the rib cage. If you feel pain in this area you should contact your Donor Center right away, as this can be a risk.</p> <ul style="list-style-type: none"> • Based on limited long-term data from healthy people who have received filgrastim, no long-term risks have been found so far. <p>Normal individuals are at risk for developing cancer, including leukemia, lymphoma or other blood diseases throughout their life time. It is unknown whether filgrastim increases or decreases an individuals risk of developing cancer. The data being collected during follow-up will help establish if there are any positive or negative long-term effects from receiving filgrastim.</p> <p>If you think you are having any serious or unexpected symptoms, contact the Donor Center right away at () _____.</p>

<i>DONATING PBSCs</i>	
Risks	<p><i>Most people have:</i></p> <ul style="list-style-type: none"> • Pain and bruising where the needles are put into the arms. • Lowered platelet count. <p>In addition to collecting PBSCs, the blood cell separator also collects platelets. Platelets help stop bleeding. If your platelet count after the first donation is too low, the second donation may be cancelled. Platelet counts usually return to normal levels within two to four weeks after collection of PBSCs.</p> <p><i>Some people have:</i></p> <ul style="list-style-type: none"> • Lightheadedness. • Nausea. • Numbness and tingling. <p>To prevent clotting, your blood will be mixed in the machine with a liquid called an “anticoagulant” during the PBSC collection. When the blood is returned to you, the anticoagulant can cause numbness and tingling of the fingertips or around the mouth. If you feel numbness and tingling, you must tell the nurse running the machine. These symptoms are easily treated with calcium, but if not treated could progress to muscle cramps.</p> <p><i>Very few people:</i></p> <ul style="list-style-type: none"> • Faint due to short-term low blood pressure. • Experience chills during the process. • Experience severe bleeding in the arm. • Have a loss of blood from a breakdown of the blood cell separator machine. If the machine does breakdown you could lose about 1½ cups of blood. This is unlikely to cause you harm. • There is a small (about 1 in 1,200) risk of being hospitalized for observation of side effects from the donation (for example lightheadedness, nausea).

Additional Risks

Donating for a recipient can cause strong feelings, especially if the transplant does not succeed. These feelings may range from stress during the process to great joy or feeling sad after the donation. By donating for this recipient, you are doing all you can to help them. You cannot control the success of the transplant, or whether the recipient lives or dies. You should not feel personally responsible for the outcome.

You may be asked to donate again for the recipient if the donated cells do not grow in the recipient or if the recipient’s disease is not cured. If you are asked to donate again, you are free to say no.

After You Donate Either Bone Marrow or PBSCs

After your donation, you will be called on the phone and asked questions about how you are feeling physically. These calls will start two days after the donation and will be made each week until you feel you are back to normal. You will be called again at one month, six months and then yearly after that.

You will also be asked to give a small blood sample (1½ teaspoons) at one month and six months after your donation, and then yearly after that. These samples will be used to measure your blood cell counts and to see how you are healing from the donation.

Quality of Life Surveys

To see how donation has affected your life, and how you have dealt with it, this study also asks questions about the quality of your life.

If you can answer the following three questions with a “yes,” you will be called and asked questions about your quality of life.

- Do you read or speak English?
- Do you have access to a phone?
- Are you able to complete a survey?

You can ask to have a written copy of the questions sent to you before you are called. The people calling will arrange a time that works for you. The calls will take 30 minutes or less and will happen on this schedule:

- Within four weeks before your donation.
- On Day 4 of filgrastim injections (*only for PBSC donors*).
- At two days after your donation.
- Every week after your donation until you have reported that you are fully well again for four weeks in a row.
- At six months after your donation.
- At one year after the donation.

The questions you will be asked include:

- How are you recovering physically?
- How well are you doing emotionally?
- How has the donation affected your everyday activities?
- How do you feel about the donation experience?
- What is your age, gender, race, marital status, work status, and what level of schooling have you had?

What are the possible side effects and risks of answering questions?**ANSWERING QUESTIONS FOR THE QUALITY OF LIFE STUDY**

There are no physical side effects or risks to being in the quality of life part of the study. It will take at least three extra hours of your time over one year. Some people may feel awkward answering questions about themselves, but you may skip any questions that bother you.

3. What do I do if I am injured in this study?

The risk of serious injury to donors participating in this study is thought to be small. If you are injured, treatment (to include first aid, emergency treatment and other needed care) will be on hand for you. The NMDP will pay for this treatment. Please call your Donor Center Coordinator right away at

() _____ if you are injured.

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

4. Do I have to agree to be in this study?

No, it is up to you if you want to participate in this study. If you decline to participate, the NMDP will not remove you from the Registry unless you ask for this to be done. Your decision to decline participation will not change your relationship with your Donor Center or the NMDP. There will not be any penalty or loss of benefits. Your decision to decline participation will not affect your right or access to health care or any other service that you are entitled to receive at your Donor Center.

5. Are there alternatives to being in this study?

Yes. If you decide you do not want to take part in this study, you may be asked to donate either bone marrow or PBSCs for the recipient without participating in this study. In that case, the type of donation will not be decided randomly.

6. How long will I be in this study?

As part of your normal donor follow-up, each year you will be asked to give a blood sample and answer some questions about how you are feeling physically. This information will be shared with the study for three years. You will be called with questions about your quality of life for one year.

You will be informed of any new finding which may affect your decision to continue your participation in this research study.

7. Can I stop being in this study?

Yes, you may stop taking part in this study at any time. If you want to withdraw, you are asked to tell your Donor Center Coordinator. Your choice to stop will not change your relationship with your Donor Center or the NMDP. There will not be any penalty or loss of benefits. Your choice to stop will not affect your right or access to health care or any other service that you are entitled to receive at your Donor Center.

If you choose to stop before you donate bone marrow or PBSCs: It is important you know that if you decline to donate after the intended recipient begins to get treatment to get ready for the transplant, he or she will most likely die. If you have any questions about this statement, please contact your Donor Center Medical Director.

8. Will it cost me money to be in this study?

No. There is no cost to you for the check-ups, donating the cells or the surveys.

9. Will I be paid to be in this study?

No. You will not be given any payment for being in this study.

10. Are there rewards to being in this study?

You will not receive direct payment or reward for being in this study. But, this study may help future recipients in need of transplants, as well as future donors.

11. How does the NMDP use donor data?

As part of your participation in this study, your demographic and health information will be entered into the NMDP Research Database. The NMDP collects some data on all donors. This helps the NMDP make sure it is doing the best job it can and learn how to improve where needed.

By signing this consent form, you allow _____ (Donor Center) to give the NMDP your demographic information (for instance: gender, age and ethnic background) and health information that was taken as part of the donation process (for instance: results from infectious disease testing and the physical exam and information on healing from the donation). This information will be used by the NMDP to evaluate operation of the Registry, to report to its funding agencies, and to conduct research. In addition, people doing studies approved by the NMDP may use this information for research.

This authorization does not have an expiration date. You have the right to cancel this authorization at any time by notifying the NMDP in writing that you are canceling the authorization. The address for the NMDP is 3001 Broadway Street NE, Suite 500, Minneapolis, MN 55413. If you cancel this authorization, any identifiable health information will be removed from the NMDP Research Database. If you cancel your authorization, this will not affect your right or access to healthcare or any other services you are entitled to receive at _____ (Donor Center).

12. Will my health information and surveys be kept private?

We will do our best to make sure that the personal information in your health record is kept private. We cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Groups that may look at and/or copy health records for research, quality assurance and data analysis include:

- The NMDP
- The BMT CTN
- The NMDP Institutional Review Board (IRB)
- The National Institutes of Health (NIH) and other government agencies, like the Food & Drug Administration (FDA), involved in keeping research safe for people.

Steps used to keep your data private are:

- To label your data with a nine-digit identification (ID) number instead of your name. This ID number is chosen at random and does not contain any identifying information about you.
- To limit who sees your data.
- To keep your data in locked files.
- To destroy all papers when they are thrown away (for instance, by shredding).
- To use special, protected computer systems.

13. Who can I contact with questions or concerns about this study?

The doctors for this study are:

Dr. _____ () _____
(Donor Center Medical Director)

Dr. John Miller (800) 526-7809
(NMDP Medical Director)

For questions about your rights while taking part in this study, please contact Roberta King, Institutional Review Board (IRB) Administrator, at (800) 526-7809.

14. Donor/Participant’s Signature (NMDP DID: _____)

I have been given a copy of all 18 pages of this form. I have read it, or it has been read to me. I understand this information and have had my questions answered. I agree to take part in this study.

Donor/Participant’s Signature Date

Donor/Participant’s Name Printed

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research 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.

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

Interpreter’s Signature Date

ATTACHMENT A

WHY IS THIS STUDY NEEDED?

The main goal of this study is to find out if there are differences in the outcomes of unrelated donor transplants based on whether blood-forming cells are taken from the bloodstream (PBSCs) or from the bone marrow.

Blood-forming cells are needed for transplantation. The greatest number of blood-forming cells are found in the bone marrow, while only a few blood-forming cells are normally found in the blood. In the past, blood-forming cells were always taken from the bone marrow. However, it is now known that a drug called “filgrastim” can increase the number of blood-forming cells in the blood so much that transplants can be performed using these cells taken from the blood.

When the NMDP compared the past survival of recipients who received an unrelated donor marrow transplant with recipients who received an unrelated donor PBSC transplant, there was no difference in survival between the two groups. This may have been because the recipients in each group did not have the same characteristics (different ages, different disease stages).

In this study, the donor and recipient will be randomly assigned (much like the toss of a coin) to either the PBSC group or the bone marrow group. By randomly assigning the recipients to receive either PBSCs or bone marrow, the characteristics of the recipients in each group should be similar. This makes it fairer to compare the two groups. With similar types of recipients in each group, the study should be able to find out if recipients who receive one type of donation do better after transplant than recipients who receive the other type of donation, or if recipients in both groups have similar results from their transplant.

There are also goals of this study specifically related to the donor. These goals are: 1) to examine any difference in the physical side effects PBSC donors and bone marrow donors have; 2) to examine any difference in the time it takes donors to recover from PBSC donation and marrow donation; and 3) to examine any difference in quality of life issues between the two types of donations, such as how the donation affects donors emotionally, how the donation affects the daily activities of donors, and how the donors feel about the donation experience.

ATTACHMENT B**WHY DO I NEED THESE BLOOD TESTS?*****Standard Blood Tests***

Tests are done on your blood to make sure it is safe for you to donate PBSCs or bone marrow. Any increased risk might mean that you would not be allowed to donate, or that only one of the two methods of donating would be advisable for you. These tests also protect the recipient getting your donation.

Blood Tests for Diseases

Your blood will be tested for infectious diseases including HIV, Hepatitis and West Nile Virus.

If your check-up or blood tests reveal anything that is not normal, you will be told. The NMDP or your Donor Center may also be required by law to notify your state public health agency if you test positive for Hepatitis B, Hepatitis C, the virus that causes AIDS (HIV) or other infectious diseases.

Check for Sickle Hemoglobin

Your blood will be tested for sickle hemoglobin. This test may result in genetic information that is new to you. There have been reports of severe reactions to filgrastim in persons with sickle cell disease. If your blood test is positive for sickle hemoglobin, you will not be able to participate in this study. However, you may still be asked to donate bone marrow for this recipient.

Pregnancy Test

If you are a woman of childbearing years, you will be required to take a pregnancy test. You must not donate bone marrow if you are pregnant. You must not take filgrastim if you are pregnant. This medication could cause serious problems for an unborn child. You must make sure that you do not get pregnant while taking filgrastim and for 48 hours after the last shot.

Extra Blood Samples for Research in this Study

Your blood will be tested for antibodies specific to germs that cause infection, for example, Hepatitis B. The antibody levels in your blood may be compared against the antibody levels in the recipient's blood after the transplant.

These samples are also used to better understand tissue matching between donors and recipients.

ATTACHMENT C**DEFINITIONS**

Anesthesia is the giving of a drug or drugs designed to relieve pain and/or cause loss of consciousness.

Apheresis is a process where a machine divides blood into its separate parts. Blood is removed from one arm of the donor, passed through the machine, which separates out the needed type of cell(s), and returns the remaining blood to the donor. Over time, the donor's body naturally replaces the blood cells that are removed.

A **Central Line** is a sterile tube put into one of the larger veins, usually in the groin area (femoral vein), the neck area (internal jugular) or just below the collarbone (subclavian vein).

Demographic Information are facts about the part of the country where you live; what sex, race and age you are, and what ethnic group(s) you belong to. These facts help people study the health data. It does not include your name.

Filgrastim is a drug that causes the bone marrow to produce more blood forming cells than usual. When these cells go into the bloodstream they are often called peripheral blood stem cells (PBSC). They can be collected from the bloodstream. Filgrastim is also called "G-CSF" and marketed in the U.S. as Neupogen[®]. Filgrastim has been approved by the Food & Drug Administration (FDA) to collect PBSCs from recipients getting transplants of their own cells. It is also approved to treat recipients with cancer getting chemotherapy, for recipients getting bone marrow transplants and for recipients with diseases causing very low white blood counts.

An **Institutional Review Board (IRB)** is a group of people who review research methods and results to protect your rights and safety.

PBSC are "peripheral blood stem cells." This is another term for the blood forming cells circulating in your bloodstream that can be taken by a machine.

Platelets are special blood cells that help you stop bleeding by making clots.

Blood forming cells are cells found in the bone marrow and bloodstream that rebuild your blood, bone marrow and the immune system.

A **Syringe** is used to inject or withdraw a fluid. It has a hollow needle to break the skin and fluid is either injected into the body through the needle or fluids such as blood are withdrawn from the body.

A **Teaspoon** is a common unit of measurement. One teaspoon is equal to about five milliliters. There are three teaspoons in a tablespoon, 48 teaspoons in a cup.

APPENDIX B-3

ASSENT TO PARTICIPATE FORMS

Assent to Participate in Research (Ages 7 to 11 years old)



1. Title of Research Study

A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cells with Marrow Transplantation from HLA Compatible Unrelated Donors

2. Principal Investigator Contact Information at Your Institution

Name/Title/Phone number/

3. Contact information for Emergencies after Hours or on Weekends or Holidays

Name/Phone number/

You are being invited to be in a research project. This research project is about deciding which kinds of donor cells work better for transplants. Donor cells can come from bone marrow or blood. Your doctors want to learn whether it is better to use bone marrow or blood for other children who need a transplant in the future.

You should talk to your parents about this research project. If you have questions, ask your parents or your doctor.

You have a disease in your blood cells and the disease makes you sick. To help you get better, the doctors will give you strong medicines to make the bad blood cells go away.

The medicines may make you throw up, lose your hair and have mouth sores.

After these strong medicines, you will get a transplant of new cells from a donor who is a person you do not know. The cells will come from the donor's bone marrow or from the donor's blood. The cells should make new and healthy blood in your body.

Your parents, doctors, and nurses will explain what happens with the transplant. You should ask them about anything you do not understand. They will answer your questions.

You don't have to be in this research project. Your doctors and nurses will not be mad at you if you don't want to be in the research project. If you decide you don't want to be in this research project, you may still receive a transplant for your disease.

Sign your name on the line below if you want to be in this research project. You can keep a copy of this form at home.

Minor's Signature

Date

Print Name of Minor

Age of Minor

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 assent:

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 to Participate in Research (Ages 12 to 17 years old)



1. **Title of Research Study**

A Phase III Randomized, Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell versus Marrow Transplantation from HLA Compatible Unrelated Donors

2. **Principal Investigator Contact Information at Your Institution**

Name/Title/Phone number/

3. **Contact information for Emergencies after Hours or on Weekends or Holidays**

Name/Phone number/

4. **Invitation to Participate in a Research Study**

You are being invited to join a research study because you have a disease that may be treated with a transplant of bone marrow or blood cells from a healthy person not related to you. This form gives you information to help you decide if you want to be in this study. You should read this form and ask any questions you have before agreeing to be in the study.

It is your choice whether or not to join this study. The medical staff at your transplant center will tell you about other treatment options before you make your decision about joining this study. If you do not join this study, you may still have a transplant for your disease.

5. **Purpose of the Study**

This study will look at two kinds of blood stem cell transplants, bone marrow and peripheral blood stem cell (PBSC), and their side effects. At this time, doctors use both types of blood stem cells for transplant. If you join this study, the type of cells used for your transplant will be picked by a computer program. The goal of this study is to see which type of blood stem cell transplant (bone marrow or PBSC) has better results.

An important part of this study will look at how patients recover after transplants. Researchers want to know what the effects are from each type of blood stem cell used for the transplant and how long they last.

Good effects might include:

- Quick recovery of blood counts after transplant
- No relapse (return) of disease
- High cure rates
- Few infections
- Able to return to important activities in life

Bad effects might include:

- Slow recovery or no recovery of blood counts after transplant
- Relapse (return) of disease
- Severe graft-versus-host disease (GVHD)
- Serious infections
- Not able to return to important activities in life

6. Study Procedures

If you agree to join this study, the donor will also need to agree to join the study. A donor could decide not to join this study, but still agree to give you cells for your transplant. If that happens, you can still have your transplant without being in this study, or another donor who does want to join this study may be found.

Since this study looks at the results of two different kinds of transplants, bone marrow and peripheral blood stem cell (PBSC), the kind of transplant you will receive will be decided randomly, like a coin toss. Neither you nor your doctor chooses the type of transplant; the type of transplant you will receive is determined by a computer program. Half of the patients in the study will have a bone marrow transplant. The other half will receive a PBSC transplant. Saying yes to joining the study means that you are willing to accept either type of transplant.

One part of the study will involve collecting your medical information. Your medical information will be collected for three years. The study coordinators at your center will collect information from your medical record chart every week for 100 days, then at 6 months, 1 year, 2 years and 3 years.

If you are 16 or 17 years old, another part of the study will ask questions about your physical and emotional health. This information will be collected for five years. A trained interviewer will contact you by telephone before your transplant, then 6 months, 1 year, 2 years and 5 years after your transplant. These telephone interviews will last approximately 15-25 minutes and will be done at a convenient time for you. They will include questions about side effects, health problems and how well you can do things that are important to you. When you are contacted, you may skip any questions you don't want to answer.

As part of the standard transplant procedure, you will need to take many medications and have other medical treatments as part of your transplant. Your doctors will explain these during discussion of your medical care. Even if you decide not to join this research study, you will still need to take medications and have other medical treatments as part of your transplant.

7. Possible Discomforts and Risks of Being in the Research Study

The bone marrow and PBSCs from the donor contain blood stem cells, which allow your blood counts (red blood cells, white blood cells, and platelets) to recover. Blood stem cells make all the blood cells in the bone marrow and serve the entire body. It is possible that even after the transplant your bone marrow will not work well enough and you will be at an increased risk of infections and even death. Early after transplant, the risk of getting an infection might be less after a PBSC transplant, because the blood counts return faster than with bone marrow. Later, the risk of infections might be increased in PBSC transplants, because graft-versus-host disease (GVHD) might be worse and last longer. Blood counts will be done often to track recovery of the bone marrow. You will get platelets and red cells as needed to keep your counts at a healthy level.

There is a risk that the blood stem cells may not grow after being given to you. This is called graft failure. This risk may be less with PBSCs, since PBSCs contain more blood stem cells than bone marrow.

Graft-versus-host disease (GVHD) is a common problem after unrelated donor transplantation. After the cells in the product start to grow, there is a risk that the donor cells might react against your body. GVHD it can show up as a skin rash, or liver or stomach problems, like feeling sick to your stomach, throwing up, not feeling hungry, stomach cramps, diarrhea, and bleeding of the gut. Chronic GVHD may occur later after transplantation and can cause problems with the eyes, mouth, lips, throat and liver. You will get medicines to help prevent GVHD, but sometimes people get it anyway. If you do,

there are other medicines used to help treat it. The chance of getting GVHD might be more with PBSCs, because PBSC transplants have more donor cells.

Relapse of your disease might occur after transplant, especially in patients with advanced disease. This risk may be decreased by PBSC transplantation.

If one type of transplant does have better results, and you are not randomly assigned to that study group, you may not receive the same benefits as those in the study group with overall better results.

If you are 16 or 17 years old, you will complete quality of life interviews. These interviews will not cause you any physical discomfort, although it is possible that you will find some of the questions or topics upsetting. If you do, there will be someone available to speak with you. They will be able to refer you to appropriate counselors or other support people.

8. Possible Risks and Discomforts from the Standard Transplant Procedure

As part of the standard transplant procedures, you will face risks from the transplant itself and from treatments given before and after the transplant. These risks are no different than the risks you would face if you had a transplant but did not join the study. Your doctor thinks these risks are less than the risk from the disease for which you are receiving a transplant.

Your organs may be damaged by the chemotherapy or irradiation given to you to prepare you for the transplant, or by other medications given to you after the transplant. We expect these risks to be the same whether you receive bone marrow or PBSCs. If you want more information about additional risks and the drugs that will be used for your conditioning regimen, it is available for you.

As part of a standard transplant procedure you may develop an infection after the transplant. The new cells from the donor may not grow in you (graft failure). You may develop graft-versus-host disease (GVHD). Your disease could relapse.

When the bone marrow or PBSC are given to you through the catheter, there are usually few side effects. Sometimes people may have a headache, chest pain or trouble breathing, a slight fever, or blood in the urine. Very rarely, it may cause an allergic reaction.

9. Alternatives Treatments Available if You Don't Want to be in the Study

Participation in this study is entirely voluntary. You don't have to join this study. What you and your family decide will not affect current or future health care you receive at this institution. If you are not in this study, you might have a transplant with marrow or blood stem cells anyway.

10. Possible Benefits to Participating in the Study

This research study is comparing the treatment results of bone marrow and PBSC transplants. At this time doctors do not know if one type of transplant has better results than the other, or if they both have the same results. If one type of transplant does have better results, and you are randomly assigned to that study group, you may benefit from participating in the study. The knowledge gained from this study may help future patients who need a blood stem cell transplant.

As a result of the bone marrow or PBSC transplant your disease may be put in remission or continue in remission.

11. Withdrawing From the Study

You can decide to leave the study at any time, for any reason, without notice. If you want you can withdraw from the study but still get a blood stem cell transplant. If you leave 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.

12. Protection of Your Privacy and Confidentiality of Your Research Records

Your participation in this research study, and your medical and quality of life information, will be kept private and confidential.

Scientific and medical findings resulting from a study may be presented at meetings and published so that the information can be useful to others. Your name would not be used in these presentations and publications.

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

13. Blood Samples for Research Purposes

You will be asked to give blood samples to see if infection-fighting cells are working and to help better understand tissue matching between donors and recipients in this study. You do not have to participate in this part of the study.

If you agree, you will provide blood samples up to 7 times (10-100 mL each time or approximately 1-7 tablespoons) between the time transplant is initiated and two years after (up to a total for all 7 blood draws of 430 mL or approximately 2 cups). The samples will be saved for future testing. The blood can usually be drawn from your central line at the time of other blood collections. If this is not possible, then it will be drawn directly from a vein.

In addition, part of this study will look at if vaccinations after transplantation can help prevent infection. You will get vaccinations for diphtheria, tetanus, Hepatitis B and pneumococcus. Blood will be drawn for medical tests to see if the vaccinations are working. If you do not agree to give blood samples for research, your doctor may still recommend vaccinations as part of your medical treatment.

The doctors conducting this study may choose to do some additional research tests on the blood samples.

You don't have to be in this research. If you don't want to give blood samples for research you can still be in the other parts of the study. Your care will not be changed if you decide not to give these blood samples for research purposes. Please mark your choice below (check only one box):

I agree to have blood drawn for research purposes.

I do not agree to have blood drawn for research purposes.

Signature

Date

14. Minor’s Assent

I have been told about this study’s purpose, procedures, possible benefits and risks. I have been given a chance to ask questions and they have been 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 Minor

Date

Print Name of Minor

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.

APPENDIX C
LABORATORY PROCEDURES

APPENDIX C – LABORATORY PROCEDURES

The laboratory procedures performed under this protocol include:

1. HLA Typing
2. Characterization of Graft
3. Immune Reconstitution
4. Chimerism
5. Acquisition of Natural Killer Cell Receptors in Recipients of Unrelated Transplants

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, -B, and -C at intermediate resolution, and DRB1 at high resolution, consistent with NMDP standard procedures.

After Transplantation: High resolution HLA typing of cryopreserved patient and donor samples is conducted as an ongoing research study by the NMDP. Data will be shared with the BMT CTN.

2. GRAFT CHARACTERISTICS

2.1 Rationale: The impact of the cellular constituents of the graft on post-transplant outcome is likely a complex effect that is a function of the absolute numbers of immune cells in the graft (T cells, NK-cells, B-cells, monocytes, and dendritic cells) as well as interactions among these different donor cells, and their interactions with residual host cells. Storek et al. has noted that the kinetics of CD45RA^{bright} “naïve” CD4 T cells is most correlated to the numbers of CD45RA^{bright} CD4 T cells in the allograft marrow or PBSC allo-graft from HLA matched siblings (Storek 2001). A detailed analysis of the cellular constituents of the graft in patients receiving allogeneic marrow or PBSC could help validate or reject the hypothesis that the content of donor CD34 and donor dendritic cells are significant factors in regulating post-transplant immune reconstitution and the incidences of post-transplant GVHD and relapse. Recent reports have suggested that the content of donor dendritic cells are associated with the incidences of chronic GVHD, and relapse (Waller, 2001), and that the number of transplanted CD34 cells is associated with the incidence of acute and chronic GVHD (Przepiorka, 1999). Other reports have shown that mobilization of PBSC with G-CSF results in a relative increase in the frequency of type 2 dendritic cell progenitors (DC2p) compared with un-stimulated blood mononuclear cells (Arpinati 2000). Thus it is likely that the content of donor CD34 and type 2 dendritic cells will vary significantly between allogeneic marrow grafts and PBSC grafts that are collected after G-CSF stimulation.

2.2 Assays: Studies will be conducted in keeping with the BMT CTN MOP on graft characterization. Samples of the marrow or PBSC graft will be sent to a central reference laboratory for flow cytometric analysis of the content of CD34 cells, the CD38-negative subset of CD34 cells, ALDH-bright progenitor cells, T cells, B-cells, NK-cells, monocytes, and dendritic cells. The test samples will be shipped to the reference laboratory at the same time that the graft is shipped from the collection center to the transplant center, so that the analysis of the cell content will be performed at approximately the same time as the graft is infused into the recipient. Samples will be shipped at 2-8°C on “cold-packs” in order to prevent accidental overheating that may impair cell viability. Pilot experiments storing samples of marrow or PBSC grafts at 2-8°C versus 20°C have not shown any significant differences in recovery of viable CD34 cells or the recovery of various subsets of immune cells (Table 2). The flow cytometric analysis will be performed using a panel of flow cytometry assays, each containing multiple fluorescently labeled monoclonal antibodies. The FACS panel that will be used is shown in Table 3.

2.3 Calculation of absolute cell counts for manipulated products: Some products are manipulated between the time of arrival at the transplant center and infusion. In some cases, plasma or red cells are depleted, while in others a subset of the product is cryopreserved. For such products, the doses of cell subsets transplanted can be estimated by adjusting the cell subset count at the reference lab multiplied by the proportion of total cells infused divided by the total cell received by the transplant center. Such a method assumes that travel and manipulation of the product did not affect any cell subset in a selective manner.

3. MEASUREMENTS OF POST-TRANSPLANT IMMUNE RECONSTITUTION

3.1 Sample shipping and analysis: Blood samples will be shipped at 2°-8° C to a central reference laboratory for measurement of peripheral T cell subsets, the numbers of T cell receptor excision circles (TREC)-positive CD4 and CD8 T cells, and the frequencies of anti-viral T cells using the tetramer assay and the pattern of cytokine synthesis by intracellular staining and flow cytometric assays. Plasma samples will be analyzed for IL2 and IL7 levels. Serum samples will be shipped to the reference laboratory for quantitative immunoglobulin levels and analysis of standard antibody titers to diphtheria toxin and tetanus antigen (dT). Serum for measuring pneumococcal antibodies, *Haemophilus influenzae* type B-specific IgG antibodies, Hepatitis B antibody as well as the titers of opsonophagocytic antibodies to pneumococcus will be sent to the central reference laboratory. The schedule for obtaining and shipping samples is listed in Tables 6 and 7 of Appendix C below.

3.2 Rationale and methods for measuring post-transplant T cell function: PBSC grafts contain more donor immune cells than marrow grafts and therefore may lead to improved reconstitution. Storek, et al. compared the kinetics of immune reconstitution among 115 cancer patients randomly assigned to receive either marrow or PBSC allografts from HLA matched siblings (Storek 2001). Recovery of CD4 T cells was slower among recipients of marrow versus PBSC allografts while proliferative responses of T cells to HSV, VZV, or PHA in vitro did not differ between recipients of marrow versus PBSC transplants. There was a significant difference

in the incidence of post-transplant infections, with recipients of marrow grafts experiencing a 2.4 fold higher rate of severe infections. The rate of fungal infections was 10/46 among recipients of marrow grafts and 2/36 among recipients of PBSC grafts (Storek 2001). The frequency of T cells, NK cell, B cells and dendritic cells will be measured in the blood of transplant recipients in order to test the hypothesis that the content of donor CD34 cells and donor immune cells in the graft has a material impact on the kinetics and quality of post-transplant immune reconstitution. Tetramer staining and flow cytometric assays will measure anti-CMV and anti-EBV CD8 T cells in samples from A2+ and/or B7+ recipients (circa 60% of patients). The frequency of functional anti-CMV specific T cells will be measured by the frequency of T cells that synthesize TNF in response to in vitro exposure to CMV antigens. The frequency of anti-aspergillus T cells will be assessed by measuring cytokine (γ -IFN and IL-4) synthesis following incubation with aspergillus antigen in-vitro. Plasma IL-7 and IL-2 levels will be measured by ELISA or chemiluminescence assays from the heparinized tube of blood used to measure peripheral blood T cells. The levels of IL-2 and IL-7 will be correlated with the levels of T cells in the blood to test the hypothesis that poor cellular immune reconstitution may be due, in part, to low blood levels of these cytokines (Okamoto 2002).

3.3 Rationale and methods for measuring post-transplant B-cell function: Comparison of recovery of serum immunoglobulin levels among a 115 patients randomized to receive marrow or PBSC allo-grafts from HLA matched siblings did not reveal any significant difference in the levels of serum Ig or circulating B-cells post-transplant (Storek 2001). Of note, this study did not compare humoral responses to vaccines, but did find lower rates of infections among the recipients of the PBSC grafts. In order to compare in vivo functional humoral immunity between the PBSC and marrow recipients, the response to vaccination with the heptavalent pneumococcal conjugate vaccine and to Hepatitis B will be measured. Pneumococcal infections are a long-term risk after transplant and, given the increased prevalence of penicillin resistant *S. pneumonia*, penicillin prophylaxis is not universally effective (Kulkarni 2000). However, polysaccharide epitopes such as those in the 23-valent pneumovax vaccine, are T cell independent antigens. As such, the pneumovax vaccine is not highly immunogenic, especially when administered in the first year after transplantation. Conjugate vaccines, which are T cell dependent and provide longer lasting immunity have been found to be more immunogenic in both infants and bone marrow transplant recipients (Barra 1992). A recent study administered the heptavalent pneumococcal conjugate vaccine (Prevnar, Wyeth Lederle Laboratories) to recipients (and half of the donors) at 3, 6, and 12 months after a T cell repleted allogeneic transplant (Molrine 2002). By month 12, over 60% of recipients had protective immunity to all 7 serotypes, although at month 3 and 6, humoral responses remained low in the half of patients whose donors had not been immunized. An increase in the frequency of patients with protective antibodies was seen following the third vaccination with PPV23 at 12 months, indicating that multiple early vaccinations with the protein conjugate vaccine can elicit protective humoral antibody responses when given within the first year post-transplant (Molrine 2003). Since the Wyeth vaccine is conjugated to a nontoxic variant of diphtheria toxin (CRM), an attractive strategy to augment humoral responses to the glycoprotein polysaccharide vaccines in adults within the first year post-transplant would be to sequentially immunize transplant recipients with the carrier protein (diphtheria toxin) followed by vaccination with the pneumococcal conjugate vaccine (7 valent) 2 weeks later, and finally the 23-valent polysaccharide pneumococcal vaccine a few months later.

Antibody response to the conjugated vaccine, however, represents a best-case scenario. If patients do not respond to the conjugated vaccine, they will not respond to the unconjugated vaccine or wild type infection. Unfortunately, the ability to respond to the conjugated vaccine does not predict for response to bacterial carbohydrate antigens. To evaluate the recipient's ability to produce an antibody response to wild type bacterial carbohydrate antigens, we will test for *Haemophilus influenzae* type B-specific IgG antibodies that cross-react against *E. coli* K-100 present in gut flora.

Immunization with Hepatitis B will serve as a potentially informative “neo-antigen” for the circa 40-50% of donor-recipient pairs that are both sero-negative to test the integrity of the primary humoral immune response post-transplant and responding patients may be protected from infection. The hypothesis would be that recipients of PBSC would receive more donor T cells and may respond to vaccinations starting at six months post-transplant at a higher frequency than recipients of marrow allografts. Demonstration of immune-responsiveness among transplant recipients receiving vaccine starting at six months post-transplant could lead to a reduction of some of the morbidity and mortality due to infection seen within the first year post-transplant.

3.4 Immunophenotype assays of lymphoid subsets and dendritic cells: Blood samples will be obtained from patients at 1, 3, 6, 12 and 24 months post-transplant. Aliquots of peripheral blood will be stained with the panels described in Table 4 by the central reference laboratory, and the percentage of nucleated cells with each phenotype determined using standard Cell-Quest (or similar) analysis templates. The reference laboratory will send the coordinating center the results from a CBC with differential performed on the shipped sample as well as the calculated numbers of cells/mcL of each phenotype as determined by the results of the FACS analysis. The reference laboratory will calculate the absolute numbers of subsets of immune cells in the blood based upon the absolute number of leukocytes in the blood and the percentage of leukocytes that are T, B, NK, monocyte, or dendritic cells subsets as defined by multiparameter flow cytometry.

3.5 Assays for antigen-specific T cells: Blood samples from patients who receive transplants from donors who have the HLA A2 or B7 allele will be obtained at 3, 6, 12 and 24 months post-transplant. These will be shipped to the central reference laboratory for FACS analysis of the frequency of anti-CMV and anti-EBV specific T cells using a tetramer FACS assay on the mononuclear cell fraction obtained from fresh (not frozen) samples. Tetramers will be incubated with PBMC obtained from transplant recipients at the time points described above, and the frequency of CD3, CD8, tetramer+ T cells will be assessed by flow cytometry (Altman, 1996). A subset of approximately 60% of transplant patients is predicted to be either A2+ and/or B7+, but they should be evenly distributed between the two arms. Phycoerythrin-labeled HLA A2 and HLA B7 tetramers that stain antigen specific T cells that recognize immunogenic CMV peptides will be synthesized by the tetramer core facility at the central reference laboratory. HLA-B0702 tetramers loaded with (TPRVTGGGAM), the amino acid number 417-426 of lower matrix protein pp65-of CMV) and HLA-A 0201 tetramers, loaded with (NLVPMVATV), the amino acid number 495-503 of the pp65 protein will be used to identify CMV specific T cells from patients transplanted with HLA A2 and HLA B7 donors, respectively (Singhal, 2000; Keenan, 2001). EBV specific T cells will be assayed using phycoerythrin-labeled HLA A2 tetramers loaded with the EBV/BMLF1 peptide containing aa 280-288 (GLCTLVAML, Chen,

2001). In addition, the presence and number of aspergillus-specific, CMV-specific and tetanus-specific T cells will be determined by secreted cytokines measured by ELISA and FACS following *in-vitro* incubation with antigens at 3, 6, 12 and 24 months after transplant (Centeno-Lima 2002; Hebart 2002). For CMV, the assays will include FACS for cytoplasmic IL2, IFN-g and TNF-a, and no ELISA. For Aspergillus, the assays will only include ELISA for IL2, IL4, IL10 and IFN-g and no FACS. For Tetanus, the assays will include FACS for cytoplasmic IL2 and ELISA for IL-2, IL-4, IL-10 and IFN-g. Appropriate controls should be included in the assays. See Table 1 below.

Table 1: Cytokines for FACS and ELISA Assays

	CMV	Aspergillus	Tetanus	Control
FACS IC Assay	IL2 INF-g TNF-a		IL-2	IL-2 IFN-g TNF-a
ELISA Assay		IL-2 IL-4 IL-10, IFN-g	IL-2 IL-4 IL-10 IFN-g	IL-2 IL-4 IL-10 IFN-g

IC = intracytoplasmatic

3.6 TREC assay for de novo T cell generation: The central reference laboratory will prepare a mononuclear cell suspension from patient blood samples collected at 3, 6, 12 and 24 months post-transplant. Cell separations will be performed to isolate CD3+/CD4+ and CD3+/CD8+ cell subsets for batch analysis of signal joint T cell receptor excised circles (TRECs). IL-7 and IL-2 levels will be measured by the central reference laboratory using ELISA or chemiluminescence assays on samples of plasma obtained from the tubes of blood used to measure T cell numbers. The levels of IL2 and IL7 will be correlated with the numbers TREC CD4 and CD8 (Okamoto 2002). A summary of post-transplant studies in cellular immune reconstitution is shown in Table 5.

3.7 Immunoglobulin levels: Quantitative immunoglobulin levels will be measured by the central reference laboratory on patient samples collected prior to transplant (baseline) and 6, 11, 12 and 24 months post-transplant (Table 5).

3.8 Vaccination schedule: In order to increase the effectiveness of the pneumococcal 23 valent polysaccharide vaccine administered post-transplant, transplant recipients will receive sequential vaccination with dT (tetanus diphtheria toxoid) at 6 months post-transplant followed by the heptavalent pneumococcal conjugate vaccine (PCV7) four weeks later at 7 months, and again at 9 months post-transplant, and then the 23-valent polysaccharide vaccine (PPV23) and the dT (tetanus diphtheria toxoid) vaccine at 11 months post-transplant (Table 5). The goal will be to evaluate the immunogenicity of the pneumococcal vaccine conjugate when it is administered after boosting with the dT carrier vaccine followed by sequential vaccination using the PCV7 and PPPV23 vaccines. ELISA and functional type-specific pneumococcal antibodies will be measured. Diphtheria and tetanus antibody will be measured prior to the first vaccination

and prior to the PPV23 vaccine. *Haemophilus influenzae* type B-specific IgG antibody measurements will also be performed on samples collected at 6, 12 and 24 months post transplant to assist in evaluating the recipient's ability to produce T cell independent immune responses to polysaccharide antigens. Approximately 60% of recipients are predicted to be seronegative for Hepatitis A. Immunization with the Hepatitis B vaccine will be used a neo-antigen, in order to assess immune response to primary antigen. The Hepatitis B vaccine will be administered at 6 months, 7 months, and 11 months after transplant, and antibody titers at 6, 12 and 24 months will be determined to compare responses in the PBSC and bone marrow recipients. All vaccinations should be given \pm 1 week of the scheduled date. Donor and pre-transplant recipient serum will be collected to measure baseline antibody titers as specified in Table 5.

3.9 Laboratory assays for antibody titers:

- i) **ELISA for diphtheria antibody and tetanus antibody** will be performed at the central reference laboratory.
- ii) **ELISA for *S. pneumoniae* antibody.** IgG antibody levels for specific serotypes of *S. pneumoniae* will be assayed by a protocol developed by George Carlone, Ph.D. at CDC. These studies will be conducted at the central reference laboratory. Serotypes that are PCV7 heptavalent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F & 23F) and a subset of serotypes present in the PPV23-valent polysaccharide vaccine (1, 3, 5, 7F, 15B) vaccines will be measured at 6, 11, 12 and 24 months post-transplant.
- iii) **Functional antibodies for *S. pneumoniae*.** Functional antibodies will be measured by an opsonophagocytic assay using HL-60 cells. Opsonophagocytic titers will be expressed as the reciprocal of the serum dilution with \geq 50% killing compared with growth in the complement control wells. These studies will be conducted at the central reference laboratory. The opsonophagocytic assay will be performed only on 11 and 12 month post-transplant patient samples that show demonstrable IgG antibodies directed against one or more of the twelve *S. pneumoniae* serotypes evaluated in this study. The measurement of functional antibodies will be limited to the analysis of the two serotype-specific antibodies (one serotype, if IgG antibody detected to only one serotype) exhibiting the highest IgG titers.
- iv) **Hepatitis B surface antigen antibody.** These will be measured using ELISA kits at the central reference laboratory. Analysis will be performed on baseline donor serum samples and on patient serum samples collected at 6, 12 and 24 months post-transplant (Table 5).
- v) **ELISA for *Haemophilus influenzae* antibodies.** Quantitative total IgG antibody levels against *H. influenzae* Type B (HIB) capsular polysaccharide will be measured using ELISA/EIA kits at the central reference laboratory. Analysis will be performed on patient serum samples collected at 6, 12 and 24 months post-transplant.

- vi) **Stored serum and subsequent assays.** If, during the conduct of the study, investigators wish to analyze additional antibody assays, samples from frozen serum samples will be sent to the outside lab with no identifying information, except for a unique study number. All serum specimens will be stored for a 2-year period following enrollment of the last patient on the study. Specimens will be stored in a locked freezer at -80°C .

4. CHIMERISM

Recommendations for chimerism assay: Demonstration of donor cells in lymphoid and myeloid lineages can assess the relative engraftment potential of PBSC compared to marrow. Since all patients on this trial will receive myeloablative conditioning regimens, we hypothesize that there will be little if any difference in donor chimerism between PBSC recipients and marrow recipients. Therefore, chimerism testing will not be mandatory in this study. However, routine chimerism data generated by transplant center laboratories will be reported. Chimerism results will be reported as “percent donor DNA.”

5. ACQUISITION OF NATURAL KILLER CELL RECEPTORS IN RECIPIENTS OF UNRELATED TRANSPLANTS

This is a supplemental study to this protocol conducted by Jeffrey S. Miller, Daniel Weisdorf, Claudio Anasetti, and Peter Parham.

5.1 Background: Natural killer cells comprise approximately 10 – 15 % of resting normal donor blood. Interestingly, they comprise a much higher proportion of blood lymphocytes early after bone marrow or peripheral blood stem cell transplantation. There has been a growing interest in NK cells, given the discovery over the past five years of specific receptors that recognize Class I MHC molecules. A recent publication by Ruggeri, et al, suggests that T-cell depleted haplo-identical transplant by donors who are mismatched at a known Killer Immunoglobulin-like Receptor (KIR) ligand (Cw3-group, Cw4-group or Bw4) correlates with protection from relapse, less GVHD and better survival. The complexity of the KIR system is in part limited by the lack of known ligands for many of the receptors. The Perugia analysis is clinically intriguing but leaves some complicated biologic questions unanswered. Understanding this receptor status and how well it correlates with recipient KIR ligands may be of importance for better donor selection and improving unrelated donor (URD) transplant outcomes. The principal study goal is to evaluate the NK cell receptor repertoire and the functional acquisition of these receptors on NK cells in patients who recover from unrelated donor transplant. A functional NK repertoire may be associated with better protection from GVHD and infections and might differ in patients receiving PBSC or BM transplantation.

5.2 Preliminary Data: We have already accessed donor/recipient samples from the National Marrow Donor Program Sample Repository. From this repository, donor peripheral blood mononuclear cells (PBMNC) are available as well as cells from the recipient at approximately Day 100. We have used several approaches to analyze NK cell receptor acquisition after transplant including flow cytometry, quantitative RT-PCR, and intracellular cytokine staining.

Our current data on 36 donor/recipient sample pairs (collected retrospectively) can be summarized as follows: 1) KIR reconstitution early after transplant is diminished in a majority of patients, 2) KIR reconstitution is diminished to a greater extent in recipients of unmanipulated compared to T-cell depleted grafts, and 3) less KIR expression is associated with enhanced interferon- γ production in developing NK cells and CD94/NKG2A is reciprocally increased in those with low KIR expression. Further study will correlate these laboratory endpoints with clinical outcomes after URD transplantation.

5.3 Limitations to Current Retrospective Analysis and Samples Requested: Despite rapid progress in studies using retrospectively collected donor/recipient pairs, there are important limitations with this analysis. Available repository samples are limited to a single, early post-transplant time point. Our in vitro studies predict that NK cell receptor acquisition develops progressively over time. This is supported by studies from the Parham laboratory in allogeneic transplant patients. Therefore, kinetic analyses are needed to study the completeness of NK cell receptor reconstitution. To accomplish this goal, we propose prospective sample collection (30 ml blood at each time point) from the donor and recipient pre-transplant and from the recipient at 3, 6, and 12 months after transplant. Applying this analysis to the randomized trial also provides the advantage of correlation with detailed immunologic and infectious disease outcomes that will be collected in conjunction with this trial.

5.4 Objectives

- a. The **primary objective** of this study is to assess NK cell receptor acquisition (KIR, NKG2, LILR, NKP30/44/46, others) and NK cell function (cytotoxicity and cytokine production) during the first year after allogeneic URD transplantation. Until the BMT CTN Protocol 0201 trial is complete, this objective will be met irrespective of knowledge of graft source, transplant variables or clinical outcomes.
- b. The **secondary objective** will not be reached until after completion of and reporting of the randomized study. We plan to determine whether graft source (BM vs. PBSC) impacts on the frequency and completeness of NK cell receptor reconstitution and NK cell function. In this large prospective cohort, we will determine whether NK cell receptor status correlates with clinical outcomes (infectious disease, relapse, GVHD) and the number of activating vs. inhibitory NK receptors. We will test the hypothesis that KIR reconstitution is delayed by GVHD, favors CD56^{+bright} NK cell (cytokine producing) reconstitution and this diminishes CD56^{+dim} NK cell (directly cytotoxic) alloreactivity as a mechanism to protect against relapse. These analyses will be performed in conjunction with the BMT CTN database for the BMT CTN Protocol 0201 trial, which will collect the relevant clinical endpoints.

5.5 Experimental Plan: Paired donor /recipient samples will be thawed (including at least 2 post-transplant time points) and analyzed in parallel. We have a 2-tiered approach to analyze KIR expression. The first is based on flow cytometry using antibodies recognizing one or more KIR gene products [(DX9 recognizes KIR3DL1), (GL183 recognizes KIR2DL2, KIR2DL3, KIR2DS2), (EB6 recognizes KIR2DL1, KIR2DS1)]. The limitations of this analysis are that some antibodies recognize more than one gene product and that monoclonal antibodies are not

currently available for all KIR. Therefore, in addition to flow cytometry, RNA extracts will be amplified for KIR expression. We have already validated real time quantitative PCR reactions for a majority of KIR genes. To control for NK cell number, quantitative real time PCR will be performed from gene products expressed in all NK cells (KIR2DL4 and CD56/NCAM). We will need genotyping studies to further investigate whether the absence of a KIR transcript is due to the absence of a gene or the absence of expression. Control cell lines and a panel of known normal donors will be included with each analysis. We have already established a good correlation between protein level by flow cytometry and real time quantitative PCR data using standard curves. We will also analyze other NK receptors including NKG2, LILR, and NKp30/44/46 receptors and other families as reagents become available and validated. Function will be measured by cytotoxicity or cytokine productions assays in the presence or absence of KIR ligands. As new reagents or NK cell related genes or receptors are identified, these samples may be used for new studies. However, within this study, analyses are limited to studies on NK cell expressed gene products and NK cell function. They will not be used for other purposes.

5.6 Samples:

Donor: 30 mL heparinized blood (green top tubes), pre-donation (prior to G-CSF if PBSC)

Recipient: 30 mL heparinized blood (green top tubes), pre-transplant (before conditioning)
30 mL heparinized blood (green top tubes) at 3, 6 and 12 months post-transplant

To limit blood drawing volumes, if needed, the post-transplant samples can be collected a few days or up to 4 weeks before or after the requested times.

For pediatric subjects, the volume requested is 15-20 mL heparinized blood at the same time points.

Samples are to be sent by overnight express in a temperature certified shipping kit:

Dr Jeffrey Miller
Attn: Sue Fautsch
University of Minnesota
Cancer Center Research Building, Room 521
425 E. River Road
Minneapolis, MN 55455

Phone: 612 625-6165

6. LABORATORY SPECIMEN COLLECTION, STORAGE AND SHIPPING PROCEDURES

Standard procedures for collection, storage, and shipping of specimens will be followed according to the NMDP and the NHLBI guidelines. Samples will be given a unique alphanumeric code that contains no personal identifiers. Transplant Center Coordinators will hold the link to the code. Laboratory staff will not have access to the link.

7. LABORATORY CONTRACTS AND REMAINING SAMPLES

All laboratory studies will be performed at laboratories under contract with the NMDP on behalf of the BMT CTN. The laboratory contract specifies that any remaining serum must be stored at the laboratory for the duration of the study. If the investigators choose to perform additional studies on these remaining samples, a formal amendment will be made to the protocol. Any amendments to the protocol are subject to the DSMB and IRB approval process.

At the end of the study, the BMT CTN will either instruct the laboratory to destroy any remaining samples or to transfer the remaining samples to the NHLBI sample repository in Maryland. These samples will be paired with the respective donor or recipient sample and given unique bar code designations that cannot be linked back to the donor or the recipient. An NHLBI Biologic Specimen Repository Utilization Committee will advise the Institute on requests for specimens to perform research with these anonymous samples. If an investigator request for these samples is approved by the committee, the NHLBI may provide a panel of the specimens requested using unique code numbers. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the investigator only after completion of his/her research protocol. Samples sent to researchers cannot be linked with any remaining sample at the repository.

After completion of all cellular assays, the samples will be destroyed. Only serum samples remaining from the laboratory assays for antibody titers will be shipped to the NHLBI sample repository.

Table 2: Effect of Storage Time and Storage Temperature on the Numbers of Viable CD34 Cells, T cells and Dendritic Cells in Blood and Marrow Grafts

Analyses after 72 hours:

Median percentages of initial value	2-8°C Marrow HPC	Room Temp Marrow HPC	2-8°C Blood HPC	Room Temp Blood PBSC
Viable CD34	100%	100%	40%	16%
Viable CD3	60%	51%	54%	48%
Viable DC2p	74%	54%	67%	32%

Table 3: Flow Cytometry for Graft Characterization

Tube #	Class of Cells	Cell Types	Measured Blood Cell Subsets	Antibodies
1	Progenitor Cell	Viable CD34 cells	Viable nucleated cells CD34 cells CD34/CD38- cells/kg	anti-CD45 (FITC) anti-CD34 (PE) anti-CD38(APC) 7AAD
2	Progenitor Cell	ALDH ^{bright} cells	ALDH ^{bright} CD34 cells ALDH ^{bright} CD34-negative cells/kg	BAAA (FITC) anti-CD34 (APC) anti-CD45(PE)
3	Progenitor Cell	ALDH negative control	Negative control for BAAA staining	BAAA (FITC) + DEAB IgG1-(APC negative control) IgG1-(PE negative control)
4	Progenitor Cell	ALDH compensation	BAAA control	BAAA IgG1 (APC negative control) IgG1-(PE negative control)
5	Progenitor Cell	ALDH compensation	PE control	BAAA IgG1-(APC negative control) CD3-(PE)
6	Progenitor Cell	ALDH compensation	APC control	BAAA CD3-(APC) IgG1-(PE negative control)
7	Lymphoid Subsets	T cell subsets	CD4 CD8 CD25+	anti-CD4 (PerCP) anti-CD8 (FITC) anti-CD25 (PE) anti-CD3 (APC)
8	Lymphoid Subsets	NK and $\gamma\delta$ T cells	CD56+ $\gamma\delta$ T cells	anti-CD56 (PE) anti- $\gamma\delta$ TCR (FITC) anti-CD16 (PerCP) anti-CD3 (APC)
9	Lymphoid Subsets	B-cells & monocytes	CD5+ B-cells CD14+ monocytes	anti-CD5 (PerCP) anti-CD14(PE) anti-CD2 (FITC) anti-CD19 (APC)
10	Dendritic Cell Subsets	DC subsets	DC1 and DC2 subsets	anti-lineage (FITC) anti-CD123(PE) anti-HLADR (PerCP) anti-CD11c(APC)
11	Isotype Controls	Isotype Ig	Non-specific staining	irrelevant (FITC) (PE) (PerCP) (APC) conjugates to murine monoclonal Ab

Table 4: Flow Cytometry for Immune Reconstitution

Tube #	Class of Cells	Cell Types	Measured Blood Cell Subsets	Antibodies
1	Lymphoid Subsets	T cells	CD4 CD8 CD25+	anti-CD4(PerCP) anti-CD8 (FITC) anti-CD25 (PE) anti-CD3(APC)
2	Lymphoid Subsets	NK and $\gamma\delta$ T cells	CD56+ $\gamma\delta$ T cells	anti-CD56 (PE) anti- $\gamma\delta$ TCR (FITC) anti-CD16 (PerCP) anti-CD3 (APC)
3	Lymphoid Subsets	CD8 T cell Subsets	Naïve and activated CD8 T cells	anti-CD8 (APC) anti-Ki67(FITC) anti-CD62L (PE) anti-CD45RA (TC)
4	Lymphoid Subsets	CD4 T cell Subsets	Naïve and activated CD4 T cells	anti-CD4 (APC) anti-Ki67(FITC) anti-CD62L(PE) anti-CD45RA (TC)
5	Lymphoid Subsets	B-cells & monocytes	CD5+ CD27 B cells CD14+ monocytes	anti-CD5 (PerCP) anti-CD27 (FITC) anti-CD14(PE) anti-CD19 (APC)
6	Dendritic Cell Subsets	DC subsets	DC1 and DC2 subsets	anti-lineage (FITC) anti-CD123(PE) anti-HLADR (PerCP) anti-CD11c(APC)
7	Isotype Controls	Isotype Ig	Non-specific staining	irrelevant (FITC) (PE) (PerCP) (APC) conjugates to murine monoclonal Ab

Table 5: Summary of Immune Reconstitution Assays for Donors and Patients and Post-transplant Vaccination Schedule for Patients

	Baseline Donor	Baseline Patient	1 m	3 m	6 m	7 m	9 m	11 m	12 m	24 m
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Measures of Cellular Immunity										
FACS analysis			X	X	X				X	X
Tetramers assay				X	X				X	X
TREC analysis				X	X				X	X
Plasma IL-7 and IL-2 levels				X	X				X	X
T cell responses to tetanus, CMV, and Aspergillus antigens				X	X				X	X

Immunoglobulin and Antibody Titers¹										
dT Antibodies		X			X			X	X	X
S. pneum. Ab and ops					X			X	X	X
Anti-HBsAg titer	X				X				X	X
Quantitative Ig		X			X			X	X	X
H. influenzae B Ab Titer					X				X	X
Natural Killer Cell Receptor Acquisition	X	X		X	X				X	

¹ Antibody titers should be drawn just before vaccination.

	Baseline Donor	Baseline Patient	1 m	3 m	6 m	7 m	9 m	11 m	12 m	24 m
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Vaccination Schedule²										
dT vaccine					X			X		
PCV7 vaccine						X	X			
PPV23 vaccine								X		
Hep B vaccine					X	X		X		

² Vaccinations should be given ±1 week of the scheduled dates.

Table 6: Collection and Shipping Procedures and Collection Schedule for Patient Blood Samples

	TYPE OF SAMPLE	TYPE OF PROCESSING AND STORAGE	DATES SAMPLES OBTAINED	SHIPPING SPECIFICATIONS	LOCATION OF TEST PERFORMED
FACS Analysis	17 mL peripheral blood ((2) 8.5 mL fill ACD-A yellow top tubes)	No additional processing; do not centrifuge. Store at 2-8°C until shipped.	1, 3, 6, 12, and 24 months post-transplant.	Ship priority overnight FedEx on frozen gel packs to Emory University; samples should not be in direct contact with the gel packs.	Dr. Edmund Waller's Lab at Emory University
CBC with Differential	3 mL peripheral blood ((1) 3 mL fill EDTA lavender top tube)	No additional processing; do not centrifuge. Store at 2-8°C until shipped.	1, 3, 6, 12, and 24 months post-transplant.	Ship priority overnight FedEx on frozen gel packs to Emory University; samples should not be in direct contact with the gel packs.	Dr. Edmund Waller's Lab at Emory University
TREC analysis; T cell responses to tetanus, CMV, and Aspergillus antigens; Tetramer FACS analysis	34 mL peripheral blood sample for all analyses ((4) 8.5 mL fill ACD-A yellow top tubes)	No additional processing; do not centrifuge. Store at 2-8°C until shipped.	3, 6, 12, and 24 months post-transplant.	Ship priority overnight FedEx on frozen gel packs to Emory University; samples should not be in direct contact with the gel packs.	Dr. Edmund Waller's Lab at Emory University
Immunoglobulin and Antibody Titers	10 mL peripheral blood ((1) 10 mL fill red top tube, no anticoagulant)	Sample should be placed upright in a sample rack and allowed to clot at room temperature for 30 minutes. Centrifuge red top tube at 900 x g or 2100 rpm. Extract serum carefully without disturbing the clot. Transfer 500 µL aliquots to 10 cryovials and freeze at -70°C in a scientific grade freezer.	At baseline prior to transplant and at 6, 11, 12, and 24 months post-transplant.	Batch ship quarterly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the NHLBI Repository.	Esoterix Laboratory
Plasma IL-7 and IL-2 Levels	6 mL peripheral blood ((1) 7 mL fill EDTA lavender top tube)	Centrifuge the EDTA containing whole blood samples at 900 x g or 2100 rpm for 10 minutes within 30 minutes of collection. Extract the separated plasma. Transfer 500 µL aliquots to 6 cryovials and freeze at -70°C in a scientific grade freezer.	3, 6, 12, and 24 months post-transplant.	Batch ship quarterly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the NHLBI Repository.	Esoterix Laboratory
Natural Killer Cell Receptor Acquisition	30 mL peripheral blood ((3) 10 mL fill sodium heparin green top tube)	No additional processing; do not centrifuge. Store at 2-8°C until shipped.	At baseline prior to transplant and at 3, 6, and 12 months post-transplant.	Ship priority overnight FedEx on frozen gel packs to University of Minnesota; samples should not be in direct contact with the gel packs.	Dr. Jeffrey Miller's Lab at University of Minnesota

Table 7: Collection and Shipping Procedures and Collection Schedule for Donor Blood and Product Samples

TEST	TYPE OF SAMPLE	TYPE OF PROCESSING AND STORAGE	DATES SAMPLES OBTAINED	SHIPPING SPECIFICATIONS	LOCATION OF TEST PERFORMED
Baseline Antibody Titer	10 mL peripheral blood ((1) 10 mL fill red top tube, no additive)	Sample should be placed upright in a sample rack and allowed to clot at room temperature for a minimum of 30 minutes prior to packaging the sample for shipment.	At baseline: any time after donor signs consent and prior to first filgrastim injection/marrow collection.	Ship priority overnight FedEx at room temperature to Esoterix Laboratory.	Esoterix Laboratory
Cellular Composition	2-4 mL product sample ((2) 5 mL sterile polyethylene screw top tubes, no additive)	Collect and package an aliquot of product for shipment. If two day PBSC collection, first sample is stored overnight at 2-8° C and shipped with Day 2 sample.	Day of collection.	Ship priority overnight FedEx at 2-8° C on frozen gel packs to Emory University; samples should not be in direct contact with the gel packs.	Dr. Edmund Waller's Lab at Emory University
Natural Killer Cell Receptor Acquisition	30 mL peripheral blood ((3) 10 mL fill sodium heparin green top tube)	No additional processing; do not centrifuge.	At baseline: any time after donor signs consent and prior to first filgrastim injection/marrow collection.	Ship priority overnight FedEx at 2-8° C on frozen gel packs to University of Minnesota; samples should not be in direct contact with the gel packs.	Dr. Jeffrey Miller's Lab at University of Minnesota

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APPENDIX D
HUMAN SUBJECTS

APPENDIX D – HUMAN SUBJECTS

Subject consent: Candidates for the study will be identified as described in Chapter 4. The PI or his/her designee at each transplant or donor center will contact the candidates, provide information about the purpose of the study, obtain consent and register them onto the study. A template of the consent form will be provided by the network for each center to customize to meet the local requirements and have reviewed and approved by the local IRB.

Confidentiality: Confidentiality will be maintained by assigning patients and donors identifier codes. The keys relating to the patient's or donor's identity with the ID code will be kept at each Center and at the NMDP separately from the research database.

Participation of women and minorities, children and other populations: Women and ethnic minorities will be included in this study. There is no lower age for participants.

Justification for including minors: The transplant procedures described in this protocol are considered non-research, standard therapy at U.S. transplant centers. Both bone marrow and peripheral blood stem cell (PBSC) transplants have been successfully used to treat blood disorders such as leukemias and myelodysplasia in pediatric and adult populations. In addition, the conditioning regimens and GVHD prophylaxis regimens included in the protocol are non-research, standard regimens. Therefore, in this protocol, the transplant procedure itself is not considered a research procedure and was not included in the risk/benefit analysis for inclusion of minors in research.

The following research procedures were included in the risk/benefit analysis:

- Randomization
- Quality of life interviews (16 and 17 years of age only)
- Blood draws for immune reconstitution studies

The research in this protocol satisfies the conditions set forth in 45 CFR 46.406: “*Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.*”

The research meets the following conditions:

1. *The risk represents a minor increase over minimal risk.*
 - In all likelihood, all children invited to participate in this protocol will receive a hematopoietic stem cell (HSC) transplant regardless of whether they participate in this protocol. Since it is unknown if the overall survival from a HSC transplant differs depending on whether the source of the stem cells is bone marrow or peripheral blood, the randomization process represents a minor increase over minimal risk to the standard transplant procedure.
 - Quality of life (QOL) interviews will only be conducted on minors 16 and 17 years of age. There are no physical risks associated with the QOL interviews, but there is a minor

increase over minimal risk as to loss of confidentiality or psychological distress caused by the questions. There are procedures in place to decrease these risks.

- Blood draws for immune reconstitution studies are an optional part of the study. The minor may participate in the randomization, and if applicable, the QOL interviews, and opt-out of the blood draws for the immune reconstitution studies. Although these blood draw volumes fall well within the minimal risk limits for healthy adults, the fact that these are pediatric, post-transplant patients slightly increases the risk of the blood draw. However, since these tests have no bearing whatsoever on patient care, the patient's physician would eliminate the blood draw if it posed additional risk for the patient.

2. *The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.*

- In all likelihood, all children invited to participate in this protocol will receive a hematopoietic stem cell transplant regardless of whether they participate in this protocol. Randomly assigning the transplant product the minor will receive does not inherently alter the standard transplant procedure. The transplant experience on the protocol is commensurate with the transplant experience off the protocol.
- The majority of minors invited to participate on this protocol will not take part in the QOL portion of the study. For those 16 and 17-year-old minors who will participate in the QOL interviews, the interviews are commensurate with the interviews these minors would have with Child Life Coordinators or other similar support staff at the transplant center following a standard transplant.
- The blood drawn for the immune reconstitution studies will most likely be drawn at the time of other blood draws for the standard transplant procedure. Since in most cases additional vein sticks will not be required, and the amount of blood drawn for these research tests is relatively minor in relation to all the other blood draws that are part of the standard transplant procedure, these blood draws are commensurate with those of the standard transplant procedure.

3. *The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition, which is of vital importance for the understanding or amelioration of the subject's disorder, or condition.*

- Within the transplant community there is shift in medical practice from performing bone marrow transplants to performing peripheral blood transplants despite the fact that there are presently no data to support this shift in practice. This study is the first prospective, randomized clinical trial to compare the results of these two types of transplant using unrelated donors. This study is of vital importance in understanding the best treatment options for patients in need of an unrelated donor hematopoietic stem cell transplant. The results could well be different in pediatric populations than in adult populations; therefore, it is important to include pediatric patients in this study.
- Since quality of life issues are an important aspect of evaluating the results of each type of transplant, the quality of life interviews in the 16 and 17 year olds will provide

valuable information in determining the impact each type of transplant has on the quality of life of older minors.

- The additional research tests examining immune reconstitution after transplant will provide data on any differences the source of the hematopoietic stem cells may make in restoring immune reconstitution after a transplant. Since immune reconstitution is directly related to post-transplant infections, a major contributor to transplant-related mortality, results of this portion of the study will be important to further understanding and treating this significant complication of unrelated donor hematopoietic stem cell transplantation.

4. *Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in CFR 46.408.*

- The research procedures do not provide any direct benefit to the health and well being of the minors; therefore, assent will be sought from all minors aged 7 to 17 years old.
- Age appropriate assent forms will be used to obtain assent from minors 7 to 11 years old and minors 12 to 17 years old. Minor assent must be documented by a signature on the Assent Form for Participation in the study.
- The research in this protocol is covered by 45 CFR 46.406; therefore, the signatures of both parents are required on the legal guardian consent form, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
- The minor may only participate in the research if the minor and both parents agree to the minor's participation. If either parent or the minor declines participation in the study, the minor shall not be enrolled in the study.

APPENDIX E
DONOR MANAGEMENT

APPENDIX E – DONOR MANAGEMENT

Donor eligibility will be confirmed as described in Section 2.5 of the protocol. In addition, donor management will be in accordance with the NMDP Donor Center Manual of Operations.

Donors' eligibility determinations and enrollments will occur following issuance of a work-up request. Because none of the work-up requirements are unique to the protocol, the donor consent decision may be made at any time prior to donor clearance. However, the invitation to participate in the protocol must be extended at the donor information session. At any time during the work-up procedure, if the donor declines to participate in the protocol, this decision must be communicated immediately to the NMDP Search and Transplant Services Department. *At the donor information session, the following information will be provided:*

PURPOSE OF THE TRIAL

This trial has been undertaken to compare the established blood stem cell source, bone marrow, against the newer source, PBSC. In making this comparison, we are interested in both donor and recipient experiences (outcomes). There is no foregone conclusion that one product is better than the other (for either donors or recipients), if that were the case, the trial would not be necessary. While some experts may have opinions about the comparison, these opinions cannot be verified by facts. The purpose of this trial is to provide scientifically valid information to allow a comparison.

POTENTIAL ADVANTAGES OF EACH PRODUCT

Donors will be informed about what is being compared to determine the potential advantages of each product for themselves and their recipients. The major outcome for donors is the incidence of adverse events and serious adverse events. We are also interested, however, in the donors' quality of life experiences with each type of donation. For transplant recipients, we will be measuring engraftment, graft-versus-host disease, risk of relapse and survival.

The NMDP has been conducting a non-randomized comparison of bone marrow and PBSC since July 1999. This comparison suggests, but does not prove, the following associations.

For Donors¹ –

Symptoms from donation	Similar in both groups. PBSC donors experience most of their symptoms before donation, but bone marrow donors have symptoms after donation.
Recovery from donation	PBSC donors recover faster after donation.
Satisfaction with donation	Both bone marrow and PBSC donors are comfortable with their decisions to donate and both groups feel the donation experience was positive.

¹ Data provided by Galen Switzer who has conducted an NMDP-funded comparison of donor experiences following bone marrow and PBSC donation.

For Recipients –

Engraftment of neutrophils and platelets	Clearly occurs earlier with PBSC, but no difference in overall engraftment
Risk of graft-versus-host disease	May be higher with PBSC, particularly chronic GVHD
Immune reconstitution	May be faster with PBSC
Risk of relapse	No obvious differences
Survival	No obvious differences

RECIPIENT DROPOUT

Donors should receive information about the enrollment process for donors and recipients. They should understand that the recipient has consented to participate in the clinical trial, but will ultimately be confirmed eligible only in the days immediately preceding the start of conditioning therapy. It is anticipated by the study investigators that up to 15% of enrolled donor-recipient pairs will be removed from study before the start of conditioning. In this instance, participation in the study will be terminated. Donors should understand that they may still be asked to provide a blood stem cell product for the recipient if an alternative approach to transplantation is available. But, in such cases, the transplant and the results of the transplant will not be included in the clinical study.

DONOR EDUCATIONAL MATERIALS

The NMDP has developed educational materials for donors considering the randomized clinical trial. These materials should be provided prior to the donor’s consent decision. Questions from donors may be directed to donor center personnel or to Dr. Dennis Confer, NMDP Chief Medical Officer (612-362-3425, dconfer@nmdp.org) or Dr. John Miller, NMDP Donor Center Medical Director (612-884-8534, jmiller5@nmdp.org).

APPENDIX F

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APPENDIX F – REFERENCES

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