BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic HCT

BMT CTN PROTOCOL 1202
Version 3.0

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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL #1202

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic HCT

Study Chairpersons: John Levine, M.D. and John Hansen, M.D.

Objective: The goal of this protocol is to establish a cohort of biologic samples collected prospectively from patients treated in BMT CTN centers that will be a shared biospecimen resource for conducting future allogeneic hematopoietic stem cell transplantation (HCT) correlative studies.

Accrual Objective: A minimum of 1,500 patients will be enrolled.

Accrual Period: The estimated accrual period is 4 years.

Eligibility Criteria: All U.S. Allogeneic Transplant Donors and Recipients weighing 10 or more kg may participate in the collection of samples.

Treatment Plan: Conditioning regimens, GVHD prophylaxis, and other supportive care will follow institutional guidelines.

Study Duration: Patients will be followed for 24 months post-HCT; long-term follow-up data will be collected through usual procedures of the Center for International Blood and Marrow Transplant Research (CIBMTR).

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CHAPTER 1

1. BACKGROUND

While hematopoietic stem cell transplantation (HCT) offers the only cure for many patients with malignant and non-malignant hematologic diseases, this treatment is associated with significant risks, leading to high rates of morbidity and mortality. There is a critical need for more effective prevention and treatment strategies for HCT-associated complications. The most serious of the latter include graft-versus-host disease (GVHD), cancer recurrence, organ toxicity and opportunistic infection. Although some clinical variables (e.g., recipient age, donor-recipient human leukocyte antigen [HLA] mismatch) predict higher risk of some events (e.g., GVHD, infection), no diagnostic tests exist that reliably predict occurrence, severity or response to therapy of any of these complications. Recent compelling results from single center studies suggest that biomarkers can be identified that stratify patients into discrete risk groups for some outcomes and for overall mortality. However, these relatively small studies generally lack the statistical power or validation necessary to allow their results to be incorporated into practice. One key factor in the success of biomarker studies is the quality of clinical outcomes data that is linked to the specimens being analyzed. An adequate resource for these studies requires longitudinal sample collection integrated with longitudinal collection of comprehensive, standardized, high quality clinical data regarding complications, from onset to resolution, and regarding other clinical variables affecting risk of post-HCT outcomes.

The Resource proposed in this application will address the important problem that no multicenter biospecimen collections exist that contain appropriate types and/or numbers of specimens, together with detailed, rigorously reviewed clinical data collected from adequate numbers of patients, for biomarker studies. We propose to address this clear unmet need through a multi-center initiative to uniformly collect and store high quality biological specimens and high quality clinical data from a large, prospective cohort of patients and their donors. This Resource will be made available to the biomedical community and is expected to facilitate studies that will establish the utility of specific biomarkers for risk assessment, diagnosis and monitoring to allow more rational treatment strategies. These studies are also likely to provide mechanistic insights and to identify new therapeutic targets leading to development of more targeted and effective therapies.

The goal of this protocol is to establish a cohort of biologic samples collected prospectively from patients treated in BMT CTN centers that will be a shared biospecimen resource for conducting future allogeneic HCT correlative studies. This resource is designed to allow genomic, proteomic and transcriptional data to be integrated with high quality clinical phenotype and outcomes data to identify risk factors for development and severity of acute GVHD, chronic GVHD, organ toxicity, relapse, mortality, infection and other clinically significant complications occurring after allogeneic HCT.

To achieve this goal, patients and donors will be recruited and consent obtained at the time that they enroll on BMT CTN protocols where enrollment occurs at or before transplantation or prior to start of conditioning for patients enrolled on non-BMT CTN studies or treated as standard of

care. Samples will be collected: (1) from patients and donors pre-transplant; and, (2) from patients post-transplant on a calendar schedule through the first 3 months post-HCT. For patients co-enrolled on BMT CTN studies, clinical data will be collected in the context of the primary transplant protocols. For patients not enrolled on BMT CTN protocols, clinical data on early post-transplant events will be collected using the same data collection forms and systems that are used on BMT CTN trials. Additional clinical data for both BMT CTN and non-BMT CTN patients will be available from data submitted to the Center for International Blood and Marrow Transplant Research (CIBMTR) using the CIBMTR Comprehensive Report Forms. This protocol also leverages ongoing pre-transplant donor-recipient sample collection performed by the CIBMTR and National Marrow Donor Program (NMDP). Success in establishing this shared resource will inspire future investigator initiated research proposals and will allow investigators to take advantage of National Institutes of Health (NIH) funding initiatives.

CHAPTER 2

2. ELIGIBILITY

2.1. Inclusion Criteria Hematopoietic Stem Cell Recipients

1. Recipients of **first** allogeneic hematopoietic cell transplants that are transplanted in U.S. centers that participate in the NMDP/CIBMTR's "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries" and receive a cord blood graft or receive a bone marrow or peripheral blood graft from a related donor or from an unrelated donor in an NMDP-affiliated Donor Center or Registry participating in that same protocol.

   This transplant and donor center restriction is to allow linkage with pretransplant donor specimens collected under the NMDP/CIBMTR protocol. Current data indicate that >90% of donors approached under this protocol agree to provide samples.

2. Patients with any malignant or non-malignant hematologic disorder will be eligible for enrollment on this protocol. Upon reaching accrual of 1500 patients, only non-Caucasian adults and pediatric participants will be eligible for enrollment. A subset of 240 sequential patients with acute leukemia in first or second remission will also provide research samples for gene expression studies. A minimum of 200 African American participants will be enrolled on this protocol.

3. Children may participate in this study but must weigh at least 10 kilograms given the volume (100 mL) and number of blood draws during this study (see Section 4.3.3 for blood volume adjustments for patients weighing between 10 and 20 kg). Subjects must weigh at least 30 kg to provide research samples for gene expression studies (additional 40 mL). A minimum of 200 pediatric participants, defined as <18.0 years at the time of enrollment, will be enrolled on this protocol.

4. All participants or parent/legal guardian must sign an informed consent for this study. Because studies using this resource will require linking with clinical data collected by CIBMTR, all participants or parent/legal guardian must also consent to participate in "Protocol for a Research Database for Hematopoietic Cell Transplantation and Marrow Toxic Injuries".

   NMDP/CIBMTR research sample repository and CIBMTR research database protocols and consent forms referenced above are found at:
   http://www.cibmtr.org/DataManagement/ProtocolConsent/Pages/index.aspx

2.2.Inclusion Criteria Hematopoietic Cell Donors

The data and samples obtained from patients on this protocol are linked to donor data and samples obtained from a separate NMDP/CIBMTR protocol, "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries." **No donor specimens** will be collected under this protocol. Samples from donors will be obtained under the protocol specified above using the standard NMDP mechanism for the collection of donor samples.

2.3.Conditioning Regimens

This protocol allows institutional choice in conditioning regimen.

2.4.GVHD Prophylaxis

This protocol allows institutional choice in GVHD prophylaxis.

CHAPTER 3

3. BIOMARKER CORRELATIVE OUTCOMES AND DATA COLLECTION

The study is designed to capture the outcomes listed below as main outcomes of interest for future correlative studies. Data collection will focus on fields necessary for rigorous scientific study of these endpoints. For the first 100 days post-HCT, highly detailed data is collected. After Day 100, summary data is collected, primarily using CIBMTR forms, through 2 years post-HCT. Additional guidance for the data collection and definitions for the outcomes is found in the BMT CTN 1202 Biomarker Data Management Handbook.

3.1.Acute GVHD

The date of onset, severity, target organ involvement, treatment, and evolution over time, including response to treatment of acute GVHD is the main outcome of interest for future testing of the collected samples.

For each assessment period all medications given for GVHD prevention and/or treatment are collected.

Through Day 100 when the diagnosis of GVHD is uncertain, or when GVHD is present, but there is more than one simultaneous possible cause of GVHD symptoms (e.g. C. difficile infection in the setting of proven GI GVHD), all etiologies, proven and possible, as part of recording diagnostic certainty in the database (definite, probable, uncertain) for future analyses will be collected.

Weekly GVHD staging and treatment will be collected from Day 0 to Day 100 will be collected using the BMT CTN AdvantageEDC data reporting system. After Day 100, acute GVHD assessments are reported on CIBMTR forms 2100 and 2200 at Days 100, 180, 1 year and 2 years using FormsNet.

3.2.Chronic GVHD

The date of onset, severity, target organ involvement, and evolution of chronic GVHD through the first 2 years post-HCT Chronic GVHD assessments at Day 100, 180, 1 year and 2 years are submitted using both AdvantageEDC and FormsNet. The BMT CTN Chronic GVHD Provider Survey (see BMT CTN 1202 Biomarker Data Management Handbook) is submitted via AdvantageEDC. Additional information regarding chronic GVHD will be collected on the CIBMTR forms 2100 and 2200 and submitted using FormsNet.

3.3.Infection

Only Grade 3 severe infections occurring through Day 100 will be collected. These include:

Grade 3 Bacterial Infections:

a. Bacteremia with deep organ involvement
b. Severe sepsis with bacteremia
c. Fasciitis requiring debridement
d. Pneumonia requiring intubation
e. Brain abscess or meningitis without bacteremia
f. *Clostridium difficile* toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea.

Grade 3 Fungal Infections:

a. Fungemia, including candidemia
b. Proven or probable invasive fungal infections (e.g. Aspergillus, Mucor, Fusarium, Scedosporium)
c. Disseminated fungal infections
d. *Pneumocystis jiroveci* pneumonia

Grade 3 Viral Infections:

a. Severe VZV infection with either associated coagulopathy or organ involvement
b. CMV end organ involvement
c. EBV Post-transplant lymphoproliferative disorder (PTLD)
d. Adenovirus with end organ involvement (except adenoviral conjunctivitis or upper respiratory tract disease)
e. All lower respiratory tract viruses
f. Viral encephalitis or meningitis

The infections will be reported on an event driven basis using the BMT CTN AdvantageEDC data reporting system**.**

3.4.Relapse/Progression

Recurrence or progression of the disease for which HCT was performed through 2 years post-HCT

Research sample collection is discontinued in patients who relapse within the first 100 days post-HCT therefore relapses that occur within 100 days post-HCT will be reported through the BMT CTN AdvantageEDC system. Relapse/Progression occurring after Day 100 will be reported using CIBMTR post-HCT disease specific forms at Days 100, 180, 1 year, and 2 years.

3.5.Acute Liver Injury/SOS/Kidney Injury

The diagnosis of veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS) is defined using the Baltimore criteria:[1]

Total bilirubin ≥ 2 mg/dL and either a liver biopsy showing VOD or SOS **OR** at least 2 of the following 3:

- Ascites
- Weight gain ≥5% above baseline weight
- Hepatomegaly, or presence of a liver biopsy showing VOD or SOS

The diagnosis of thrombotic microangiopathy (TMA) is defined using BMT CTN consensus criteria[2] which requires the presence of:

- RBC fragmentation and ≥2 schistocytes per high-power field on peripheral smear
- Concurrent increased serum LDH above institutional baseline
- Concurrent renal and/or neurologic dysfunction without other explanations
- Negative direct and indirect Coombs test results

Renal dysfunction is considered as either a doubling of serum creatinine from baseline (where baseline is the serum creatinine before hydration and conditioning) or 50% decrease in creatinine clearance from baseline.

VOD/SOS and TMA will be collected on CIBMTR Form 2100 on Day 100 using FormsNet.

3.6.Lung Injury

The occurrence of lung injury as defined below will be collected through 2 years post-transplant.

The diagnosis of Idiopathic Pneumonia Syndrome (IPS) is defined by NIH Consensus Criteria[3] and requires all three of the following criteria:

- Multilobar infiltrates on chest radiograph (CXR) or computed tomography (CT) that are not due to fluid overload.
- Presence of clinical symptoms (hypoxia, requirement for supplemental oxygen, dyspnea, cough, or rales).
- Absence of lower respiratory tract infection (by broncho-alveolar lavage [BAL] or surgical lung biopsy).

Bronchiolitis Obliterans Syndrome (BOS) is defined using NIH Consensus Criteria[4] and requires all the following criteria to be met:

- Forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio < 0.7 and FEV1 < 75% of predicted.
- Evidence of air trapping or small airway thickening or bronchiectasis on chest CT, **OR** residual volume > 120%, **OR** pathologic confirmation of constrictive bronchiolitis.
- Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or computed tomographic

scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or bronchoalveolar lavage).

COP was previously termed bronchiolitis obliterans with organizing pneumonia (BOOP). No consensus criteria for COP have been established following HCT, but recommendations have been published and will be used for this study.[5] The diagnosis of COP can be made on the basis of:

- Lung biopsy showing organizing pneumonia **OR** both of the following:
- Radiographic evidence of patchy or diffuse, "fluffy" consolidations, ground glass opacities, and/or nodules on chest radiograph or CT scan
- Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or computed tomographic scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or bronchoalveolar lavage)

Pulmonary function tests are NOT required to make the diagnosis of COP, but commonly reveal a forced vital capacity < 80% predicted (a restrictive defect).

Lung injury data will be collected using CIBMTR forms 2100 and 2200 at Days 100, 180, 1 year and 2 years using FormsNet.

3.7.Transplant-related Mortality (TRM)

TRM is defined as death from causes other than relapse/progression of the disease for which the transplant was performed.

Transplant-related mortality/Death is reported using CIBMTR Forms 2900 and post-HCT disease specific forms using FormsNet at whichever time point (Day 100, 180, 1 year, or 2 years) occurs first after death up to 2 years post-HCT. The date and primary and contributing causes of death will be captured.

3.8.Graft Failure

Graft failure is not an endpoint on this study, but requires definition because research sample collection is discontinued in subject who experience graft failure.

Graft failure is defined as failure to ever engraft neutrophils (persistent ANC < 500/mm^3) or irreversible decline (without additional cell infusions) to ANC < 500/mm^3 following an initial engraftment. Graft failure should not be declared prior to Day 28 for marrow or peripheral blood transplants or prior to Day 42 for cord blood transplants. An exception to this rule is if the treating center determines graft failure occurred earlier than these timepoints AND additional cells were infused (ie, subsequent HCT). Late graft failure (neutropenia following initial engraftment) should only be declared if the ANC is consistently below 500/mm^3 and the neutropenia is persistent.

3.9.Real-Time GVHD Data Analysis

Near real-time (8-10 weeks post diagnosis) data reviews of GVHD onset data will identify and resolve inconsistencies in interpretation of GVHD signs and symptoms between centers, thereby improving the quality of GVHD staging and facilitating the correlation of GVHD serum biomarkers at GVHD onset with outcomes, such as maximum severity, response to treatment and non-relapse mortality. These reviews will act as a surrogate to a single continuity grader used to resolve inconsistencies among attending physicians. The value of "near real-time analyses" will be assessed by recording all cases where the staging by the adjudication panel differed from the participating center. The number of cases where adjudication differs from the participating center will be compared to the same rate on other BMT CTN studies where this type of review is typically done after accrual is complete.

CHAPTER 4

4. ENROLLMENT, DATA COLLECTION AND SAMPLE COLLECTION/ PROCESSING

4.1.Enrollment Procedures

Patients will be registered using the BMT CTN AdvantageEDC system. Prior to initiation of conditioning regimen, an authorized user at the transplant center enters the patient demographics, consent date, and proposed start date for conditioning into Segment A in AdvantageEDC.

The planned transplant date will dictate when pre-transplant samples should be collected. The actual transplant date will be captured in the transplant form and dictate when post-transplant samples and clinical data will be collected.

A visit schedule based on transplant date is displayed for printing and is referred to as 'Segment A Follow-up.'

4.2.Study Monitoring

4.2.1. Follow-up Schedule

The follow-up schedule for calendar-driven study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the BMT CTN 1202 Biomarker Data Management Handbook.

Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data and Coordinating Center's (DCC) master database or until an exception is granted and entered into the Missing Form Exception File, as detailed in the BMT CTN AdvantageEDC^{SM} User's Guide.

All subjects participating in BMT CTN 1202 must also participate in the NMDP/CIBMTR research database study "Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries," as described in Chapter 2.

Table 4.2.1: Follow-Up Schedule

Study Visit	Target Day (± 3 Days to Day 100 Post-HCT) (± 28 Days After Day 100 Post-HCT)
1 week	7 days
2 week	14 days
3 week	21 days
4 week	28 days
5 week	35 days
6 week	42 days
7 week	49 days
8 week	56 days
9 week	63 days
10 week	70 days
11 week	77 days
12 week	84 days
13 week	91 days
14 week	100 days
6 month	180 days
1 year	365 days
2 year	730 days

4.2.2. Data Collection and Patient Assessments

Patient assessments occur according to the schedule in Table 4.2.1 above. The data collection associated with these assessments is listed in Table 4.2.2.

TABLE 4.2.2: BMT CTN 1202 Form Submission Schedule

Form	Baseline	Time Post-Transplant																	
		0	7	14	21	28	35	42	49	56	63	70	77	84	91	100	6 month	1 yr	2 yr
Enrollment Form	X																		
CIBMTR Recipient ID Form	X																		
Transplant Form		X																	
Acute GVHD Weekly Assessment Form			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Acute GVHD Supplemental Form			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Chronic GVHD Provider Survey																X	X	X	X
Laboratory Form [1]					X					X					X				
Specimen Acquisition Form		X	X	X	X	X		X		X					X				
Death Form	Event-driven form when Death occurs prior to Day 100																		
Graft Failure Form	Event-driven form when Graft Failure occurs prior to Day 100																		
Relapse Form	Event-driven form when Relapse/Progression occurs prior to Day 100																		
Infection Form	Event-driven form for all Grade 3 severe infections prior to Day 100																		
CIBMTR 2400[2]	X																		
CIBMTR 2000, 2004, 2005, 2006, disease specific form[2]		X																	
CIBMTR 2100[3]																X			
CIBMTR 2200[3]																	X	X	X
CIBMTR Disease-Specific Inserts[4]																X	X	X	X
CIBMTR 2900	Event-driven at time of death																		

Notes:

[1] Complete blood count and differentials are submitted **only** for the patients (n=240) who are providing PAXgene samples at Days 21, 56 and 90. The CBC reported should be from the day the sample is collected and need not be on the same day as the weekly GVHD assessment

[2] Used to capture baseline, pre-transplant and transplant data, including conditioning regimen and GVHD prophylaxis

[3] Used to capture acute and chronic GVHD post Day 100, as well as lung injury, VOD/SOS, TMA

[4] Used to capture relapse/progression post Day 100

4.2.2.1.Pre-transplant evaluations

No required pre-transplant evaluations are defined.

4.2.2.2.Post-transplant evaluations

Post-transplant evaluations will include:

1. Physical exam to assess GVHD and other morbidity weekly until Day 100 post-transplant, then at Days 180, 365, and 730 post-transplant. GVHD evaluation and grading to be in keeping with the BMT CTN 1202 Data Management Handbook.
2. **For the Gene expression subset only**: Complete blood counts, including white blood cell count, hemoglobin, platelet count, and differential, obtained on the same day as the PAXgene sample collection are submitted using AdvantageEDC, approximately Days 21, 56 and 90.
3. Disease status evaluation as clinically indicated.
4. Fractionated lymphoid and myeloid chimerism is recommended around Days 28 and 90.
5. All other evaluations should follow institutional guidelines**.**

4.2.3. Adverse Event Reporting

Reportable adverse events in this protocol are only those directly linked to the blood draw.

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

4.3.Collection of Research Blood Samples

4.3.1. Collection of Donor Samples

Collection of donor samples will be via NMDP Research Repository Program Genetic and Proteomic Studies.

This protocol leverages an existing institutional review board (IRB)-approved protocol for pre-transplant patient (see Section 4.3.2 below) and pre-donation donor (or cord blood unit) sample collection managed by the NMDP and CIBMTR. Pre-donation blood samples for genetic and proteomic studies are collected on all consenting related or unrelated donors.

4.3.2. Collection of Recipient Samples

The schedule for recipient sample collection is shown in Table 4.3.

Table 4.3: BMT CTN 1202 Recipient Sample Collection Schedule

Biomarker Approach	Sample Type	Subjects	Pre-HCT Day -1 or 0	Days Post-HCT						
				7 ± 2	14 ± 2	21 ± 2	28 ± 2	42 ± 3	56 ± 3	90 ±10
Proteomic	Serum (5 mL blood)	All Patients[1]	X	X	X	X	X	X	X	X
	EDTA Plasma (5 mL blood)		X	X	X	X	X	X	X	X
Gene Expression	PAXgene Lysates-stabilized whole blood RNA (15 mL blood)	240 Patients[2]				X			**X**	X
	CytoChex tube for Immunophenotyping (5 mL blood)	240 Patients[2]				X			**X**	X

Notes:
[1] Subjects weighing between 10 and 20 kg will only be required to provide a 5 mL blood sample (2.5 mL into a red-top tube for serum and 2.5 mL into an EDTA tube for plasma) for proteomic studies.
[2]This is a subset of the enrolled patients and will require additional samples to be collected at Days 21, 56 and 90 for gene expression studies. All proteomic samples will be collected per protocol for these patients.

Additionally, pre-conditioning recipient samples for genetic studies are collected via the NMDP "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries." Recipients **must consent** to that NMDP study in order to participate in BMT CTN 1202.

4.3.3. Collection of Patient Serum Samples for Proteomic Studies

Pre- and post-transplant patient peripheral blood samples will be collected at each of the calendar-driven time points in Table 4.3. The 10 mL peripheral blood samples (5 mL for patients weighing between 10 and 20 kg) will be split equally into Vacutainer tubes containing no anticoagulant (for serum) and EDTA anticoagulant (for plasma) shipped same-day to the BMT CTN Research Sample Repository for next-day sample processing and plasma and serum aliquot storage. A combined maximum of 20 0.250 mL serum and plasma cryovial aliquots will be prepared and stored at -80º C.

4.3.4. Collection of Patient Peripheral Blood RNA for Gene Expression Studies

Post-transplant patient samples will be collected from 240 patients enrolled on the study at each of the three calendar-driven time points shown in Table 4.3. A sub-set of 240 patients will be selected for the additional blood volume collection for WBC RNA gene expression studies. To enable the most robust correlative evaluation of the HCT transcriptome, the aim is to have this smaller subset of patients be more homogeneous and to represent the *most common* characteristics of HCT recipients. Enrollment will include consecutive patients with acute leukemia in remission pre-HCT, thereby excluding patients likely to relapse early after HCT, and

ensuring that adequate numbers of patients will be informative for risk assessment of transplant-related complications. Enrollment will continue until 240 patients are enrolled.

A 15 mL peripheral blood sample will be collected in six 2.5 mL-fill PAXgene blood RNA tubes (provided by the BMT CTN) and shipped same day to the BMT CTN Research Sample Repository for sample processing and long-term storage at -80º C. The BMT CTN Repository will process each PAXgene tube according to manufacturers' protocol for long-term storage at -80º C for a source of stabilized RNA for future studies.

An additional 5 mL peripheral blood sample will be collected in a 5 mL CytoChex tube (provided by the BMT CTN) and shipped same day to the 1202 protocol immunophenotyping laboratory. The fixative in the CytoChex tube stabilizes the WBC cell-surface markers during the transport of the sample to the laboratory. The purpose of the immunophenotyping is to characterize the WBC content of the stored PAXgene lysate samples to support future RNA expression studies. This data will be sent back to the BMT CTN Repository and stored in a secure 1202 protocol sample information database. The flow cytometry data will be provided to future investigators utilizing the PAXgene lysate samples for approved ancillary studies.

4.3.5. Sample Collection in the Event of Relapse/Progression/Graft Failure

Patients who undergo HCT for malignancy and who experience graft failure, relapse or have progressive disease within the first 100 days will **stop sample collection and BMT CTN 1202 forms submission via AdvantageEDC**. These patients will continue to submit required CIBMTR forms as part of the separate CIBMTR data collection. In order to ensure adequate numbers of patients for future analyses (90% of the planned sample size), if more than 150 patients experience graft failure or relapse in the first 100 days, additional patients will be enrolled to replace those patients who experience graft failure or relapse within the first 100 days beyond the first 150. Relapse/progression is defined as in CIBMTR HCT disease specific forms. Graft failure is defined in Section 3.8.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

The purpose of this study is to collect samples for future studies. Without specific research plans, we have modeled, for illustrative purposes, power calculations for genome-wide association studies (GWAS), proteomic and transcriptional studies that can potentially be conducted in the future assuming various settings.

5.1.Genetic/DNA Sample Sets and Future Studies

The DNA resource created by this proposal would not be of sufficient size for a stand-alone GWAS discovery study, but it could contribute significantly as an independent study population for candidate gene validation studies or for validating 'hits' from GWAS discovery studies. The decreasing cost of customized arrays such as the ImmunoChip and exome sequencing of selected genes, increases the likelihood that a well characterized cohort like the one we propose will become an important addition to the growing global "genetic and phenotype database (dbGaP)" maintained by the National Center for Biotechnology Information. A sample size of 1500 would be sufficient for candidate gene validation studies of common variants and common phenotypes. Suppose we want to focus on acute GVHD as the primary outcome and plan to perform separate analyses for recipients of related and unrelated HCT. Assuming approximately equal proportions of patients with related donor and unrelated donor results in 750 patients with each donor type. The patients in each donor-type group will be divided into two equal groups of 375 for testing and validation. Table 5.1 shows the difference in cumulative incidence of acute GVHD between genotypic polymorphisms that can be detected with 80% power with a sample size of 375. In this scenario, the outcome is defined as the cumulative incidence (p) of experiencing acute GVHD at 6 months, which may range from 20% for grade 3-4 aGVHD to 50% for grade 2-4 aGVHD. The power calculations were based on a Chi-square test of binomial proportions assuming the markers have dominant effect on the outcome. The detectable differences were computed for various outcome probabilities, minor allele frequencies (MAF), and number of SNPs being tested simultaneously using a two-sided overall type I error rate of 0.05 with Bonferroni correction for multiple comparisons. In general, validation sample sizes of 375 in each donor type provide sufficient power to detect a minimum difference ranging from 14% to 18% with 1 SNP, ranging from 18% to 23% with 10 SNPs, and from 22% to 28% with 100 SNPs.

Table 5.1: Detectable Difference with 80% Power

Outcome probability (*p*)	1 SNP		10 SNPs		100 SNPs	
	10% MAF	20% MAF	10% MAF	20% MAF	10% MAF	20% MAF
.20	.17	.14	.23	.18	.28	.22
.50	.18	.15	.23	.20	.28	.23

5.2.Proteomic Studies

One of the major goals of proteomic studies is to identify biomarkers or biomarker panels which can reliably predict patient's prognosis, and to confirm their accuracy of prediction. Therefore, we assessed the ability of the proposed resource to support such modeling and validation studies. In the context of future serum biomarker studies, modeling and validation may be conducted by stratifying patients by conditioning regimen (MA vs. NMA) and donor type (HLA-Identical sibling [ID sibs] vs. matched unrelated donor [MUD] vs. mismatched unrelated donor [MMUD]), resulting in 6 separate subpopulations for potential modeling and validation. Using CIBMTR data, we estimate that 26% of patients receive MA Sibs transplant, 19% NMA Sibs, 22% MA MUD, 19% NMA MUD, 8% MA MMUD, and 6% NMA MMUD. Assuming patients in this study follow a similar subpopulation distribution, and after splitting each subpopulation into testing and validation sets, we expect to have 195 MA Sibs, 144 NMA Sibs, 165 MA MUD, 144 NMA MUD, 59 MA MMUD, and 43 NMA MMUD available for analysis. In the validation stage, researchers are interested in prediction accuracy of the biomarker levels for subsequent clinical outcomes, described through sensitivity and specificity. Table 5.2 shows the widths of 95% confidence intervals for these measures when the clinical outcome has probabilities ranging from 20% to 50% for each subpopulation assuming an underlying specificity of 75% and sensitivity of 70%. In general, there are sufficient sample sizes in the groups receiving matched sibling and matched unrelated donor transplant to estimate specificity and sensitivity with reasonable precision.

Table 5.2: Width of 95% Confidence Interval for Specificity and Sensitivity

Outcome probability (*p*)	Underlying probability	HLA-id Sibs		Matched Unrelated		Mismatched Unrelated	
		MA (n=195)	NMA (n=144)	MA (n=165)	NMA (n=144)	MA (n=59)	NMA (n=43)
20%	Specificity (75%)	.14	.16	.15	.16	.25	.29
	Sensitivity (70%)	.29	.34	.31	.33	.52	.61
50%	Specificity (75%)	.17	.20	.19	.20	.31	.37
	Sensitivity (70%)	.18	.21	.20	.21	.33	.39

5.3.Transcriptional Gene or Protein Expression Studies (240 patient subset)

Typically gene expression microarray studies are conducted with modest sample sizes.[6, 7] For example, consider a case control design comparing expression levels between those with acute GVHD and those alive without aGVHD. The power depends on the fold change in expression level as well as the coefficient of variation (CV), defined as the ratio of the standard deviation of the expression level to its mean. Sample sizes to detect a 2-fold change are given in the table below for CV values of 0.25 and 0.5 for various significance levels to account for multiple testing of genes.

Table 5.3: Sample Sizes Needed to Detect a 2-Fold Change in Expression Levels

CV	P<0.01	P<0.001	P<0.0001
0.25	10	16	20
0.5	26	38	50

The sample sizes needed to support gene expression studies are typically small, we propose to collect 240 donor and patient samples for this resource. We plan to obtain carefully matched case and control samples, particularly for less common indications, transplant types, or donor types. Table 5.4 shows the expected number of samples available for several transplant types or donor types from these 240 samples, based on recent CIBMTR data and assuming simple random sampling of gene expression samples. This size resource will provide reasonable numbers of samples even for less common settings. Although oversampling of rare indications is an alternative way to increase our available samples for those settings, we do not consider that here. This is because it is likely that even the more common transplant types display substantial heterogeneity which it is desirable to control, and having a larger set of samples to select from will help reduce heterogeneity. Finally, note that in addition to case control studies comparing gene expression between those developing GVHD and those without, collection of both donor and recipient samples will facilitate studies comparing expression levels between the donor and recipient.

Table 5.3.1: Expected Demographic Characteristics of Patient/Donor Pairs for 240 Gene Expression Samples

	Related Donor	Unrelated donor		
		PB or BM		UCB
		Matched	Mismatched	
Myeloablative conditioning	60	46	17	16
RIC/NST conditioning	45	37	11	9

5.4.African American Cohort

Table 5.4 shows the minimum detectable difference in gene frequency among African American recipients compared to Caucasian recipients with at least 80% power for a sample size of 200 African Americans and 1200 Caucasians. The detectable difference was calculated for various gene frequencies among Caucasians and for various numbers of genes being tested simultaneously using a two-sided overall type I error rate of 0.05. Bonferroni correction was used to correct for multiple comparisons in scenarios where two or more genes are being tested simultaneously. When only one gene is considered, the proposed sample size provides sufficient power to detect a minimum difference of 8% - 11% in gene frequency in African American recipients compared to Caucasian recipients. When the frequencies of 50 genes are compared simultaneously, this study is powered to detect a minimum change of 13% - 16%.

Table 5.4 Detectable difference in gene frequency among African American recipients compared to Caucasian recipients with 80% power

Number of genes	Gene frequency in Caucasian population				
	10%	20%	30%	40%	50%
1	08%	10%	11%	11%	11%
5	10%	12%	13%	13%	13%
10	11%	13%	14%	14%	14%
50	13%	15%	16%	16%	16%

5.5.Pediatric Cohort

One of the hypotheses to address is whether the concentration of GVHD biomarkers is lower in children than in adults at the time of GVHD onset. The power to detect a two-fold difference in biomarker concentration with a coefficient of variation (CV) of 2 was calculated for various rates of grade II- IV GVHD (Table 2) using a two-sided overall type I error of 0.05. Bonferroni correction was used to correct for multiple comparisons in scenarios where two or more biomarkers are being compared simultaneously. Assuming Grade II – IV GVHD occurs in 45% of children and 50% of adults, there is more than 90% power to detect a two-fold difference in biomarker concentration between children compared to adults when up to 50 biomarkers are compared simultaneously. When Grade II – IV GVHD occurs in 35% of children and 40% of adults, there is more than 90% power to detect a difference of this size when up to 10 biomarkers are compared simultaneously and there is 83% power when 50 biomarkers are compared simultaneously.

Table 5.5 Power to detect a two-fold difference in biomarker concentration between children and adults with CV=2

Number of biomarkers tested	GVHD probability in Children vs. Adults (n_1 = number of children, n_2 = number of adults)		
	45% vs. 50% (n_1=90, n_2=650)	40% vs. 45% (n_1=80, n_2=585)	35% vs. 40% (n_1=70, n_2=520)
1	.99	.99	.98
5	.98	.97	.95
10	.97	.96	.92
50	.93	.89	.83

APPENDIX A

HUMAN SUBJECTS

1. Patient Consent

A conference will be held with the patient and family to discuss this study. The Principal Investigator or another designated physician will conduct the conference. The consent document should be reviewed with the patient and family.

Informed consent from the patient will be obtained using a form approved by the Institutional Review Board of the institution enrolling the patient.

2. Confidentiality

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

APPENDIX B

INFORMED CONSENT and ASSENT FORMS

Informed Consent to Participate in Research

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)

Your Name: _____

Study Title: Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)

Protocol: BMT CTN #1202

Principal Investigator:

Principal Co-Investigator:

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

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

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this study because we want to learn more about what makes related and unrelated (allogeneic) bone marrow, blood stem cell and umbilical cord blood transplants work well.

This study will include at least 1,500 participants enrolled over a 4 year period. Your study participation will last for 2 years after your transplant.

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

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

2. Study Purpose

We invite you to join this research study because you are already receiving a transplant. For this study, we are collecting health information and extra blood samples from transplant patients, like you. If you agree to join the study, we will ask for: 1) information about your health after your transplant (such as graft-versus-host disease (GVHD)) and 2) samples of your blood before and after your transplant that we will use in future research studies.

We will use your health information and blood samples in future studies, but we don't know what the studies will be about right now. For example, we may use your health information and blood samples to learn more about graft-versus-host disease (GVHD) or cancers that come back (relapse). Your health information and blood samples may also be used for studies that aren't about transplant.

3. Right to Ask Questions and/or Withdraw

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

[insert contact info for site PI]

If you decide not to continue being in the study, you may choose not to allow future blood samples or data collection. You can also decide to have any blood samples you already provided destroyed; however, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

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

You do not waive any legal rights by signing this form.

Your study doctor may decide to remove you from being in the study without your permission if your study doctor feels it is in your best interest.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study

4. Your Health Information and Blood Samples

If you agree to provide your health information and blood samples for future research, here is what will happen:

a.) Your health information (this will not include personal information such as your name) will be collected during the 2 years you are participating and given to the BMT CTN. This information will be tied to your blood samples and will be made available to researchers for future studies.

b.) We will collect blood samples before and after transplant.

- Before your transplant: We will collect about 1 tablespoon of blood 1 time.
- After your transplant: We will collect about 2 tablespoons of blood 7 times over 90 days. Each blood draw will be about 1-2 weeks apart.
- The blood will be drawn either from a central line or from a vein in your arm.

c.) The blood samples will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores and sends out samples for approved research studies. All research samples will be coded. A small sample of your blood may be sent to a laboratory partnering with BMT CTN Repository to count and describe the different white blood cell types in the sample. This information will be sent back to the Repository and stored with the other sample-related information.

d.) Materials stored in the Repository will be used mainly by doctors and researchers in the BMT CTN network. In the future, the unused blood samples and health information will be made available outside of this network (see section ‘e’ below).

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

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

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). It is very unlikely that the NCBI could identify you, or link you to your information or research samples.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

5. Risks and Discomforts

The risk of injury while being in this study is considered small.

If your blood samples are collected from your arm (instead of your central line), you may bleed a little bit and/or develop a small bruise. Infection from blood draws is rare, but may happen. If you are uncomfortable at the sight of blood you may feel light-headed or faint.

A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and health information to make sure that your personal information will be kept private. It's very unlikely that your personal information will be given to someone else (see the Privacy, Confidentiality and Use of Information section below).

6. Possible Benefits

Taking part in this study will not make your health better. You will not get any direct benefit from taking part in this study. The information from this study will help doctors and researchers learn more about how well unrelated transplant works as treatment for people with a blood disease.

This information could help people with a blood disease who may need a transplant in the future.

7. Privacy, Confidentiality and Use of Information

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

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

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Some of your health information will be taken from another research database you signed up for called the "Research Database for Hematopoietic Cell Transplantation and Marrow Toxicities."

Information about your transplant from your original medical records may be seen by or sent to the following organizations:

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

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

This data bank can be accessed by you and the general public at:

www.ClinicalTrials.gov. Federal law requires study information for certain studies to be submitted to the data bank.

8. Physical Injury as a Result of Participation

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

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

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

9. Payment

You will not be paid for taking part in this study.

10. Costs and Reimbursements

It will not cost you anything to participate in this study. You or your insurance will not be charged for tests that are only done for this study.

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

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

11. Questions about Your Rights

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

12. HIPAA

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose research purpose

A. Purpose:

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

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)

B. Individual Health Information to be Used or Disclosed:

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

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

C. Parties Who May Disclose My Individual Health Information:

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

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

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

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

Principal Investigator and the researcher's staff

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

Study Sponsors

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

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

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study. My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time.

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

G. Potential for Re-disclosure:

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

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

H. Genetic Information Nondiscrimination Act (GINA)

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

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

I. This authorization does not have an expiration date.

13. Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below.

If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

Statement of Consent for Research Samples

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

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

I voluntarily agree that my blood and health information can be stored indefinitely by the BMT CTN Repository for research to learn about, prevent, or treat health problems.

- ❑ I agree to allow my health information and blood samples to be stored for research.
- ❑ I do not agree to allow my health information and blood samples to be stored for research.

_____ _____

Signature Date

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with donation of blood samples to the BMT CTN Repository 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: _____ Date: _____

An oral translation of this document was administered to the subject in _____ (state language) by an individual proficient in English and _____ (state language).

Pediatric Assent to Participate in Research

Study Title: Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)

Protocol: **BMT CTN 1202**

A. Why am I here?

We invite you to join this research study because you are already receiving a transplant. For this study, we will ask you for information about your health (health information) and extra blood samples.

B. Why are you doing this study?

We are collecting health information and blood samples from transplant patients, like you, to learn more about what makes transplants work well. We will use your health information and blood samples in future research studies.

C. What will happen to me if I join the study?

If you say you want to be in the study, we will ask you for a few things:

- Information about your health after your transplant.
- Some blood samples before and after your transplant.
  - Before your transplant: We will collect about 1 tablespoon of blood 1 time.
  - After your transplant: We will collect about 2 tablespoons of blood 7 times over 90 days. Each blood draw will be about 1-2 weeks apart.

We will use a small needle to collect the blood from a vein in your arm or we will collect it from your central line.

You will be in the study for about 2 years after your transplant. The study will include at least 1,500 people.

D. Will the blood draw hurt?

If we collect your blood from a vein in your arm, it may feel like a pinch. It will hurt for a minute and the place where the needle went may be red and sore. You may get a little bruise from the needle, but it will go away in a few days.

E. What if I have questions?

You can ask any questions that you have about the study. If you forget to ask a question and think of it later, you can call me:

[*insert office number*].

You can also ask your question the next time you see me.

You can call the study office at any time to ask questions about the study.

F. How will you use my health information and blood samples?

We will use your health information and blood samples in future studies, but we don't know what the studies will be about right now. Doctors may use your health information and blood samples to learn more about how people respond to transplant. Your health information and blood samples may also be used for studies that aren't about transplant.

G. Who will use my health information and blood samples?

Your blood samples will be used by doctors and researchers with the BMT CTN. If your blood samples aren't used, other researchers can ask for permission to use them. The BMT CTN will say if your blood samples can be used by other researchers. They do this to make sure your blood samples are being used correctly.

H. How will you store my health information and blood samples?

Your blood samples will be kept at a place called the BMT CTN Repository. A repository is a place that protects, stores and sends out blood samples for research studies.

All research samples will be tied to a number. This number will not be linked to your name or other identifying information.

I. Will the study help me?

This study will not help you, but it may help other people who need a transplant in the future.

J. Will I be paid to be in the study?

No, you will not be paid to be in the study. It will not cost you anything to be in the study either.

K. Do I have to be in this study?

If you do not want to be in the study, you need to tell us and your parent or guardian.

Your doctor will not be angry or upset if you do not want to join. You will still need to have treatment for your disease.

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

Please talk this over with your parents before you decide if you want be in the study. We will also ask your parents to give their permission for you to join this study.

Writing your name on this page means that you agree to be in the study and know what will happen to you.

If you decide to quit the study, all you have to do is tell the person in charge.

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

Signature of Child	Date
Signature of Researcher	Date

APPENDIX C

REFERENCES

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