A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other indications

Protocol Number: 10-CBA

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PROTOCOL SYNOPSIS – PROTOCOL 10-CBA

A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other indications

Principal Investigators:
The principal investigators (PIs) are transplant physicians at all participating U.S. transplant centers (TCs).

Study Design:
This study is an access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) in pediatric and adult patients with hematologic malignancies and other indications.

Primary Objective:
The primary objective of this study is to examine the incidence of neutrophil recovery of $\geq 500/mm^3$ after cord blood transplantation in a multi-institution setting using CBUs that are not Food and Drug Administration (FDA) licensed.

Secondary Objectives:
The secondary objectives are as follows:
- Assess incidence of transmission of infection
- Assess incidence of serious infusion reaction
- Determine overall survival 1 year after cord blood transplantation
- Assess cumulative incidence of acute graft vs. host disease (GVHD) grades II to IV and grades III to IV
- Assess cumulative incidence of chronic GVHD
- Determine platelet engraftment of >20,000 mcL and >50,000 mcL

Eligibility Criteria:
Inclusion Criteria
- Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
- Signed informed consent (and signed assent, if applicable) obtained prior to study enrollment
- Pediatric and adult patients of any age

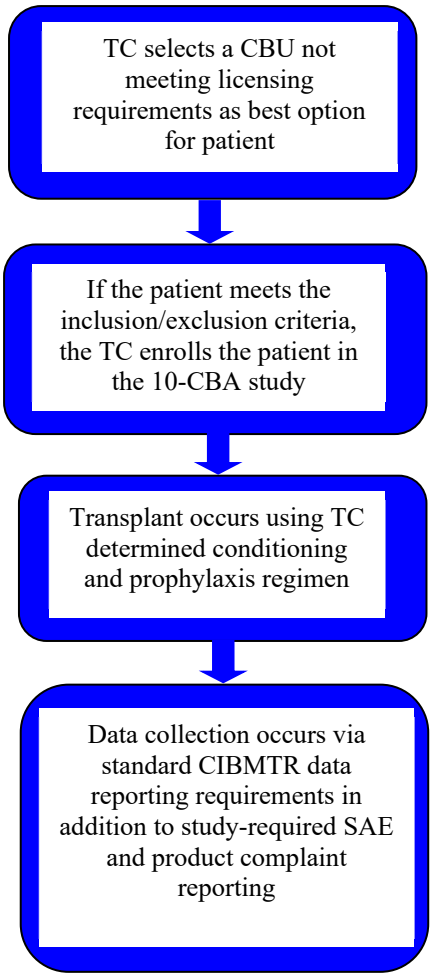
Exclusion Criteria
- Patients who are receiving only licensed CBUs
- Cord blood transplant recipients at international TCs
- Patients who are enrolled on another Investigational New Drug Application (IND) protocol to access each unlicensed CBU
- Patients whose selected unlicensed CBU(s) will be more than minimally manipulated

Treatment Description:
Treatment, including pre-transplant conditioning and GVHD prophylaxis, will occur per each TC's specifications.

Accrual Objective:
In this access and distribution protocol, U.S. patients undergoing transplantation with unlicensed CBUs will be enrolled and there is no accrual maximum.

Accrual Period:
The accrual period is open ended.

STUDY SCHEMA



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CHAPTER 1

1. BACKGROUND AND RATIONALE

Background

Hematopoietic stem cell transplantation (HSCT) is now recognized as an effective form of therapy for an increasing number of malignant and non-malignant disorders (1). Human umbilical cord blood (UCB) is an alternative source of hematopoietic stem cells (HSCs) that is capable of reconstituting hematopoiesis after intensive myeloablative therapy, thereby extending the unrelated donor pool (2-10).

Cell dose is the most important factor affecting clinical outcomes in adult patients undergoing transplantation with a single CBU (11-14). Transplantation with a cell dose of less than 2.5×10^7 nucleated cells per kilogram or a CD34 dose of less than 1.7×10^5 per kilogram is associated with higher rates of non-engraftment, non-relapse mortality (NRM) and lower survival (14). In pediatric patients, 5-year leukemia free survival following transplantation of CBU(s) with a single or double human leukocyte antigen (HLA) mismatch was comparable to transplantation with matched or single HLA-mismatched marrow and survival was possibly higher with fully HLA-matched cord blood (15). In adult patients, transplantation with CBU(s) with up to 2 HLA mismatches had comparable leukemia-free survival to transplantation with matched or single HLA-mismatched unrelated peripheral blood stem cells (PBSC) and marrow (16). However, in patients receiving cord blood, transplant-related mortality (TRM) was higher and grades 2-4 acute GVHD was lower than in patients receiving fully matched PBSC or marrow.

UCB has advantages when compared to grafts from adult cell sources including being rapidly available, having low rates of viral contamination, and having lower probabilities of severe acute and extensive chronic GVHD despite the use of HLA-mismatched grafts. However, a major disadvantage is that low graft cell dose in adult recipients leads to delayed hematopoietic recovery, an increased risk of graft failure and increased risk for TRM, which limits the application of UCB transplant in adults. Barker and colleagues at The University of Minnesota has investigated the novel approach of the combined transplantation of two CBUs in a double unit graft after myeloablative conditioning as a strategy to augment graft cell dose (17). In this study, all 21 patients receiving two CBUs engrafted at a median of 21 days and while both CBUs engrafted initially, by Day 100 one CBU predominated. Subsequent studies have demonstrated decreased relapse, increased NRM and similar leukemia-free survival in recipients of double cord transplants when compared to patients receiving matched unrelated or matched related PBSC and marrow (18-20).

These and other studies demonstrate that UCB is safe and effective for transplantation. Based on this clinical evidence the FDA has released criteria that will allow CBUs that meet the criteria to be distributed as a licensed biologic drug.

Rationale

In 1997, the FDA announced a risk based approach to the regulation of human cellular and tissue-based products including UCB (21, 22). The approach was finalized as the three final rules for Human Cells, Tissues, and Tissue-Based Products (HCT/Ps) that were effective on March 29, 2004 (requirement for establishment registration) and on May 25, 2005 (donor eligibility and

Good Tissue Practices) (23-25). These rules were designed to: prevent the transmission of communicable disease, minimize contamination and preserve integrity and function during processing, outline safety and effectiveness requirements for cells from unrelated donors or when HCT/Ps are more than minimally manipulated, assure labeling is clear, accurate and not misleading and monitor and communicate with industry via establishment registration (22). In October 2009, the FDA released a final licensure guidance entitled *Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*, which outlines ways a cord blood bank (CBB) may apply for licensure of unrelated, allogeneic CBUs (26). CBBs may submit a biologics license application (BLA) to manufacture licensed CBUs as defined in the guidance for specified hematologic and non-hematologic disorders. CBUs meeting the criteria will be considered licensed and will be able to be distributed as a licensed biological drug.

However, as of October 20, 2011, those CBUs that do not meet the manufacturing requirements for licensure can only be distributed for transplantation if the transplant will occur under an IND research protocol. These CBUs are in current and future inventory at domestic and international CBBs that can't be demonstrated to meet licensing requirements.

In addition to the licensure guidance, the FDA published a companion guidance in August 2011 entitled *Investigational New Drug Applications (INDs) for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications* (27). This guidance provides advice to assist sponsors in submission of an IND application for distribution of CBUs that do not meet licensure requirements when they are needed for transplantation of a patient with a serious or life-threatening disease and there is no satisfactory alternative treatment. Sponsors of an IND may include CBBs, registries (such as NMDP) and individual physicians serving as sponsor-investigators.

After licensing criteria are implemented there will be an extensive current inventory of CBUs that does not meet the licensing criteria but has a high likelihood of containing the CBU that is the best available match for a patient. Accordingly, the purpose of this protocol is to provide access to, and distribution of CBUs that do not meet the manufacturing requirements for licensure when they are the best available option for a patient with a serious or life-threatening disease in need of transplantation. This IND provides a single, efficient model that benefits from NMDP established relationships with an extensive network of CBBs, registries, TCs and physicians, yet it does not limit options for other potential IND sponsors. The protocol will allow both U.S. and international CBBs to distribute CBUs under this IND as long as they meet the requirements established by the NMDP. It is likely that the majority of CBUs collected previously will not meet licensure requirements and will need to be distributed under this (or another) IND. Similarly, while approximately 17% of domestic transplants involved a CBU from an international CBB in 2009, it is anticipated that most of these CBBs will chose not to hold an IND for distribution of a small number of CBUs to the U.S.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is an access and distribution protocol for unlicensed cryopreserved CBUs for transplant of pediatric and adult patients with hematologic malignancies and other indications. The study will enroll an unlimited number of transplant recipients at participating TCs based on well-defined inclusion and exclusion criteria, when the best graft source is determined to be a domestic or international CBU that does not meet FDA licensure requirements. The follow-up schedule and affiliated data collection forms for the unlicensed cord blood recipients are the standard CIBMTR data forms and procedures.

All recipients receiving at least one unlicensed CBU facilitated under the NMDP IND will be enrolled in the study and will be assessed for: neutrophil engraftment, serious infusion reaction, transmission of infection from CBU, survival, acute and chronic GVHD, and platelet engraftment.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of this study is to examine the incidence of neutrophil recovery of $\geq 500/mm^3$ after cord blood transplantation in a multi-institution setting using CBUs that are not FDA licensed.

2.2.2 Secondary Objectives

The secondary objectives are as follows:

- Assess incidence of transmission of infection
- Assess incidence of serious infusion reaction
- Determine overall survival 1 year after cord blood transplantation
- Assess cumulative incidence of acute GVHD grades II to IV and grades III to IV
- Assess cumulative incidence of chronic GVHD
- Determine platelet engraftment of >20,000 mcL and >50,000 mcL

2.3 Patient Eligibility

Inclusion Criteria

- Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
- Signed informed consent (and signed assent, if applicable) obtained prior to study enrollment
- Pediatric and adult patients of any age

Exclusion Criteria

- Patients who are receiving only licensed CBUs
- Cord blood transplant recipients at international TCs
- Patients who are enrolled on another IND protocol to access each unlicensed CBU

- Patients whose selected unlicensed CBU(s) will be more than minimally manipulated

2.4 Graft Selection

Criteria for the CBU(s) selected will be determined by the TC. The selected CBU, or at least one of the selected CBUs for a multiple cord blood transplant, must be unlicensed. Unlicensed CBUs selected by the TC must include:

- For a single CBU transplant, a post-processing dose of $\geq 2.5 \times 10^7$ total nucleated cells (TNC)/kg recipient weight is recommended, with minimum allowable dose of $\geq 1.0 \times 10^7$ TNC/kg recipient weight
- Proof of sterility – sterility will be reported at time of release
- Results of an assay for cell viability (e.g. colony forming units (CFU), CD34+ viability, Trypan Blue or other staining method(s) or another functional assay supporting cell viability)
    - If a post-processing / pre-freeze cell viability assay was not performed by the CBB or does not meet current minimum requirements, cell viability from a thawed retention sample or segment representative of the cord blood product will be performed prior to transplantation
    - If no cell viability assay can be performed, the TC will confirm the CBU remains the best match for the patient for transplant
- Any hemoglobinopathy testing done by the CBB (including testing for sickle cell and beta thalassemia) will be communicated with the TC
- Identity testing: HLA-A, -B, -C, -DRB1 by DNA-based technologies at a resolution sufficient to determine concordance with the original HLA typing must be confirmed prior to transplant
    - High resolution HLA-DRB1 typing must be performed prior to shipment of the CBU and may be performed at the recruitment, extended typing or confirmatory/verification typing stages.
    - This testing may be performed in a laboratory designated by the CBB or the NMDP or another national registry.
    - The laboratory performing this testing must be capable of carrying out DNA-based HLA typing and be accredited by ASHI, EFI, or CAP.
- It is recommended that each CBU is at least 4/6 HLA-matched at HLA-A, -B, and -DRB1, with a minimum allowable HLA match of 3/6 at HLA-A, -B, and -DRB1

Unlicensed CBUs selected by the TC must not include:

- Compromised traceability to product or maternal identity suggestive of mix-up such as discrepant HLA typing on identity confirmation
- Positive microbial culture of CBU (bacterial and/or fungal)
- Positive hemoglobinopathy testing indicating CBU is:
    - Homozygous for sickle cell and/or ß thalassemia disease
    - Heterozygous for both sickle cell and ß thalassemia trait
    - Severe alpha thalassemia (hemoglobin H disease)
- Positive/reactive result for Infectious Disease Markers (IDM) (FDA licensed/cleared/approved donor screening test or other laboratory IDM test as part of relevant medical records):

  - Human immunodeficiency virus (HIV) types 1 and 2
  - Hepatitis B Virus (HBV)
    - Hepatitis B Surface Antigen (HBsAg) test
    - HBV NAT test
  - Hepatitis C Virus (HCV)
  - T cruzi/Chagas Disease
  - West Nile Virus (WNV)
- No Infectious disease test result for:
  - Human immunodeficiency virus (HIV) type 1 /type 2 antibody test
  - HIV p24 Antigen or HIV nucleic acid test (NAT)
  - HBsAg test
  - HCV antibody test
- No bacterial sterility testing performed on CBU
- Collection and storage of CBU(s) in vials

2.5 Dosage and Handling

For a single CBU transplant, a post-processing dose of $\geq 2.5 \times 10^7$ TNC/kg recipient weight is recommended, with minimum allowable dose of $\geq 1.0 \times 10^7$ TNC/kg recipient weight. The maximum dose of dimethyl sulfoxide (DMSO) should not exceed 1mL (gram) of DMSO per kilogram of recipient weight per day of administration.

The CBU should be handled, stored and prepared according to the manufacturer's instructions or validated institution procedures. In the case of transplantation of multiple CBUs, the subsequent CBU(s) should not be thawed until it is confirmed that the patient has recovered from the side effects from the prior CBU infused.

Supplies and reagents that come in contact with the cellular therapy product shall be of the appropriate quality/grade for the intended use and, whenever possible, be FDA-approved. Supplies and reagents that are not FDA approved, but are available outside the US, such as Dextran in normal saline, may be used under this protocol.

2.6 Thaw and Infusion Treatment Plan

Recommendations for preparation and infusion of CBU are as follows:

- CBU manipulation: minimal manipulation is allowed and should be conducted per the manufacturer's instructions or validated institution procedures.
  - Minimal manipulation is defined by current FDA guidelines
  - *CBUs that are not red cell reduced must be washed.*
  - Thaw and reconstitution or wash methods should be based on a sufficient dilution ratio based on the original cord blood volume.
- Premedications: the patient should be premedicated prior to infusion per institution standard operating procedures.
- CBU administration: the CBU intravenous infusion should be performed according to manufacturer's instructions or per institution standard operating procedures.
  - A standard blood filter should be used.
  - The time from the initiation of thaw to completion of infusion should be minimized, preferably within 2 hours.

- Multiple cord blood transplants:
    - Thaw CBUs independently, thawing the second CBU after the first CBU is successfully infused.
    - Infuse CBUs independently.
    - Should a reaction occur resulting from infusion of the first CBU, appropriately manage the reaction before second CBU is thawed for infusion.
- Infusion toxicities: Patient monitoring is recommended during the infusion, per institution standard operating procedures. The infusion should be discontinued in the event of serious toxicity and/or product complaint. The infusion is discontinued based on clinician assessment and in accordance with institution standard operating procedures. See chapter 4 for adverse event and product complaint reporting details.

2.7 Patient Conditioning, Transplant, and Post-Transplant Care

The conditioning regimen, transplant, GVHD prophylaxis and supportive care for the transplant patient will be determined by the individual institution performing the transplant and reported to the CIBMTR on the appropriate case report forms (CRFs).

2.8 Toxicities and Risks

Transplant-related toxicities attributed to the product infusion will be reported to the CIBMTR on the appropriate CRFs. Toxicities potentially associated with the infusion of the CBU include DMSO toxicity and side effects from intact and hemolyzed red cells and may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, fluid overload, headache, dyspnea, hemoglobinuria, allergic reaction, acute renal failure, and in rare cases infusion reaction resulting in death. If toxicities are serious, they must be reported in an expedited fashion to the NMDP per the reporting instructions outlined in Section 4.3.1.

Transplant-related risks attributed to receiving CBUs include delayed neutrophil and platelet recovery and lower rates of engraftment compared with PBSC or marrow. In addition, cord blood is a single-source product; industry-standard practices assure donor mothers that their children will never be contacted for an additional donation request. Cord blood transplant complications that could be best managed with additional nucleated cells require novel strategies such as additional CBUs or a switch to an adult donor. Rarer risks can include seroconversion or development of a communicable disease (limited by stringent IDM screening), or transmission of a rare disease or genetic disorder to the recipient due to scant medical history on the newborn donor.

CHAPTER 3

3. PATIENT REGISTRATION AND ENROLLMENT

3.1. Approaching Patients, Eligibility, and Obtaining Consent

In instances where an unlicensed CBU is determined to be the best transplant option, patient enrollment in this study is required when the selected unlicensed CBU is facilitated under the NMDP IND. Facilitation includes NMDP/Be the Match facilitated the procurement, collection, and/or transportation of the product.

All participants in this access and distribution protocol must provide informed consent and, if applicable, assent prior to study enrollment. At the time of CBU order, the TC will enroll the patient.

If a previously-enrolled participant requires a subsequent transplant using unlicensed CBUs and at least one CBU is procured under the NMDP IND, the patient must be re-consented and re-enrolled in the study at the time of CBU order.

CHAPTER 4

4. SAFETY

4.1. Data Safety Monitoring

The NMDP Donor and Patient Safety Monitoring Advisory Group (DPSM) will review a summary of adverse events regularly. The report will be made available to participating TCs. If the DPSM recommends protocol or informed consent changes, they will be distributed to the participating PIs. It is the responsibility of each PI to forward the distributed communication to their local Institutional Review Board (IRB) per local reporting policies.

4.2. Reporting Product Complaint Data

Upon receipt of the CBU, the TC will complete written confirmation that the product was received. If the integrity of the CBU is compromised at receipt (or at any time after receipt), the TC should report to NMDP within 3 business days using the Product Complaint form in the FormsNet3 Recipient module. Examples include: a broken CBU, compromised shipping conditions, a contaminated product, or viability lower than expected. The NMDP will notify the CBB and conduct an investigation per NMDP standard procedures for these complaints. The NMDP will report manufacturing complaints that are determined to be related to the manufacturing of a distributed CBU to the FDA annually.

NMDP as trial sponsor and central monitoring entity will be responsible for reporting all adverse events that meet Office of Human Research Protections (OHRP) definition of unanticipated problem to OHRP.

4.3. Reporting Serious Adverse Events

Because all or most U.S. recipients participating on this protocol will be receiving potentially toxic preparative therapy, significant regimen-related toxicity is anticipated. Likewise, substantial mortality and non-engraftment of a transplanted CBU are anticipated. This data will be captured via filing of appropriate CIBMTR CRFs. The CIBMTR/NMDP will not report non-engraftment or complications that are attributed to the natural course of the disease, relapse, or chemotherapy and/or radiation toxicity.

4.3.1. Reporting Instructions for the Investigator

All serious recipient adverse events (SAEs) categorized below will be reported in accordance with the FDA requirements for adverse event reporting. All serious adverse events determined to be caused by or probably caused by the CBU based on objective evidence must be reported promptly under this IND protocol using the Adverse Event form in the FormsNet3 Recipient module. Reporting of serious adverse events that result in death or a life-threatening event should occur as soon as possible, but no later than 24 hours of learning of the event. Other SAEs should be reported within three working days.

- Recipient seroconversion to any of the FDA-listed relevant communicable diseases within six months of CBU infusion which, upon investigation, is determined to be caused or potentially caused by the CBU
- Recipient bacteremia related to a contaminated CBU
- Recipient develops any of the FDA-listed relevant communicable diseases within six

months of CBU infusion which, upon investigation, is determined to be caused or potentially caused by the CBU

- Serious infusion reaction within first 24 hours after infusion

4.3.2. NMDP Reporting Requirements to the FDA

A medical monitor will review all serious adverse events reported by the clinical trial site and be responsible for determining severity and relationship to the product. Any serious adverse event that is determined to be possibly linked to the product will be investigated by the NMDP Quality Assurance Nurses to determine if there is a causal relationship requiring expedited reporting. The NMDP will submit expedited reporting to FDA only for unexpected serious adverse events and for expected serious adverse events that occur at a frequency higher than usual.

If, during the investigation of the serious adverse event, a problem(s) with manufacturing practices is discovered, the NMDP will contact the appropriate CBB to initiate corrective action for the CBB-specific procedures and report under 4.2 above, as applicable.

CHAPTER 5

5. DATA MANAGEMENT

5.1. Data Reporting

The data collection forms for the subjects enrolled on this study include the standard CIBMTR data collection forms (including Adverse Events and Product Complaints meeting study reporting requirements) in the FormsNet3 Recipient module, and study-specific CIBMTR data collection forms in the Medidata Rave application.

Many important data elements for the study are collected on the standard CIBMTR reporting forms and therefore timely and accurate completion of these forms is essential.

5.2. Data Capture Methods

All TCs participating in this protocol are already reporting baseline and outcome data on all transplant recipients to the CIBMTR. Data reporting requirements for this protocol will be fulfilled by those data. There are no additional follow-up data requirements for this protocol.

CIBMTR data reporting time points used in this study:

- Baseline – time of transplant
- Infusion data – at time of transplant
- 100 days post-transplant
- 6 months post-transplant
- 1 year post-transplant
- At time of patient's death

TCs must continue to complete standard CIBMTR follow-up reporting on these patients beyond the study time point of one year per CIBMTR reporting requirements.

FormsNet3 CIBMTR Recipient forms

Please refer to Data Management manual for required forms. Standard CIBMTR data report forms can be found at:
http://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx

Medidata Rave application study forms

Study Event	Form name	Submission timeframes
Enrollment	Demographics	Due at the time of CBU order (required prior to CBU shipment)
	Inclusion/Exclusion	
Transplant	Transplant	Due within 1 week after transplant date. Form should **not** be completed prior to transplant.
Study Exit	Study Exit (if applicable)	Due when qualifying criteria met (see Off Study Criteria in section 6.4)

5.3. Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for patient safety, a decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. All protocol deviations will be documented in the Medidata Rave application by the study sponsor.

Study sites are also required to note deviations in patient medical records and report them to their local IRB in accordance with local policies. All protocol deviations will be compiled centrally by the CIBMTR Protocol Coordinator and reported to the NMDP DPSM.

Protocol deviations should be discussed with the CIBMTR Protocol Coordinator.

5.4. Study Monitoring

The PI will permit study-related remote and/or centralized monitoring visits by representatives of the CIBMTR or designees, and regulatory inspection(s) (e.g., FDA) to ensure proper conduct of the study and compliance with all FDA safety reporting requirements. Access must be provided to source documents, data collection forms, consent and assent forms, and any other study documents.

CHAPTER 6

6. STATISTICAL CONSIDERATIONS

6.1. Study Design

This study is a multicenter access and distribution protocol, to allow access to cord blood transplantation for patients whose best graft source is determined to be a CBU from U.S. or international CBBs not meeting FDA licensure requirements. Patients will be enrolled and followed prospectively to assess outcomes after transplant, from data collected using CIBMTR forms. The study is observational since the choice of the best available CBU will be left to the discretion of the patient's transplant physician. As the registry of licensed CBU grows, enrollment on this protocol is expected to gradually decline in relation to the overall number of CBUs used for transplantation. This study is descriptive in nature and there is no accrual limit.

6.2. Study Endpoints

The primary endpoint is neutrophil engraftment. Other important secondary endpoints include platelet engraftment, acute GVHD grades II-IV or III-IV, chronic GVHD, overall survival at 1 year, transmission of infection, and serious infusion reaction.

6.3. Data Analysis Plan

Interim descriptive analyses will be performed for primary transplants annually. As the eligibility for this protocol is very broad, analyses will be done separately for several pre-specified subgroups. First, analyses will be conducted separately for patients transplanted for malignant diseases and those transplanted for non-malignant diseases. They will also be analyzed separately for transplants using single CBU and those using multiple CBUs. Further separation of the study population such as adults vs. pediatrics and myeloablative vs. nonmyeloablative conditioning regimens will be considered depending on the patient numbers. In particular, neutrophil and platelet engraftment will only be analyzed using transplants with myeloablative conditioning regimens.

Baseline characteristics will be described using frequencies/percents or median/range as appropriate.

Transplant outcomes will be described with confidence intervals as follows. Probability of neutrophil and platelet engraftment, and probability of developing acute or chronic GVHD will be described using the cumulative incidence estimate (28), with death prior to engraftment or death prior to development of GVHD as competing risks, respectively. Overall survival will be described using the Kaplan-Meier estimator (29). In addition, a descriptive summary of product related relevant communicable disease agents or diseases (RCDAD) will be provided as well as listing of patients who experience serious infusional toxicity within 24 hours.

Due to the fact that the previous NMDP CBU protocol, *A centralized cord blood registry to facilitate allogeneic unrelated donor umbilical cord blood transplantation,* contained stopping rules, many years of data on the safety and efficacy of umbilical cord transplant using CBUs in our inventory have been reported. These data have shown that umbilical cord transplant is a comparably safe and effective alternative to bone marrow and PBSC transplantation. Therefore, stopping rules are not necessary for this protocol.

6.4. Disposition of Subjects

The number of subjects enrolled in the study and the disposition of all subjects will be summarized. Subjects who discontinue study will be listed according to the off-study criterion that applies.

Off-Study Criteria

Study sites must complete the Study Exit form in the Medidata Rave application for any subjects meeting one of these criteria:

1. Subject withdrawal
2. Transplant canceled: CBU(s) **not** shipped under NMDP IND
3. Substituted non-NMDP IND CBU: CBU(s) **not** shipped under NMDP IND
4. Substituted other cell source (BM, PBSC): CBU(s) **not** shipped under NMDP IND
5. Subject determined ineligible

Study subjects should **not** be exited after CBU(s) shipped under the NMDP IND. Subjects should **not** be exited for the following reasons:

1. Subject death *after* CBU(s) shipped under the NMDP IND
2. Transplant canceled *after* CBU(s) shipped under the NMDP IND
3. Substituted non-NMDP IND CBU(s) *after* CBU(s) shipped under the NMDP IND
4. Substituted other cell source (BM, PBSC) *after* CBU(s) shipped under the NMDP IND

Please contact the CIBMTR Protocol Coordinator with any questions or concerns regarding study exits.

Appendix A - REFERENCES

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