

CHAPTER 1

BACKGROUND AND CORD BLOOD BANK (CBB) ORGANIZATION

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1.1 OVERVIEW OF THE CORD BLOOD TRANSPLANTATION STUDY

Bone marrow transplantation (BMT) from HLA-identical sibling donors has been successfully utilized in the treatment of high-risk or recurrent hematological malignancies, bone marrow failure syndromes and selected hereditary immunodeficiency states and metabolic disorders. Use of allogeneic BMT has been limited both by the lack of suitable donors, and because of the risk of life-threatening complications that arise when donor and recipient are not immunologically identical, namely, graft failure and graft-versus-host disease (GVHD).

In an attempt to increase the availability of suitable donors and reduce the morbidity and mortality associated with allogeneic bone marrow transplantation, clinical investigators worldwide have evaluated placental and umbilical cord blood as an alternate source of hematopoietic stem and progenitor cells for transplantation. Early successes with the transplantation of umbilical cord blood have prompted considerable investigation in this stem cell source. Numerous laboratory investigators have subsequently confirmed the high frequency of primitive hematopoietic progenitors and have begun to describe the functional capacities of the neonatal immune system. As a result of these clinical and laboratory observations, large scale banking of umbilical cord blood for clinical transplantation has been initiated in the U.S. and Europe.

As of December 1996, umbilical cord blood from sibling and unrelated donors has been used to reconstitute hematopoiesis in more than 375 patients with malignant and non-malignant disorders treated with myeloablative therapy. Reports from individual institutions and the International Cord Blood Transplant Registry (ICBTR) suggest that umbilical cord blood contains sufficient numbers of hematopoietic stem and progenitor cells for both early and late engraftment at least in recipients weighing less than 40 kilograms. Moreover, limited comparisons with young patients transplanted with bone marrow from sibling donors suggest that the risk of severe acute graft-versus-host disease (GVHD) may be lower in those transplanted with umbilical cord blood. To date, too few patients have been transplanted to know what are the true risks and benefits of this stem cell source.

1.1.1 Unrelated Donor Umbilical Cord Blood Transplantation

As a result of the early successes with umbilical cord blood from sibling donors, pilot programs for the banking of unrelated donor umbilical cord blood have been proposed in many countries worldwide and initiated in New York, Milan, Dusseldorf, Paris and London. Potential benefits of banked umbilical cord blood include: 1) absence of donor attrition, 2) rapid availability, and 3) minimal risk or inconvenience to the donor. Additional advantages which remain to be determined include: 1) low risk of transmissible infectious diseases, such as cytomegalovirus and Epstein-Barr virus, 2) lower risk of acute and chronic GVHD as compared to unrelated-donor marrow transplants, and 3) ability to tolerate HLA mismatched transplants.

1.1.2 **Summary**

The aim of this research is to establish Cord Blood Banks (CBB) and develop standardized collection, processing, and cryopreservation procedures. These banks will collect, process and store up to 15,000 cord blood units which can be used in unrelated hematopoietic stem cell transplantation. In addition to the CBBs, transplant centers will participate in this research project. The purpose of the transplant study is to accurately describe 180-day survival and other events after umbilical cord blood transplantation.

1.2 OVERVIEW OF CBB ORGANIZATION

The participating investigators in the Cord Blood Transplantation Study (COBLT) collaborate through an organization designed to maintain a continuity of operations and to facilitate effective communication and cooperation among the units. The National Heart, Lung and Blood Institute (NHLBI) Project Officer, the NHLBI-appointed Chairperson, the Principal Investigators from the Transplant Centers (TC), the Cord Blood Banks (CBB), and the Medical Coordinating Center (MCC) comprise the Steering Committee, which is responsible for the design, execution, and analysis of the study.

The success of a multi-center endeavor depends on the cooperation of the staff in all participating units to perform their tasks and responsibilities in an efficient, effective, and timely manner. The participating units in the COBLT study (i.e., Transplant Centers, Cord Blood Banks, MCC, and Program Office) are shown in Exhibit 1-1. The Transplant Centers' approach to treatment administration is defined by the COBLT protocol. An independent Manual of Procedures describes the study organization, the transplant center data forms, and special transplant center study procedures.

This CBB Standard Operating Procedures (SOP) manual describes the study organization, study procedures, and data forms for the Cord Blood Banks. This chapter will provide a detailed description of the CBB organizational structure as well as define the roles and purposes of the collaborating CBBs.

1.2.1 Organization

UCLA and the Carolinas' Cord Blood Bank at Duke University are the two NHLBI-funded Cord Blood Banks in the COBLT study. Cord Blood Banks are responsible for collecting, screening, testing, freezing and shipping all cord blood units, and for collecting all clinical, laboratory, demographic, and other data pertaining to the cord blood units. They are also responsible for ensuring donor confidentiality and maintaining linkage for all donor units. Exhibit 1-2 shows the organizational structure for the Cord Blood Banks.

Each Cord Blood Bank is led by a Principal Investigator who is responsible for ensuring that all aspects of the COBLT Standard Operating Procedures are followed. Other key Cord Blood Bank staff include the Medical Director, processing coordinator, collection/distribution coordinator, laboratory technicians and assistants, and administrative personnel. The responsibilities of the Principal Investigator, Processing Coordinator and Collection/Distribution Coordinator are further defined below.

EXHIBIT 1-1
COBLT Study Participating Units

Transplant Centers

Dana-Farber Cancer Institute
Duke University
Fred Hutchinson Cancer Research Center
Indiana University
University of Minnesota
University of California - Los Angeles
Children's Hospital of Los Angeles
Additional Centers (TBA)

Cord Blood Banks

Carolinas' Cord Blood Bank
University of California - Los Angeles

HLA Reference Laboratories

University of California, Los Angeles
University of California, San Francisco
Navy Medical Research Institute

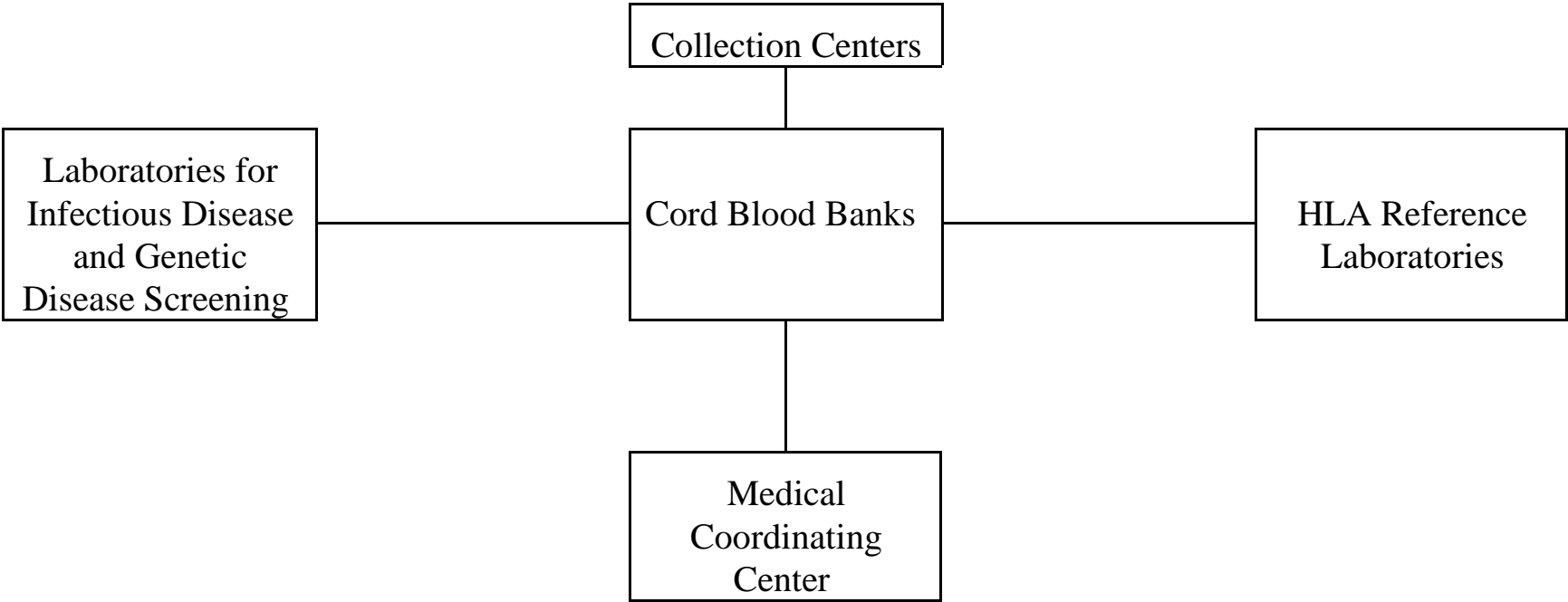
Program Office

NHLBI
Division of Blood Diseases and Resources Program Office
Office of Biostatistics Research

Medical Coordinating Center

The EMMES Corporation

EXHIBIT 1-2
Cord Blood Banks Organizational Chart



1.2.2 **Functions of the Principal Investigator**

The primary responsibility of the Principal Investigator (PI) is to direct the activities of COBLT personnel in the Cord Blood Bank. The PI is responsible for maintaining communications with all collaborating laboratories and collection centers. Other duties of the PI include the following:

- Represent the Cord Blood Bank at meetings of the Steering Committee and Technical Subcommittees
- Coordinate the scientific and administrative operations of the Cord Blood Bank
- Ensure adherence by Cord Blood Bank personnel to the procedures described in and required by the COBLT Standard Operating Procedures
- Spend sufficient time in the Cord Blood Bank to adequately observe study procedures
- Ensure that personnel performing COBLT procedures are properly trained and certified
- Communicate with the Medical Director regarding the release of CBUs from quarantine and other relevant clinical issues
- Ensure the confidentiality of all donors while maintaining linkage between cord blood units (CBU) and donors.
- Ensure a confidential file of all notification records associated with donors testing positive for an infectious disease or genetic screening test.
- Assure the Cord Blood Bank's fiscal responsibility in the disposition of COBLT funds

1.2.3 **Functions of the Processing Coordinator**

The Processing Coordinator is responsible for supervising daily operations in the Cord Blood Bank and serves as a primary contact for the Medical Coordinating Center (MCC). The duties of the Processing Coordinator include:

- Ensure the accuracy, completeness, and consistency of reported data
- Ensure compliance with the COBLT Standard Operating Procedures, with particular concern to all aspects of CBU processing
- Notify the MCC of changes or impending changes in the Cord Blood Bank personnel, address(es), or telephone number(s)
- Maintain a file of correspondence with the MCC
- Maintain an up-to-date CBB Standard Operating Procedures

- Check completed data forms for accuracy and completeness
- Ensure that donor names, social security numbers, and any other personal identifiers are removed from all materials sent to the MCC
- Submit complete data to the MCC in a timely manner
- Communicate with the MCC regarding data processing matters concerning study forms and edit messages as appropriate
- Report irregularities or problems that can affect the data quality to the PI and the Protocol Monitor
- Track every cord blood unit received by the processing laboratory and its disposition
- Ensure that specimens for HLA typing, infectious disease screening, and genetic disease screening are collected and shipped to appropriate laboratories
- Participate in regularly scheduled, structured telephone calls with the Protocol Monitor from the MCC
- Other duties as defined by the Steering Committee, Technical Subcommittees, or Data and Safety Monitoring Board (DSMB)

1.2.4 **Functions of the Collection/Distribution Coordinator**

The Collection/Distribution Coordinator is responsible for supervising daily operations in the Collection Centers. The Collection/Distribution Coordinator regularly communicates with the Processing Coordinator and PI regarding issues related to the collection of the cord blood units, obtaining informed consent and medical chart data collection. The duties of the Collection/Distribution Coordinator include:

- Ensure that potential Cord Blood donors receive appropriate information about the study, including the Informed Consent statements
- Ensure that Informed Consent is obtained in a timely manner in accordance with CBB procedures
- Collect necessary maternal history and samples
- Collect CBUs according to the procedures specified in the CBB - SOP
- Supervise the transport of CBUs to the CBB and may also coordinate release and transport of CBUs to transplant centers

Each Processing and Collection/Distribution Coordinator will be given a copy of the CBB Standard Operating Procedures.

1.3 **FUNCTIONS OF THE MEDICAL COORDINATING CENTER**

The Medical Coordinating Center will collect data from the CBBs, distribute HLA types and performs searches. Other responsibilities are further defined in the COBLT Transplant Center - Manual of Procedures.

1.4 RECRUITING ADEQUATE NUMBERS OF PATIENTS

A critical task for all clinical studies is the enrollment of adequate numbers of patients, a task that often proves to be more difficult than anticipated. A recruitment goal has been established for each Transplant Center based on each Principal Investigator's assessment of the number of patients available. Each Transplant Center should develop a plan for tracking transplants and transplant candidates to ensure meeting this recruitment goal and review this plan continually throughout recruitment in order to determine its effectiveness. The plan must outline methods to identify and enroll minorities and women, in strict adherence to National Institutes of Health (NIH) and Department of Health and Human Services (DHHS) policies, as originally stated in the Request for Proposals for the COBLT Study. If the Transplant Center is not achieving its recruitment goal in a timely fashion, the plan will be modified.

1.4.1 Anticipated Accrual of Minority and Female Subjects

Minority Donors. Racial and ethnic groups vary in the diversity of their human leukocyte tissue antigens (HLA) haplotypes. In groups where many members have similar HLA types, not as many potential donors are needed. In groups with wide polymorphism among their HLA types, relatively more donors are needed. This may be mitigated somewhat by the ability to perform HLA-mismatched transplants.

By contract each cord blood bank must recruit a specific number of donors from minority populations. The number of units required from each group was calculated to enable potential transplant recipients from any group to have similar chances of finding a suitably matched cord blood unit from within the study's cord blood banks. This approach will maximize the number of minority transplant patients enrolled in the study. The targets for the cord blood bank are 43% Caucasian, 30% African-American, 17% Hispanic, and 10% Asian-American cord blood units. It is anticipated that approximately 51% of units will come from male donors and 49% from female donors, reflecting the proportion of births.

Minority Transplant Recipients. The population of patients eligible for this trial is restricted to patients who are able to find an unrelated cord blood donor matched or slightly mismatched for their HLA type from the study's cord blood banks. Previous studies in unrelated donor marrow transplantation have not indicated that outcomes are related to race or ethnicity.

The sample size for this study is approximately 400 patients. Based on the ethnicity of the first 156 unrelated cord blood transplants performed by the seven participating transplants centers, we estimate that the study will comprise the following numbers of patients:

<u>African American</u>	<u>Asian/Pacific Is.</u>	<u>Caucasian</u>	<u>Hispanic</u>	<u>Native American</u>
51	13	302	31	2

Exploratory analysis of engraftment and disease-free survival will be conducted to determine if there is evidence of a minority group effect in this study.

The number of unrelated cord blood transplants is increasing each year. The number of minority cord blood transplants is expected to increase faster than the number of Caucasian cord blood transplants.

This is due to the emphasis and contract requirements placed on the COBLT blood banks to recruit specified numbers of donors from all the minority groups.

If the results of this study show that cord blood contains sufficient numbers of cells to reconstitute adult size patients without an unacceptable increase in graft failure and relapse, it is likely that cord blood transplants will become more common and the number of transplants for minority patients will increase. Thus, despite the relatively small number of minority patients expected to enroll in this trial, the study may have a significant impact on the future of transplants for minority patients.

Based on previous studies in similar patient populations, we expect to enroll approximately 60% male patients and 40% female patients. Comparison of engraftment and disease-free survival by gender will be conducted in this study to determine if there is evidence of a gender effect on outcome.