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CHAPTER 1

STUDY ORGANIZATION

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STUDY ORGANIZATION

The participating investigators in the Cord Blood Transplantation Study (COBLT Study) 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 and Cord Blood Banks, and the Principal Investigator from the Medical Coordinating Center (MCC) comprise the Steering Committee, which is responsible for the design, execution, and analysis of the study. This Manual of Procedures describes the study organization, data forms, and special Transplant Center study procedures. The approach to treatment administration is defined by the COBLT Study protocol. This chapter will provide detailed description of the COBLT Study organizational structure as well as define the roles and purposes of the collaborating units.

1.1 PARTICIPATING UNITS

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 different participating units in the COBLT Study (i.e., Transplant Centers, MCC, and Program Office) are shown in Exhibit 1-1. Rosters for the staffs of all participating units are provided in Appendix A.

1.1.1 Transplant Centers

There are 6 Transplant Centers with contracts with the NHLBI to perform the COBLT Study. Additional centers also participate for the performance of the COBLT study through subcontracts with the MCC and are reimbursed on a per patient basis. The Transplant Centers' approach to treatment administration is defined by the COBLT Study protocol.

EXHIBIT 1-1
COBLT Study Participating Units

Transplant Centers

Cardinal Glennon Children's Hospital
Case Western Reserve University
Children's Hospital of Los Angeles
Children's Hospital of New Orleans
Children's Hospital of Orange County
Children's Hospital of Philadelphia
Children's Hospital of Pittsburgh
Children's Medical Center of Dallas
Children's Mercy Hospital
Children's National Medical Center
City of Hope National Medical Center
Dana-Farber Cancer Institute
DeVos Children's Hospital
Duke University
Fred Hutchinson Cancer Research Center
Hackensack University Medical Center
Indiana University
North Shore University Hospital
North Texas Hospital for Children
Roswell Park Cancer Institute
Texas Transplant Institute
University of California – Los Angeles
University of California – San Francisco
University of Florida
University of Minnesota
University of Rochester – Strong Memorial Hospital
Vanderbilt University Medical Center

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

National Heart, Lung & Blood Institute
Division of Blood Diseases and Resources Program Office
Office of Biostatistics Research

Medical Coordinating Center

The EMMES Corporation

Transplant Centers are responsible for recruiting, examining, and treating study participants and for collecting all clinical, laboratory, demographic, and other data required by each study. Each Transplant Center is directly led by a Principal Investigator who is personally responsible for ensuring that all aspects of the COBLT Study protocol are followed. Other key Transplant Center staff include participating cord blood transplant physicians, Clinic Coordinators, and technicians.

The Clinic Coordinator is responsible for such critical matters as:

- Appointment scheduling
- Ensure the accuracy, completeness, and consistency of data reported
- Handle communications regarding patient searches for donors, patient registration, data processing matters concerning study forms, and edit messages as appropriate with the MCC
- Ensure compliance with the COBLT Study Manual of Procedures and the COBLT Study protocol
- Participate in regularly scheduled, structured telephone calls with the Protocol Monitor from the MCC

The staff of the Transplant Center carry out the provisions of the Manual of Procedures and the COBLT Study protocol. They are responsible for registering and maintaining follow-up of all participants. The responsibilities of the Principal Investigator and Clinic Coordinator are further defined in Chapter 6.

1.1.2 **Cord Blood Banks**

UCLA and Duke University are the two NHLBI-funded Cord Blood Banks for the COBLT Study. Units from non-COBLT banks are also acceptable for transplant of patients registered on the study provided they come from the New York Blood Center, are an NMDP-approved cord blood bank, or are a U.S. bank meeting Netcord-FACHT standards. COBLT 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. An additional manual, the Cord Blood Bank Standard Operating Procedures (CBB SOP), details all procedures for the Cord Blood Banks.

Each COBLT Cord Blood Bank is led by a Principal Investigator who is responsible for ensuring that all aspects of the COBLT Study Standard Operating Procedures are followed. Other key COBLT 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 in the CBB SOP manual.

1.1.3 **Medical Coordinating Center**

The MCC, located at the EMMES Corporation, Potomac, Maryland, is responsible for developing the Manual of Procedures; preparing the COBLT Study protocol; preparing the CBB SOP; collecting, verifying, and analyzing study data; ensuring that the provisions of the Manual of Procedures, the COBLT Study protocol, and the CBB SOP are carried out by all participating units; and coordinating study activities. MCC staff includes professionals in biostatistics, epidemiology, immunology, data processing, administration, and communication coordination. Consultants are used to supplement the staff for appropriate specialized tasks.

MCC staff have major responsibility for developing the statistical design, establishing the operational and analytical methodology, and analyzing the data. MCC staff are also responsible for collecting, editing, and storing all data received from the Transplant Centers and the Cord Blood Banks. Some of the specific functions of the MCC staff are to:

- Collaborate with other study investigators in developing study procedures, forms, the Manual of Procedures, and the COBLT Study protocol
- Coordinate communications among the Transplant Centers
- Coordinate communications between the Transplant Centers and the Cord Blood Banks
- Coordinate the training and certification of Transplant Center staff in standardized data collection, COBLT Study quality control procedures, and shipping of samples
- Review all data submitted on standardized COBLT Study forms for completeness and accuracy
- Create computerized data files for COBLT Study data
- Communicate with Transplant Centers regarding missing, delayed, incomplete, or erroneous data
- Prepare periodic reports on the performance of the Transplant Centers and COBLT Cord Blood Banks
- Analyze periodically the frequency of specified events and report to the Data and Safety Monitoring Board
- Prepare recruitment, technical, and statistical reports for meetings
- Assist in preparing scientific reports for publication

Detailed MCC procedures are presented in Chapter 7. Additional details are included in the MCC Procedures Manuals which are maintained at the MCC.

1.1.4 National Heart, Lung and Blood Institute Program Office

The COBLT Study Program Office is located in the Bone Marrow Transplant Branch in the Division of Blood Diseases and Resources, NHLBI. The NHLBI Project Office is responsible for the scientific monitoring and the administration of the study. The Project Officer is an active and fully participating member of the Steering Committee.

The NHLBI Project Team consists of NHLBI staff from the Division of Blood Diseases and Resources, the Division of Extramural Affairs, and the Division of Epidemiology and Clinical Applications.

The Program Office staff and members of the Contracts Operations Branch, Division of Extramural Affairs work together to administer the contract. The Biostatistics Research Branch, Division of Epidemiology and Clinical Applications, provides additional expertise in the areas of study design and biostatistics.

1.2 STUDY ADMINISTRATION

The organizational structure of the study is characterized in Exhibit 1-2.

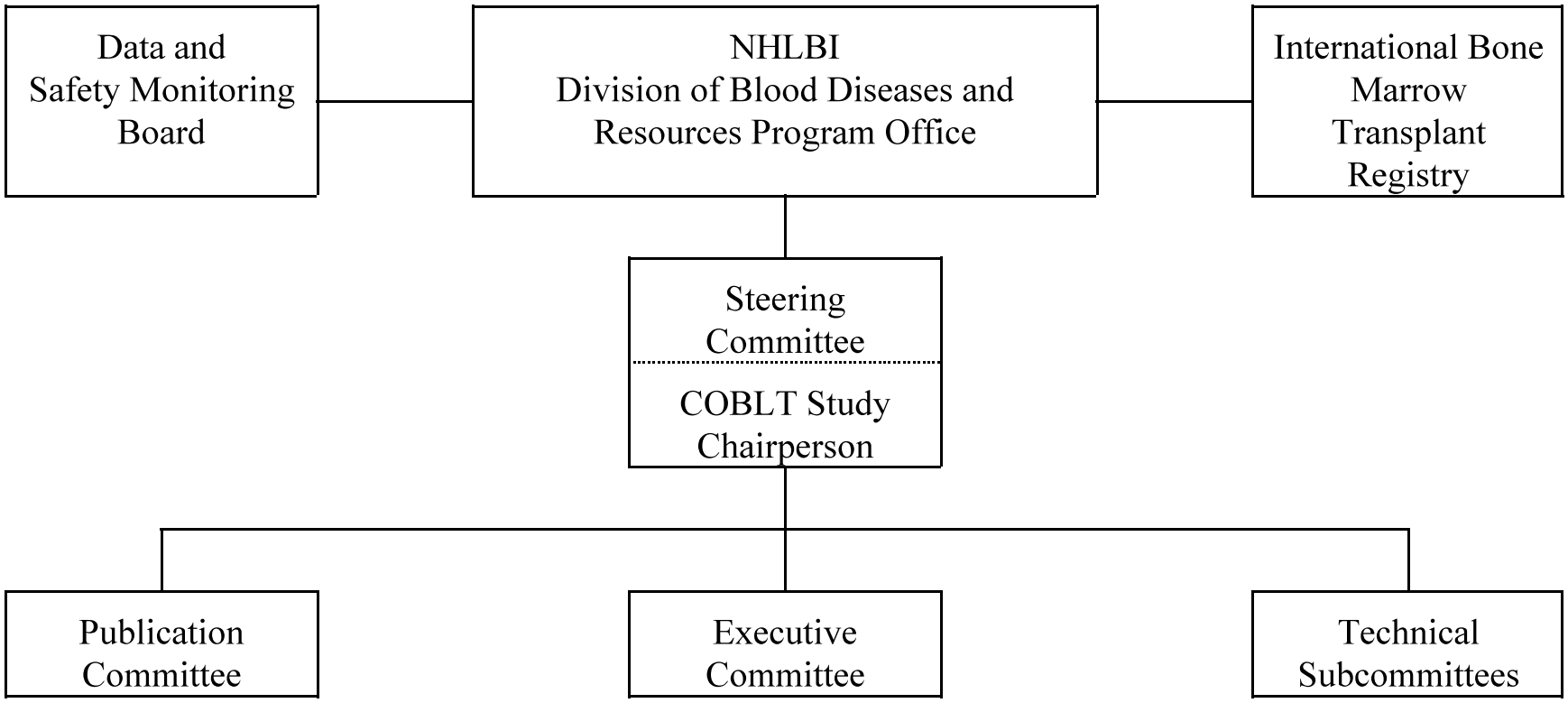
1.2.1 Study Chairperson

The Program Office at NHLBI appoints the Study Chairperson, who is primarily responsible for the scientific direction and administration of the COBLT Study. The Study Chairperson:

- Develops and maintains, with advice from other study participants, an organizational structure that meets the needs of the study and the NHLBI
- Remains informed of all operational aspects of the study and, working within the organization developed, formulates policy and takes necessary action to ensure the smooth operation of the study
- Advises the MCC Principal Investigator on data monitoring and other issues of importance to the overall conduct of the study
- Appoints study participants and non-participants to appropriate positions and committees
- Conducts the Steering Committee meetings
- Represents the Steering Committee to the Data and Safety Monitoring Board (DSMB).

The Study Chairperson is appointed for the duration of the study. If the Study Chairperson is unable to serve because of resignation, death, or serious illness, the NHLBI Program Officer will appoint a new chairperson. If the Study Chairperson is ill or unable to fulfill his or her obligation for a limited period (up to six months), he or she, in conjunction with the NHLBI Program Officer, may appoint an Acting Chairperson for that period.

EXHIBIT 1-2
Organizational Chart



1.2.2 **Data and Safety Monitoring Board**

1.2.2.1 Purpose. The Data and Safety Monitoring Board (DSMB) is an independent board appointed by the NHLBI and is responsible for:

- Reviewing the study design and, as appropriate, recommending design changes
- Assessing study data, particularly for adverse and/or beneficial effects of treatment
- Minimizing risks to participants
- Recommending changes in the study protocol as may be warranted from a review of the study data

The specific roles and responsibilities as detailed by the NHLBI Program Office are as follows:

- The NHLBI must ensure that patients are not exposed to unreasonable or unnecessary research risks, i.e., trials should not continue beyond the point when the question posed appears to be answered, or when possible adverse effects are identified. In order to provide this assurance, all clinical trials involving randomization to alternative measures must have a mechanism in place for reviewing interim data in the context of the most recent scientific literature. DSMBs are critical elements in this decision-making process.
- DSMBs should be intellectually and financially independent of trial investigators and institutions.
- DSMB members must have no financial ties to any commercial concerns likely to be affected by the outcome of the trial. Their independence must be documented in financial disclosure statements submitted by DSMB members at the time that they are asked to participate and annually thereafter.
- The number and expertise of DSMB members will be dictated by the size and complexity of the clinical trial. Typically, DSMBs consist of between three and ten members who together provide adequate representation in biostatistics, ethics, clinical trials, and the specific area(s) of research in question. The chair of a DSMB should have clinical trial experience. While DSMB meetings should be scheduled at intervals commensurate with the anticipated need, most DSMBs choose to meet every six months and to schedule interim meetings as necessary. Every DSMB will have an Institute staff member who serves as the Board's Executive Secretary to prepare minutes for each meeting which should be signed by both the Executive Secretary and the Chairman.
- Ex-officio members, who usually include a representative from the data center, a representative of the investigators (e.g., chairman of the steering committee), and other NHLBI representatives, and DSMB members should attend part or all of DSMB meetings. If required, additional consultants or investigators may be invited to specific

meetings. DSMB members may elect to hold executive sessions. The Executive Secretary, other ex-officio members, and ad hoc consultants may not vote.

- DSMBs should be formed after a protocol is approved by the NHLBI. The Institute may elect to convene a protocol review committee prior to approval that may include members who will subsequently be asked to participate as members of the DSMB. DSMB members are invited to participate by the Director, NHLBI. The DSMB will review the final protocol during its first meeting. Any protocol changes during the performance of the study will also be reviewed by the Board.

- At the end of each meeting, DSMBs should be asked to make a recommendation regarding continuation of the trial. DSMBs are responsible for defining, in general terms, the process they intend to use to reach such a recommendation at their first meeting prior to initiating any data review.

- DSMB members must be satisfied that the timeliness and accuracy of data submitted to them for review are sufficient to protect the safety and health of trial participants. Failure of investigators to provide such data will result in a recommendation to the NHLBI to discontinue the trial until a satisfactory response is received. All DSMB recommendations are directed to the NHLBI.

- A brief summary of DSMB recommendations is forwarded to the Division and Institute Directors in writing no more than two working days after a DSMB meeting; however, recommendations for major changes should be communicated verbally immediately. The NHLBI will act on recommendations expeditiously.

- DSMBs should primarily address issues of patient protection and such related matters as timely recruitment and accurate and timely data submission. All DSMB recommendations are directed to the NHLBI for resolution. The Institute may respond by expanding the number of trial centers, stopping recruitment because of inadequate rate of acquisition, or discontinuing a center with poor performance. The NHLBI may also elect to establish an *ad hoc* committee to provide assistance in these matters. Such *ad hoc* committees may include selected initial reviewers, DSMB members, and members of the relevant scientific community.

1.2.2.2 Meetings. The DSMB reviews data monitoring reports at one-year intervals or more frequently if warranted. Any DSMB member may request an additional meeting to discuss the results of interim DSMB reports.

DSMB members are expected to:

- Acquire a detailed knowledge of the COBLT Study design and goals
- Attend meetings of the DSMB, which are generally held in Bethesda, Maryland
- Devote four to five hours to prepare for each meeting by studying DSMB reports and other material submitted by the MCC and other study units

- Review interim DSMB reports and respond to questionnaires on the need for a meeting or conference call of DSMB members
- Suggest analyses, as appropriate, to be included in DSMB reports prepared by the MCC

1.2.3 **Steering Committee**

The COBLT Study Steering Committee is responsible for the daily operation of the study. The Steering Committee discusses and helps formulate and implement all policy decisions related to the conduct of the COBLT Study.

The Steering Committee consists of:

- NHLBI-appointed Chairperson
- NHLBI Project Team staff
- Transplant Center Principal Investigators
- COBLT Cord Blood Bank Principal Investigators
- MCC Principal Investigator
- Clinic Coordinator representative

The following observers may attend Steering Committee meetings:

- Co-Investigators from the Transplant Centers or Cord Blood Banks
- Clinic Coordinators from the Transplant Centers
- Coordinators from the Cord Blood Banks
- Other MCC staff

The functions of the Steering Committee include:

- Recommend to the NHLBI Program Office changes or modifications in the COBLT Study protocol that may be necessary or desirable (but not based on DSMB reports)
- Ratify major changes in the Manual of Procedures
- Review and approve all ancillary studies
- Advise and assist the MCC and the technical subcommittees on operational matters

- Resolve operational problems brought to the Executive Committee by investigators, coordinators, the COBLT Cord Blood Banks, or the MCC

- Monitor the performance of all participating centers based on information provided by the MCC. This evaluation includes assessment of the quality of data collected by center staff and adherence to the protocol. The Steering Committee advises the NHLBI Project Officer on the performance of participating centers and may recommend that NHLBI invite new participants or terminate centers showing unsatisfactory performance.

- Review decisions and recommendations of the Publications Committee

- Assume other responsibilities at the request of the Study Chairperson or the NHLBI Project Officer

The Steering Committee meets at least once a year to monitor the progress of the study and consider special issues which may arise. Additional meetings may be held during the planning stage of the COBLT Study. The Steering Committee will not have access to blinded data.

In the event that an official vote is needed, each center will have one vote. Other voting members include the NHLBI Project Officer and the MCC Principal Investigator. The Chairperson will cast the deciding vote in case of a tie.

1.2.4 **Executive Committee**

The Executive Committee is comprised of the Chairperson of the Steering Committee, the NHLBI Project Officer, and the Principal Investigator of the MCC. It is responsible for developing Steering Committee agendas and recommendations for consideration by the Steering Committee. The Executive Committee will also provide direction between meetings of the Steering Committee.

1.2.5 **Technical Subcommittees**

At present, 13 technical subcommittees have been identified. Subcommittees may be formed as needed, with the subcommittee chairpersons appointed by the COBLT Study Chairperson. The current list includes:

- Acute and Chronic GVHD. The subcommittee is responsible for making recommendations concerning grading and treatment of GVHD. A three-member panel will have the responsibility for determining the overall grade of GVHD for all patients.

  Subcommittee members: LeeAnn Baxter-Lowe, Haydar Frangoul, Stephen Feig, Andrew Gilman, Rakesh Goyal, Joanne Kurtzberg, John Wagner, Joel Weinthal, additional members to be named.

- Conditioning Regimen and GVHD Prophylaxis.

  Subcommittee members: Eva Guinan*, Joanne Kurtzberg, Eric Sievers.

- Cord Blood Allocation Review. The subcommittee is responsible for maintaining cord blood unit release procedures and recommending release requests.

  Subcommittee members: Nancy Kernan*, Joanne Kurtzberg, John Wagner, additional members to be named.

- Cord Blood Bank - Collection, Freezing, Shipping and Thawing.

  Subcommittee members: John Fraser, Joanne Kurtzberg, Mary Territo, John Wagner

- Eligibility.

  Subcommittee members: Neena Kapoor, Eric Sievers, Frank Smith*, Mary Territo, John Wagner

- Follow Up of Mother, Informed Consent, History Forms.

  Subcommittee members: Steven Feig*, Eva Guinan, additional members to be named.

- Graft Characterization of CBU.

  Subcommittee members: John Fraser*, Joanne Kurtzberg, Daniel Pietryga, Mary Territo, John Wagner, Donna Wall, additional members to be named.

- Growth Factors.

  Subcommittee members: Steven Feig, Eva Guinan, Frank Smith, Mary Territo*

- Histocompatibility. The subcommittee is responsible for resolving all issues related to patient eligibility and histocompatibility matching criteria.

  Subcommittee members: LeeAnn Baxter-Lowe*, Nancy Bunin, Mike Cecka, Haydar Frangoul, Carolyn Hurley, Jennifer Ng, Elaine Reed, John Wagner.

- IBMTR.

  Subcommittee members: Nancy Kernan, Joanne Kurtzberg, John Wagner.

- Infectious Disease Prophylaxis/Immune Reconstitution. The subcommittee is responsible for assessments of opportunistic infections, grading infections, and suggesting prophylactic treatments.

  Subcommittee members: Eva Guinan, Neena Kapoor*, Mary Laughlin, Indira Sahdev, Mary Territo, Joel Weinthal.

- Regulatory.

  Subcommittee members: John Fraser, Joanne Kurtzberg, John Wagner, additional members to be named.

- Risk Status. The subcommittee is responsible for developing the definitions of good/poor risk.

  Subcommittee members: Stephen Feig, Eva Guinan, Biljana Horn, Joanne Kurtzberg, Indira Sahdev, Joel Weinthal.

NHLBI Project Team staff, Steering Committee Chairperson, and MCC staff will be additional members on these subcommittees as appropriate.

1.2.6 **Publications Committee**

The Publications Committee will consist of the Principal Investigators of the study and members of the NHLBI Program Office, or any member's appropriate designee. Authorship on other papers will be decided by this committee.

The Publications Committee is responsible for reviewing proposed publications to ensure protection of proprietary information and patient confidentiality and to determine the public impact of publication of incomplete or premature results. No participating institution may present or publish individual findings from work performed on the study protocol without approval of the Publications Committee and the NHLBI.

CHAPTER 2

STUDY POLICIES

CHAPTER 2

STUDY POLICIES

2.1 ADHERENCE TO MANUAL OF PROCEDURES

The entire COBLT Study Group participates in the development, review, and acceptance of this Manual of Procedures. The manual is formally approved by the COBLT Study Steering Committee and the Data and Safety Monitoring Board (DSMB). It is essential to the success of the study that all COBLT Study investigators adhere to the procedures outlined herein. If any COBLT Study investigators find that, for whatever reason, adherence to these procedures is difficult or not possible, they should discuss the problem with the Study Chairperson or the Program Office.

2.1.1 FDA Form 1572 (Statement of Investigator)

This form must be filed to complete initial COBLT Study site registration and will be updated annually.

2.1.2 *Curricula Vitae* - Principal Investigators and Co-investigators

A current curriculum vitae or biographical sketch for each physician who will provide medical care is required upon initial site participation in the COBLT Study. Renewal will be requested annually along with resubmission of the Form 1572. The required documentation should be submitted to:

COBLT Study Medical Coordinating Center
The EMMES Corporation
401 North Washington Street, Suite 700
Rockville, MD 20850

2.2 INFORMED CONSENT

Written consents shall be obtained from each COBLT Study patient as part of enrollment. The Transplant Center must ensure that patients are adequately oriented to the objectives and procedures of the COBLT Study. Only after the investigator is satisfied that the patient understands the potential risks and benefits of participation in the COBLT Study will written consent be obtained.

Informed consent is also needed for any additional research procedures that may be part of an ancillary study and may expose the patient to risk or discomfort. The signed consent forms are placed in the patient's file at the Transplant Center.

Informed consent must also be obtained from each donor for the Cord Blood Banks and is described in the CBB SOP.

2.3 PROTECTION OF HUMAN SUBJECTS

Prior to enrolling patients, each participating Transplant Center must submit to the Medical Coordinating Center (MCC) and the National Heart, Lung and Blood Institute (NHLBI) Project Office a completed copy of Form OF310 that has been approved by the local Institutional Review Board (IRB) and copies of the Transplant Center's local IRB-approved informed consent statements. In addition, annual IRB approval letters must be submitted to the MCC and Project Office.

2.4 DISCLOSURE OF STUDY RESULTS

The results of the trial will be made available to participating investigators at a time specified by the DSMB and as soon as beneficial or harmful effects are established or the trial has concluded. Investigators should refrain from predicting the overall results of the study from their own Transplant Center experience.

Disclosure of COBLT Study results at appropriate times to investigators, participants, the scientific community, and the public will be coordinated closely by the NHLBI and the MCC.

2.5 ACCESS TO INTERIM ENDPOINT DATA

Because knowledge of interim results of the clinical trial could compromise the efforts by Transplant Centers to enroll and maintain follow-up of study patients, reports of such results are submitted by the MCC only to the DSMB, which is responsible for monitoring the results for safety and efficacy.

2.6 SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

2.6.1 Generation of Publications and Presentations

The Publications Committee will develop procedures for generating scientific publications and presentations emanating from the design and data collection of the COBLT Study. These procedures will be reviewed, amended, and approved by the Steering Committee. The Publications Committee will also invite suggestions for additional papers from COBLT Study investigators. It will also be the responsibility of the Publications Committee to make recommendations to the NHLBI for the appointment of writing teams for developing COBLT Study reports and designation of COBLT Study reports as either Primary or Secondary COBLT Study reports. The NHLBI will make the final designation of Primary or Secondary reports.

Primary COBLT Study reports deal with primary COBLT Study objectives; Secondary COBLT Study reports deal with secondary COBLT Study objectives or ancillary studies. Before publication, copies of Primary COBLT Study reports are sent to all members of the Steering Committee for information. Reprints of published reports are mailed to each center for distribution to staff and outside consultants. Reprints of each report are sent to the MCC for the COBLT Study library and the NHLBI.

2.6.2 **Editorial Review**

Abstracts of papers to be presented at scientific meetings and manuscripts to be submitted for publication that deal with the design of the COBLT Study or are based on COBLT Study data, whether they pertain to a single COBLT Study center, several COBLT Study centers, or all COBLT Study centers, must be approved by the Steering Committee before presentation or publication. Reports on ancillary studies must be similarly approved. The only exception is oral presentations to local groups on the design of the COBLT Study, which do not need to be approved by the Steering Committee.

Chairpersons of writing teams, in submitting a COBLT Study report for publication, should include a copy of the approval letter from the Chairperson of the Steering Committee.

2.6.3 **Authorship**

The Publications Committee will develop policies for determining authorship for all other papers.

2.6.4 **Acknowledgments**

Primary COBLT Study reports will acknowledge the participation of the COBLT Study Transplant Centers and Cord Blood Banks who participated in the study. Membership of major committees may also be acknowledged.

Primary and Secondary COBLT Study reports will acknowledge support of the study by contracts from the NHLBI, National Institutes of Health.

2.7 **ANCILLARY STUDIES**

Ancillary studies are investigations that are conducted concurrently with the COBLT Study and involve COBLT Study participants. These studies must be approved by the COBLT Study Steering Committee and the DSMB.

2.7.1 **Definition of Ancillary Studies**

An ancillary study is research on COBLT Study patients that meets the following criteria:

- The research is conducted by COBLT Study investigators on COBLT Study participants, on stored cord blood units, or on cord blood units released to COBLT study investigators.

- The goals of the study are consistent with COBLT Study objectives and are not included among the study objectives stated in a COBLT Study Protocol.

- The research requires supplementary clinical observations or procedures on COBLT Study patients or cord blood units.

- The COBLT Study Steering Committee, with NHLBI approval, has designated the study as a COBLT Study ancillary study, thus endorsing participation by the MCC in study development, conduct, data processing, and data analysis.

Studies involving cord blood units will not be considered ancillary if the units have been released to investigators who are not associated with COBLT. Note that units should only be released to investigators who have an IRB-approved research protocol.

Ancillary studies by individual COBLT Study investigators or groups of COBLT Study investigators are encouraged because they can enhance the value of the COBLT Study and increase the motivation and interest of investigators in the COBLT Study. However, to protect the integrity of the COBLT Study and to prevent a drain on COBLT Study resources, all proposals for ancillary studies, whether or not they involve the need for supplementary funds, must be submitted for approval to the Steering Committee and the DSMB.

2.7.2 **Approval of Ancillary Studies**

Approval is needed to assure that ancillary studies will not:

- Complicate the interpretation of COBLT Study results
- Result in premature release of COBLT Study outcome data
- Violate patients' rights
- Adversely affect patient enrollment or cooperation
- Jeopardize the public reputation of the COBLT Study
- Substantially divert study resources at the Transplant Centers or the Medical Coordinating Center (MCC)

Investigators wishing to conduct an ancillary study should submit a proposal through the MCC, who will distribute it to the Steering Committee. After review by the Steering Committee, the Principal Investigator (PI) of the MCC will summarize the Committee's comments and forward the proposal and comments to the Steering Committee and DSMB for secondary review, along with a copy of the comments to the applicant. If appropriate, the PI of the MCC, before forwarding the materials to the Steering Committee and DSMB, will give the applicant an opportunity to amplify, clarify, or withdraw the proposal. Amended proposals will be reviewed by the Steering Committee and the DSMB.

Proposals for ancillary studies should briefly describe the objectives, methods, and significance of the study and provide full details on procedures (e.g., laboratory procedures, examinations, questionnaires) to be carried out on patients, the extent to which visits will be prolonged, and if additional visits will be needed. The proposal should include, if appropriate, an informed consent statement.

2.7.2.1 Funding of Ancillary Studies. If no additional funds are required, the investigator may proceed with the ancillary study as soon as it is approved by the Steering Committee and DSMB. For additional funds, the investigator may submit a research grant application to a funding agency after approval by the Steering Committee and DSMB, and after consultation with the Project Officer, NHLBI.

2.7.2.2 Publication of Ancillary Study Results. Manuscripts to be submitted for publication or presentations of ancillary study data at scientific meetings must be reviewed and approved by the Steering Committee.

CHAPTER 3

ADVERSE EXPERIENCES REPORTING

CHAPTER 3

ADVERSE EXPERIENCES REPORTING

3.1 DEFINITION OF ADVERSE EXPERIENCE

An adverse experience is some unplanned, unwanted event which occurs to a person and which is possibly related to the use of protocol therapy. While some events may not appear to be associated with the use of the study treatment, a relationship may not become apparent until a number of reports accumulate from various Transplant Centers.

It is the COBLT Study policy that adverse experience reports shall be submitted even if the investigator is unsure whether a relationship exists between the adverse experience and the use of the study treatment.

Serious Adverse Experience. A serious adverse experience, as defined by the FDA as any experience that suggests a significant hazard, contradiction, side effect, or precaution. With respect to human clinical experience, a serious adverse experience includes any experience that is fatal or life-threatening or permanently disabling or requires in-patient hospitalization (or prolonged hospitalization) or, in a pregnant woman, results in a congenital anomaly, or a cancer or an overdose. (An overdose is defined as an inadvertent or deliberate administration of a treatment at a dose higher than specified in the protocol or higher than known therapeutic doses. It must be reported, regardless of outcome, even if toxic effects were not observed).

Expected Adverse Experiences. Expected adverse experiences are those adverse experiences which are listed in the Informed Consent, product inserts, or study protocol materials.

Unexpected Adverse Experiences. Unexpected adverse experiences are those which are NOT listed in the study protocol or Informed Consent.

Adverse Experiences - Association With Use of Study Treatment. A determination is made by the investigator as to what relationship, if any, the study medication has to the adverse experience.

Category Definition

Definite: Clear-cut temporal association with a positive rechallenge test or laboratory confirmation

Probable: Clear-cut temporal association not reasonably explained by the subject's known clinical state

Possible: Less clear temporal association; other etiologies are also possible

Remote: Less clear temporal association; other etiologies are probable

None: No temporal association; related to other etiologies such as concomitant medications/conditions or subject's known clinical state

The assessment may change based on information which develops later in the study.

3.2 ADVERSE EXPERIENCE REPORTING AND MANAGEMENT

Because all participants in the COBLT Study will be receiving toxic preparative therapy, significant regimen-related toxicity is anticipated for patients on all study arms. The study forms will capture information on these adverse experiences. Likewise, substantial mortality is anticipated and will be captured via filing of the Death Form.

All centers should report Adverse Experiences to the Medical Coordinating Center (MCC) as described below.

Adverse Experiences	Reporting Requirement
Unexpected and fatal or life-threatening adverse experiences	Call MCC and/or fax Adverse Experience Form within 24 hours Telephone: (301) 251-1161 Fax: (301) 251-1355
Other unexpected and serious adverse experiences	Call MCC and/or fax Adverse Experience Form within three days Telephone: (301) 251-1161 Fax: (301) 251-1355

All serious adverse events must be reported for the duration of the study. All other events will be reported via data forms submission requirements.

3.2.1 Medical Coordinating Center Reporting

All unexpected fatal or life-threatening adverse experiences will be reported to the FDA by telephone within three working days after receipt of the information following FDA guidelines (21 CFR 312.32). All other unexpected serious adverse experiences should be reported to the FDA within ten days of receipt of the information. All expected adverse experiences (i.e., those listed in the informed consent, product inserts, or study materials) not covered under the above requirements need not be reported. Although death and graft failures are not considered unexpected experiences, they will be reported to the FDA via annual reports submitted to address FDA guidelines (21 CFR 312.33).

A physician trained in Cord Blood transplantation will serve as Medical Monitor for the MCC. The Medical Monitor will review all adverse experience reports. The Monitor will also be responsible for reporting to the FDA and DSMB as required.

CHAPTER 4

DATA ANALYSIS AND REPORTING

CHAPTER 4

DATA ANALYSIS AND REPORTING

The COBLT Study analysis plan is designed to carefully monitor study accrual, data quality and timeliness, patient eligibility rates, adverse reactions, and other outcomes. While detailed analyses will be performed periodically, study progress will be monitored continuously. Technical and administrative reporting requirements for the COBLT Study consist of both interim and final reports of the scientific efforts. A complete discussion of study outcome variables and sample size and power considerations is provided in the COBLT Study protocol.

4.1 ANALYSIS PLAN

The analysis plan for the COBLT Study protocol will be developed by the statisticians at the Medical Coordinating Center (MCC) in collaboration with the Data and Safety Monitoring Board (DSMB), the representatives from the NHLBI Biostatistics Scientific Research Group, and the Steering Committee. An initial strategy will be designed during the planning phase of the protocol, with subsequent modifications occurring as the study matures. Key aspects of the plan will include data quality, study progress, and safety and efficacy monitoring. The schedule for performing these analyses is described in the COBLT Study protocol. Database assessments will be performed by the MCC to evaluate database quality on a monthly basis. In addition to these planned analyses, the MCC will expect to conduct various unplanned analyses precipitated by evolving protocol needs. Requests for such analyses will likely come from the DSMB and Steering Committee, but may also be suggested by the MCC or the NHLBI Program Office.

4.1.1 Specification of Analysis Database

Prior to performing a scheduled analysis, the master file for a protocol is copied into an analysis file. This analysis file is date-stamped with a closure date to indicate the last day for which data were included. The master file continues to incorporate new data from the centers while the analysis file is frozen. The closure date provides a reference with regard to the currency of the data on which the analyses are based. Typically, the choice of a date to close the file for analysis is dependent on the type and quantity of the analyses to be performed. Files will likely be closed approximately two months prior to a scheduled meeting.

4.1.2 Reports for Publication

The MCC will work with the Publications Committee in preparing a proposed schedule of analyses for disseminating information from the COBLT Study to the scientific community. This schedule will be based on study and data maturity. Presentations on study methods and baseline data will be scheduled during and after implementation of the recruitment phase. The timing of the release of reports on outcome data will be based on the recommendation from the DSMB.

4.2 EXPECTED ASSESSMENTS OF THE DATABASE FOR QUALITY CONTROL

Assessments of the database will occur at scheduled intervals. These assessments will be targeted at maintaining database integrity, monitoring of Transplant Centers adherence to the protocol, evaluating cumulative baseline information (e.g., patient characteristics), evaluating outcome variables (e.g., disease-free survival, GVHD incidence, graft failure incidence), morbidity, and mortality.

4.2.1 Database Quality

Database quality will be maintained through a variety of analyses which target anomalies, delinquent data, and key entry errors. Reports summarizing anomalies are sent to the Transplant Centers for resolution. A part of this process is to analyze the frequency of errors according to type to determine if certain types of errors are recurrent. Modifications to the data reporting system will be made if the errors occur frequently across Transplant Centers. If errors are localized within a Transplant Center, steps will be taken to resolve the problem by additional training to the center or modifications to the data reporting system.

4.2.1.1 Duplicate and Error Checks. The data entry system used by the MCC is designed to prohibit duplicate records. Another design feature of the data system is the examination of the individual fields and computed values within each record for illegal or conflicting entries. Variables found to be either in error or inconsistent with other data will be compared to an Anomaly Exception File.

The Anomaly Exception File is a means of documenting acceptable anomalies based on patient and visit identifiers. The Anomaly Exception File is maintained by the MCC Data Coordinator as a record of resolved queries and contains the Cord Blood Recipient ID and other form and field identifiers. Also included are the reason for the exception and the date it was entered.

4.2.1.2 Delinquent Data. The determination of delinquent data will be performed at two levels: the form level and the field level. Delinquent forms will be identified and compared to an exception list. All missing forms will be grouped by site and a report file will be generated for distribution to the appropriate Transplant Center. A missing form will continue to be requested either until the data for the form are sent and integrated into the MCC's master database or until an exception is granted and entered into the Missing Forms Exception File.

The second level of delinquent data will be at the field or variable level. Fields will be checked for values which indicate that data are missing. As with the missing form and error/anomaly review, this program will identify the missing values by Patient Number, Visit Number, form, and variable. Reports which identify missing values are generated by site and sent to the Transplant Centers. Missing values will continue to be reported until the data are received or until an exception is granted.

4.2.1.3 Key Entry Errors. Although range checks at the time of key entry will reduce the chance of errors in data entry, the accuracy of the data entered will be enhanced by double keying all patient forms at the MCC.

4.2.1.4 Database Integrity. A sample of data records will be selected for comparison with original Transplant Center records. This audit will be performed by the Protocol Monitor during Protocol Review Visits. Errors will be resolved with the Clinic Coordinator where possible. The frequency of such errors will be tabulated and reported to the Steering Committee.

4.2.2 Operational Statistics

Analyses directed at monitoring the smooth and efficient operation of the study, e.g., the adequacy of patient enrollment, the completeness of data forms, the quality of the completed data forms, study dropouts, etc., will be performed routinely. These reports will assist in identifying local problems which require resolution and will allow routine monitoring of the study to identify problems to determine if modifications of study procedures is indicated. Some of the reports which likely will be generated include:

- Number of patients screened and registered (or not) by Transplant Center and month; cumulative totals
- Percentage of error-free data forms by Transplant Center and overall
- Numbers of dropouts and missed "contacts" by Transplant Center and contact and overall

4.2.3 Patient Characteristics

The multiple characteristics of patients will be analyzed in order to describe the patient population and will include the following:

- Age, sex, race, etc.
- Level of HLA matching
- Cell dose
- Disease type
- Disease risk

4.2.4 Outcome Variables, Morbidity, and Mortality

Assessments of outcome variables, morbidity, and mortality will be performed as determined by the Steering Committee. These assessments will be prepared for meetings of the DSMB by the statisticians at the MCC. In all statistical presentations of COBLT Study data, the number of

patients on which the analysis is based, whether the result is a mean, a percentage, an incidence rate, or a prevalence rate, etc., will be shown. Standard errors, confidence limits, or other measures of sampling variability will also be provided.

4.3 REPORTING

A variety of scientific and administrative reports will be prepared by the MCC, such as:

- Monthly recruitment, screening, and follow-up reports
- Periodic protocol adherence reports for Steering Committee meetings
- Reports on protocol adherence, data quality, and outcome results for the DSMB
- Protocol violation reports for the NHLBI Project Officer, COBLT Study Chairperson, and Steering Committee

Other reports that will be prepared jointly by the MCC and Principal Investigators (PI) are:

- Reports for scientific publication to be reviewed by the Publication Committee
- Reports of adverse experiences for the National Heart, Lung, and Blood Institute (NHLBI) Project Officer

4.3.1 Reports to the Steering Committee and the Technical Subcommittees

The MCC will submit reports to the Steering Committee, NHLBI Project Officer and DSMB summarizing Transplant Center adherence to study protocol and recruitment activities. These reports will include results of Protocol Review Telephone Calls, Protocol Review Visits, Transplant Center database quality and timeliness, and protocol violations. In addition, monthly reports for the Transplant Centers will be prepared providing them with similar data. Study outcome information will not be provided.

Immediately following any DSMB meeting, NHLBI staff will communicate to the Steering Committee any changes to the status of the COBLT Study that have been recommended by the DSMB.

4.3.2 Reports to the Data and Safety Monitoring Board

Interim reports will be prepared by the MCC and distributed to the DSMB at least seven days prior to a scheduled meeting. The contents of the report will be determined by the NHLBI Program representatives and the MCC. Additions and other modifications of these reports may be directed by the DSMB on a one-time or continuing basis.

Interim reports will consist of two parts. Part one will provide information on accrual, baseline characteristics, data quality, and other general information on study status. Part two will contain

outcome data, including toxicity. Both parts of the report are confidential. All copies distributed prior to and at a meeting will be collected by the MCC following the meeting.

4.3.3 **Scientific Reports**

After approval by the Steering Committee, the MCC's statisticians will assist the investigators in preparing scientific publications. In collaborating with PIs on publications, the statisticians provide not only the tabular and graphic presentations of data, but also the study methods and results sections.

CHAPTER 5

QUALITY ENHANCEMENT

CHAPTER 5

QUALITY ENHANCEMENT

The principles of multi-center clinical studies that govern the COBLT Study quality enhancement program are:

- Uniform definitions
- Uniform criteria
- Uniform procedures
- Recruitment of adequate numbers of participants
- Maintaining complete follow-up of all, or nearly all, participants

The goal of the quality enhancement program is to maintain the scientific integrity of the study. The first three points above are addressed in detail in the COBLT Study protocol. The other points are discussed in detail below.

During multi-center studies, many anomalies can occur that may impair the validity of the data collected and thereby the scientific integrity of the study. Among these are:

- Study personnel neglecting to record certain observations on the data forms
- Study personnel failing to perform procedures in the (standard) manner specified
- Study personnel forgetting to perform specified procedures
- Inadequately trained personnel performing study procedures
- Failure of patients to appear for follow-up examinations
- Malfunctioning or improperly calibrated equipment
- Patients losing confidence in the Transplant Center or its staff

The quality enhancement program for the COBLT Study is similar to programs adopted in other multi-center studies[1-4] and is intended to prevent or minimize anomalies that may weaken the quality of the data collected, either because of missing or invalid observations.

The program is based on the following six principles:[1,2]

- Standardized training and certification of Transplant Center personnel in the conduct of study procedures

- Responsibility and accountability of the personnel at the Transplant Centers and the Medical Coordinating Center (MCC) for implementing the study and maintaining the integrity of the data collected

- Open lines of communication between the MCC and the Transplant Centers

- Routine pilot testing of forms and procedures

- Analysis of the quality of the data

- Medical review of patient eligibility and follow-up to assure compliance with protocol requirements.

5.1 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.

5.1.1 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 42% Caucasian, 35% African-American, 12% Hispanic, and 11% 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:

African American	Asian/Pacific Is.	Caucasian	Hispanic	Native American
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.

5.2 PREVENTING DROPOUTS AND MISSED CONTACTS

A primary objective of the COBLT Study is to study the clinical course of patients receiving protocol treatments and medications. To achieve this objective, it is essential that each patient be examined regularly at follow-up visits until the study is terminated or until the patient dies. Missing information can ias the results of the study. Although occasional missed visits cannot be prevented, the study could be invalid if there are many missed visits, numerous patient drop-outs, or missed specimen draws. When data are incomplete, it is difficult to predict the direction of any bias resulting from the incompleteness. The only correct way to deal with missing information is not to have any. Preventing dropouts and missed visits is a responsibility shared by the entire Transplant Center staff.

Prior to registering a patient, a line of communication should be established between the Transplant Center and the patient's primary care physician. The need for long-term follow-up and data collection should be explained and understood by the primary care physician.

5.3 INTERNAL TRANSPLANT CENTER MONITORING

5.3.1 Principal Investigator

Each Principal Investigator (PI) is responsible for ensuring that all study procedures are adhered to in the Transplant Center. He or she must spend adequate time at the Transplant Center observing study procedures and regularly reviewing, one-to-one or in group meetings, various aspects of the study to resolve any problems that may arise.

Other Transplant Center staff members are responsible for reporting problems that could affect the quality of the data to the PI.

5.3.2 Clinic Monitor

The Clinic Coordinators will serve as Clinic Monitors, and in this role will be specifically responsible for reporting problems that have affected or can potentially affect the quality of the data collected. These problems are reported to the PI and to the Protocol Monitor at the MCC. In this role, the Clinic Coordinator should also maintain an up-to-date copy of the Manual of Procedures and the COBLT Study protocol, and encourage all Transplant Center personnel to consult it frequently.

This responsibility also includes receiving regularly scheduled telephone calls from the Protocol Monitor. These calls will follow a structured format and the Clinic Coordinator is responsible for following up on any actions that may be needed as a result of the call.

5.4 EXTERNAL TRANSPLANT CENTER MONITORING

External clinic monitoring is performed by members of the MCC staff, the Data Coordinator, and the Protocol Monitor. The Data Coordinator is responsible for data editing and preparing database audits for site visits. The Protocol Monitor is responsible for placing regularly scheduled telephone calls (Protocol Review Calls) to each Transplant Center, participating in periodic site visits to each Transplant Center, monitoring the certification status of each Transplant Center, and reporting findings periodically to the Steering Committee. Each of these functions is described more fully below.

5.4.1 Data Editing

Data Editing at the MCC, conducted under the direction of the Data Coordinator, involves checking the data forms received from the Transplant Centers for completeness, legibility, adherence to the Manual of Procedures, and internal consistency. This is performed in part manually and in part by computer. The computer edit generates "error messages" regarding incomplete, questionable, or inconsistent data.

A part of the data editing process is to analyze the frequency of errors and forms past due. This information is communicated to the Transplant Centers.

5.4.2 **Computer Virus Protection**

The MCC computer staff has installed anti-viral software to protect the data system.

5.4.3 **Protocol Review Calls**

The Protocol Monitor makes regularly scheduled Protocol Review Calls to each Clinic Coordinator. Initially, these calls are made monthly, gradually tapering off to be less frequent. The calls follow a structured agenda, which is sent in advance to the Clinic Coordinators. The agenda includes the following:

- Staff changes and current or impending needs for training or certification
- Patient enrollment
- Problems in meeting the requirements of the study
- Problems in completing data forms
- Problems in data processing

These regularly scheduled telephone calls are designed to enhance positive communication. Rather than emphasizing errors made by the Transplant Center, which the MCC staff may do in other telephone calls, Protocol Review Calls give each Clinic Coordinator the opportunity to report on the many ways in which the Transplant Center is functioning properly and successfully.

The Protocol Monitor prepares for all Protocol Review Calls by reviewing the data received from a Transplant Center, information about any errors made by the center, the certification status of new staff members, notes from previous calls, and recent correspondence from the Transplant Center.

The Protocol Monitor and the Data Coordinator keep a log of telephone calls, correspondence, and site visits for each Transplant Center. The Protocol Review Calls are not a substitute for other telephone calls that may be needed to resolve problems as they occur. Such calls should be made as often as needed.

5.4.4 Site Visits (Protocol Review Visits)

Protocol review or site visits will be made to each Transplant Center by professional staff from the MCC. The site visit team may also include members of the Steering Committee, Data and Safety Monitoring Board (DSMB), a technician or Clinic Coordinator from another center, and NHLBI Project Team, when appropriate. The purpose of the visit is to exchange information, review the Center's operations, and discuss and resolve problems. The visit will be arranged in advance and a copy of the agenda made available in advance to all participants.

A quality assurance audit may also be performed at this time. Its purpose is to assure that the clinical study is being conducted according to the requirements outlined in the Manual of Procedures and that the data submitted to the MCC and the information found in source documents, such as the patient's medical record, are in agreement.

The audit will include any or all of the following areas of Transplant Center operation:

1. Organization

    - Administrative organization, staff, and facilities review
    - Administrative files
    - Communications with the MCC

2. Procedures

    - Review of study documents such as the Manual of Procedures
    - Eligibility determination and consent process
    - Adverse experience reporting

3. Data Processing

    - Data flow
    - Review of any problems with the Manual of Procedures
    - Review of data queries

4. Chart review

    - Organization of patient COBLT Study chart
    - Signed Informed Consent statement in chart
    - Patient compliance with scheduled follow-up visits and/or missed visits
    - Procedures for data handling
    - Comparison of data submitted to MCC with source documents

5.5 REFERENCES

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CHAPTER 6

TRANSPLANT CENTER PROCEDURES

CHAPTER 6

TRANSPLANT CENTER PROCEDURES

6.1 STAFFING AND ORGANIZATION

Each COBLT Study Transplant Center is staffed, at a minimum, by a Principal Investigator (PI), a Clinic Coordinator, and a laboratory technician. There may be additional physicians designated as co-investigators, as well as administrative personnel.

6.2 FUNCTIONS OF THE PRINCIPAL INVESTIGATOR

The responsibilities of the PI, who is a physician with substantial experience in both cord blood transplantation and the performance of clinical trials, are to:

- Direct the activities of the COBLT Study personnel in the Transplant Center
- Coordinate the scientific and administrative operations of the Transplant Center
- Ensure adherence by Transplant Center personnel to the procedures described in and required by the COBLT Study Manual of Procedures
- Spend sufficient time in the Transplant Center to adequately observe study procedures
- Assure the Transplant Center's fiscal responsibility in the disposition of COBLT Study funds
- Represent the Transplant Center at meetings of the Steering Committee and Technical Subcommittees

6.3 FUNCTIONS OF THE CLINIC COORDINATOR

The Clinic Coordinator is responsible for supervising daily operations in the Transplant Center and serves as primary contact for the study patients and for the Medical Coordinating Center (MCC). The duties of the Clinic Coordinator are to:

- Coordinate search activities for prospective patients
- Ensure that potential COBLT Study patients receive appropriate information about the study, including the Informed Consent statements
- Register patients in the COBLT Study
- Notify the MCC of changes or impending changes in the Transplant Center personnel, address, telephone number(s) of the Transplant Center

- Maintain a file of correspondence with the MCC
- Obtain necessary information about deceased patients (e.g., death certificates)
- Maintain an up-to-date COBLT Study Manual of Procedures and COBLT Study protocol
- Check completed data forms for accuracy and completeness
- Ensure that patient 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
- Respond to data queries from the MCC
- Ensure that personnel performing COBLT Study procedures are properly trained and certified
- Monitor Transplant Center activities for conformance to the requirements of the COBLT Study Manual of Procedures and COBLT Study protocol
    - Participate in regularly scheduled telephone calls (Protocol Review Calls) with the Protocol Monitor
    - Meet with the Protocol Monitor during Site Visits at the Transplant Center
- Report irregularities or problems that can affect the data quality to the PI and the Protocol Monitor
- Other duties as defined by the Steering Committee, Technical Subcommittees, or Data and Safety Monitoring Board (DSMB)

Each Clinic Coordinator will be given a copy of the COBLT Study Manual of Procedures - Chapter 10 for completing COBLT Study data forms.

6.4 **RECRUITMENT**

As described in Section 5.1, each Transplant Center must have a plan for tracking transplants and transplant candidates to ensure meeting the recruitment goals and requirements of the COBLT Study. The monthly recruitment report (Section 10.5) should be part of this plan. This plan will be reviewed during site visits.

6.5 ELIGIBILITY SCREENING

If a patient appears to be eligible, the following steps should be taken:

1. The plan of the study should be reviewed with the patient and any questions by the patient should be answered.

2. The patient should be asked to sign the Informed Consent statement.

3. If the patient is determined to be ineligible, the reasons for ineligibility should be discussed with the patient.

4. Patients will be followed at designated intervals according to the Follow-Up Schedule in the COBLT Study Protocol.

Once a patient has been assigned a registration number, the number remains associated with the patient and will not be reassigned.

6.6 SCHEDULING PATIENT APPOINTMENTS

After a patient has been registered, the MCC will issue to the Transplant Center a patient schedule for all the COBLT Study follow-up visits. The patient schedule specifies the target appointment dates and the maximum and minimum dates (time windows) for each follow-up visit. When scheduling appointments, the various time windows must be kept in mind. Efforts should be made to avoid missed visits and to keep follow-up visits as close to the target date as possible. If a patient is moving to an area that is not near the Transplant Center, staff should encourage the patient to return to the Transplant Center for their scheduled follow-up visits. At times when a patient is not planning to return to the Transplant Center for a follow-up visit, the Clinic Coordinator should make arrangements to obtain the necessary information through the patient's primary physician.

6.7 CHECKING COMPLETED FORMS

Before submitting data to the MCC, the Clinic Coordinator should carefully check all data for completeness and consistency. The Clinic Coordinator must also ensure that patient names, social security numbers, and any other personal identifiers are removed from all materials sent to the MCC.

Completeness and consistency. Every effort should be made to complete every field on each data form. Each form will be extensively computer-edited at the MCC. Incomplete and inconsistent items will be queried by the MCC and clarification requested.

Numerical responses. Numerical responses such as hematologic values will be computer-edited to determine whether they are within certain limits. If they are not, then an edit message is sent to the Transplant Center. This type of message is not evidence of an error, but simply a request to verify that the number is correct.

Legibility. Entries on data forms and responses to queries should be typed or clearly printed in ink.

6.8 TRANSFERRING PATIENTS

All follow-up reporting requirements of COBLT Study patients will be the responsibility of the Transplant Center which registers the patient. It is not anticipated that patients will transfer to new transplant centers; thus, no plans are developed to accommodate this situation.

CHAPTER 7

MEDICAL COORDINATING CENTER PROCEDURES

CHAPTER 7

MEDICAL COORDINATING CENTER PROCEDURES

7.1 STAFFING AND ORGANIZATION

The Medical Coordinating Center (MCC) for the COBLT Study is located at The EMMES Corporation in Potomac, Maryland. The staff at the MCC include the following:

- Principal Investigator (PI)
- Biostatisticians
- Immunologist
- Administrative Coordinator
- Data Coordinator
- Protocol Monitor
- Computer System Group

The PI directs the MCC in its responsibility to provide study design, statistical analysis, project reporting, data collection and administrative coordination. He or she works closely with the project biostatisticians who assist in protocol development, data analysis, report generation, and publications. The Data Coordinator is responsible for maintaining the currency, accuracy, and integrity of the COBLT Study databases and the training and certifying of Transplant Center and Cord Blood Bank personnel in COBLT Study forms completion. The Data Coordinator is also available for support, directly or as a liaison, in defining and solving problems associated with forms completion. The Protocol Monitor assists in training and certifying of Transplant Center and Cord Blood Bank staff in registration and laboratory procedures and participates in periodic Protocol Review Visits. The Protocol Monitor also serves as a staff specialist for dealing with problems associated with patient accrual. The Computer System Group is responsible for the design, development, installation, and maintenance of the COBLT Study data system. The hardware and software components of the COBLT Study data system are located at the MCC. The Administrative Coordinator is responsible for all logistical and administrative support.

7.2 COORDINATION AND ADMINISTRATION

One of the routine functions of the MCC is to meet the many administrative, logistic, and communications requirements of the COBLT Study.

7.2.1 Roster of COBLT Study Personnel

To maintain efficient communication among the participating Transplant Centers, the Steering Committee and other various COBLT Study subcommittees, and the NHLBI, the MCC maintains a roster of all COBLT Study personnel (Appendix A). This roster lists the names and addresses of all participating units, and the names and telephone numbers of all COBLT Study members. COBLT Study personnel also are listed alphabetically.

7.2.2 **Committee Support**

The COBLT Study is supported by a network of committees. For most committee meetings, the MCC provides logistical support. The MCC collaborates with the NHLBI Program Office to:

- Determine optimal meeting dates
- Select meeting sites based on cost and convenience
- Communicate information about meetings to committee chairperson
- Prepare meeting materials
- Provide logistical support during the meeting
- Duplicate and distribute materials prior to each meeting
- Prepare and distribute minutes of the meetings
- Follow-up on all action items after each meeting
- Coordinate conference calls

7.2.3 **Documentation**

The MCC supports the preparation, duplication, and dissemination of administrative and technical reports and manuscripts. These documents may include:

- Manual of Procedures
- Protocols
- Patient recruitment materials
- Meeting minutes
- Statistical reports
- Bibliographies
- Abstracts
- Manuscripts for publication
- Roster of COBLT Study personnel

MCC staff work closely with clinicians, statisticians, writing committees, protocol development subcommittees, scientists, and authors. The staff routinely helps to:

- Compile and organize materials
- Coordinate reviews and incorporate comments
- Summarize background materials

- Write administrative reports

- Maintain a chronology of revisions and modifications of the Manual of Procedures, the CBB SOP, and the COBLT Study protocol

7.3 STUDY PLANNING

The design of the COBLT Study is a collaborative venture that involves physicians and other health care personnel from the Transplant Centers, biostatisticians and other staff from the MCC, and the NHLBI. MCC staff participate on various COBLT Study committees involved with the design of the study. The MCC has primary responsibility for 1) evaluating the impact of protocol decisions on the scientific integrity of the study (e.g., feasibility of obtaining and maintaining patient compliance with study procedures, etc.); 2) determining the minimum required sample size, confidence limits, and power (to the extent that protocol decisions affect sample size requirements); and 3) establishing resource (personnel and equipment) requirements.

7.4 DATA MANAGEMENT

Data management is one of the main functions of the MCC. In the COBLT Study, Transplant Centers will submit data to the MCC using forms developed by the National Marrow Donor Program (NMDP) and International Cord Blood Transplant Registry (ICBTR) and supplementary forms designed and developed at the MCC in collaboration with the Steering Committee.

NMDP Forms. The following NMDP forms will be completed at the Transplant Centers using NMDP instructions and coding:

- Recipient Baseline and Transplant Data (Form 120 and appropriate ICBTR insert)

- 100-Day Follow-Up Visit of Recipient (Form 130)

- Post Transplant Follow-up Form Insert I – Severe Combined Immunodeficiency (SCIDS) (Form 130 Insert I) when applicable

- Post Transplant Follow-up Form Insert II – Wiscott Aldrich Syndrome (WAS) (Form 130 Insert II) when applicable

- Post Transplant Follow-up Form Insert III – Information for Hodgkin and Non-Hodgkin Lymphoma (Form 130 Insert III) when applicable

- Six-Month to Five-Year Follow-Up Visit of Recipient (Form 140)

- Post Transplant Follow-up Form Insert I – Severe Combined Immunodeficiency (SCIDS) (Form 140 Insert I) when applicable

- Post Transplant Follow-up Form Insert II – Wiscott Aldrich Syndrome (WAS) (Form 140 Insert II) when applicable

- Post Transplant Follow-up Form Insert III – Information for Hodgkin and Non-Hodgkin Lymphoma (Form 140 Insert III) when applicable

- Yearly Follow-up for Greater than Five Year Post Transplant (Form 150) when applicable

- Leukemia and MDS Yearly Follow-up for Relapse Post Stem Cell Transplant (Form 160) when applicable

- Recipient Death Information (Form 190)

Copies of these forms will be submitted to the Data Coordinator at the MCC.

Supplementary Forms. Supplementary forms will be completed at the Transplant Centers using instructions and coding detailed in the COBLT Study Manual of Procedures - Chapter 10. The original form will be submitted to the Data Coordinator at the MCC. A copy of the form will be kept in the patient's COBLT Study file at the Transplant Center.

Criteria for forms submission timeliness have been developed by the MCC for NMDP, ICBTR, and supplementary forms; see Chapter 10. Forms that are not received at the MCC within the specified criteria will be considered delinquent. Each month, Transplant Centers will receive a listing of delinquent forms. A missing form will continue to be requested either until the data for the form is submitted and integrated into the MCC's master database, or until an exception is granted and entered into the Missing Forms Exception File.

The MCC trains and certifies Clinic Coordinators in forms completion and submission. Certification is designed to ensure that clinical staff responsible for submitting data are familiar with the forms, instructions for supplementary forms completion, and the criteria for timeliness of 1) forms submission and 2) response to queries. Clinic Coordinators who attend a data management training session at a COBLT Study Clinic Coordinators meeting will be considered certified. Clinic Coordinators who have not attended a data management training session can be granted certification by the Data Coordinator at the MCC.

7.5 **DATA ANALYSIS AND REPORTING**

In providing statistical support for the COBLT Study, MCC biostatisticians are responsible for developing the analysis plan for the COBLT Study protocol in collaboration with the Data and Safety Monitoring Board (DSMB) and the representatives from the Biostatistics Scientific Research Group, Division of Epidemiology and Clinical Applications, NHLBI, as detailed in Chapter 4. The plan carefully monitors patient accrual, patient eligibility rates, adverse reactions, and other outcomes. Detailed analyses will be performed periodically and study progress will be monitored continuously. The biostatisticians will play a key role in reviewing the findings of the study and defining ancillary studies. They are fully trained and understand the medical aspects of the COBLT Study. They are expected to help ensure that the COBLT Study is conducted properly, progresses appropriately, and establishes the most accurate results based on the data gathered.

The COBLT Study requires continuous and comprehensive technical and administrative reporting which will be overseen by the MCC. Such reports will constitute important interim and final products of the scientific effort.

Database assessments conducted by the MCC will be targeted at maintaining the integrity of the database, monitoring adherence of the clinics to the protocol, and developing cumulative baseline and outcome assessments.

CHAPTER 8

SEARCH PROCEDURES

CHAPTER 8

COBLT CORD BLOOD BANK SEARCH PROCEDURES

Sections 8.1 through 8.6 describe the search process for cord blood units stored at the two COBLT Cord Blood Banks, Duke University and UCLA. Section 8.7 addresses requirements for using cord blood units from non-COBLT Cord Blood Banks.

Searching for a suitably matched Cord Blood Unit (CBU) stored in a participating Cord Blood Bank (CBB) is performed by using the COBLT online search system at each Transplant Center. The COBLT online search system provides a tool that enhances the ability of each transplant center to perform, update, and monitor searches at the search coordinators' convenience. It also simplifies the coordination between the Medical Coordinating Center (MCC) and the participating transplant centers.

Recipient HLA-A, HLA-B, and HLA-DRB1 typing data are compared to typing data of the CBUs in the donor registry. HLA allele designations are defined according to the WHO Nomenclature Committee for Factors of the HLA System, with the original list from December 1996. Valid designations and mappings to allele level and serological level HLA types can be found on the system by selecting "HLA Mappings"(Exhibit 8.0). The COBLT Histocompatibility Subcommittee updates this list regularly and makes decisions on the serologic equivalents.

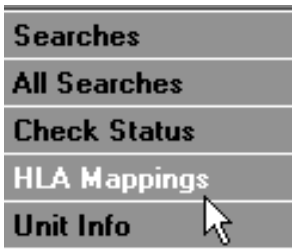


Exhibit 8.0

The COBLT study has three levels of searching and reserving COBLT CBUs - Preliminary Search, Formal Search, and CBU Reservation. Each level is described below and illustrated in Figure 8.2.

8.1 PRELIMINARY SEARCH

A preliminary search is performed to identify CBUs with a suitable cell dose and HLA type for a recipient. A preliminary search is initiated online by the transplant center. To initiate a search, select "Add/Update" (Exhibit 8.1.1). Preliminary searches performed online are available immediately for review. The first dialogue box of the add/update page is illustrated in Exhibit 8.1.2.

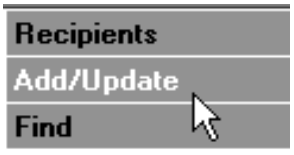


Exhibit 8.1.1

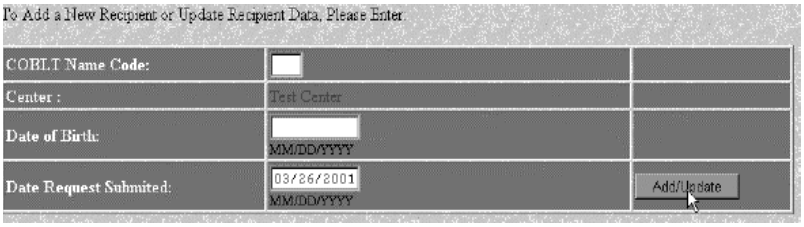


Exhibit 8.1.2

Recipient HLA typing for a preliminary search may be performed by serology or by DNA technology for Class I (HLA-A and HLA-B), and by DNA technology for HLA-DRB1. Serology may be submitted for HLA-DR, however this is not recommended. HLA typing may be updated at any time during the search process by updating recipient data online. The search algorithm will use the most recent HLA data available for each search performed to calculate a COBLT score and an "approximate" NMDP matching grade at each locus (HLA-A, -B, and -DRB1). Table 8.1.1 displays the score definitions.

Table 8.1.1
Search Report Score and Typing Grade

	Number of Potential Antigen Matches by Level of Resolution				
COBLT Score	High Resolution DNA Typed	Low-Intermediate DNA Typed	Serologic Private/split	Serologic Broad	Mis-Match
2	2				
2	1	1			
2		2			
2	1		1		
2		1	1		
2			2		
2	1			1	
2		1		1	
2			1	1	
2				2	
1	1				1
1		1			1
1			1		1

The COBLT cor a or th a a he there are pote ta atche et ee a do or a d rec pe t at o e oc e COBLT Score o a ed he there o e pote ta atch a d o e atch et ee a do or a d rec pe t at o e oc e

COBLT Search Report

o o the o o a pre ar earch or a earch report a e e ed o e or e the do e pd h t The rec pe t e de t ed the e e d t COBLT a ed at the t e the pre ar earch t tated

Report c de rec pe t or at o a d a t o pote t a atched CB The report t p to CB h ch at the COBLT L atch re re e t a d ha e a o c eated ce per o ra o rec pe t e ht O the report COBLT CB are ordered r t L atch a d th each L atch cate or crea c eated ce co t The earch report pro de the COBLT core the COBLT Cord B ood Ba code the e CB de t cat o er L t p hether or ot co r ator L t p ha ee per or ed do or eth c t BO t pe c eated ce co t C M a d C co t or each ted CB add t o the e e o re o t o d cated der eath the COBLT core The re o t o de ed a a o re o t o atch L atch or h h re o t o atch e a pe o the e e o re o t o o d e L LL

Report or e earche are a to at ca repeated e er da or a a o o th or t a re e t to d co t e the earch re e ted o e Searche ca e e te ded e o d o th ot the MCC o e Ca ce at o o a earch a a o e tated o e he a earch ca ce ed a rea o or ca ce at o t e d cated

Date:	01/07/03	From:	The COBLT Coordinating Center
Center:	Test Center	Fax:	301-251-1161
Search Performed:	01/07/03	Phone:	301-251-1355

Cord Blood Matching Results

Recipient Name:		Recipient ID:	1023357	Name Code:	AAA
Gender:	n	HLA A:	0101		DNA
DOB:	01/01/00		24XX		
Weight:	10.0	HLA B:	08XX		DNA
Ethnicity:	Unknown|Unknown		40XX		
Blood Type:	n/a Rh: n/a	HLA DRB1:	1301		DNA
			1101		

COBLT Score	CBU ID	NCC/kg (x10^7)	Confirmed	Gender ABO	Rh	Ethnicity	CFU-GM (x10^5) CD34 (x10^6)
122	W15930003223100R	9.8	N	M		Eur/W.Russia|Eur/W.Russia	6.3
LXLLHH				O	-		1.9
HLA A:	01XX 31XX						
HLA B:	08XX 40XX						
HLA DRB1:	11011 13011						

Exhibit 8.1.1.1

8.1.2 **Selecting a COBLT CBU for a Formal Search**

Within the best HLA match group (5/6 and 6/6 versus 4/6), the unit providing the highest cell dose should be selected. This criteria may be modified if within a 4/6 or 3/6 match group a CBU is available with a much greater cell dose than any CBU within the 5/6 or 4/6 HLA match group, respectively. Additional secondary selection criteria are determined by each transplant center following institutional guidelines.

8.2 **FORMAL SEARCH**

A formal search is initiated by requesting a formal search online (Exhibit 8.2.1). The formal search process enables a transplant center to place up to three units on request per recipient and to initiate confirmatory HLA typing for the recipient and CBU(s). The confirmatory HLA typing process for recipients is illustrated in Figure 8.2.

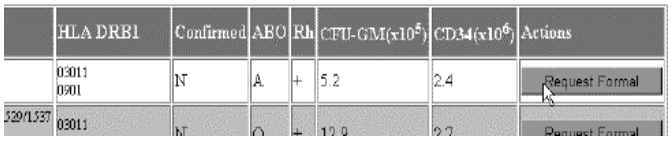


Exhibit 8.2.1

Recipients who are HLA typed by molecular DNA methods are not required to obtain confirmatory typing by COBLT HLA Laboratory prior to registration. The transplant center's HLA typing must be at high resolution level for HLA DRB1 and at least at low resolution for HLA-A and HLA-B.

COBLT CBUs on request continue to appear on COBLT transplant center search reports but a request status is indicated beside the CBU number. CBUs are placed on request for a maximum of 60 days.

COBLT CBUs may be requested by multiple transplant centers at any given time. If the MCC receives a request to reserve a unit which is on request by more than one transplant center, then the MCC will notify the other transplant centers of the reservation. The notified transplant centers will have up to three business days to notify the MCC of continued interest in that unit. If more than one transplant center continues to express interest in a particular unit, the issue will be referred to the Cord Blood Allocation Review Subcommittee with any affected members recusing themselves from the Subcommittee discussion and recommendation.

Upon receipt of a completed Formal Search online, the MCC will send a Confirmatory Typing Request for COBLT CBU(s) to the appropriate HLA reference laboratory(ies) to activate the confirmatory typing process (Figure 8.3 and 8.4).

Confirmatory typing for a recipient may also be initiated online. After confirmatory typing for a unit has been requested another option appears that allows the user to request confirmatory typing for the recipient. Upon receipt of a recipient confirmatory typing request, the MCC will send a Confirmatory Typing Request for the recipient to the appropriate HLA reference laboratory(ies) to activate the confirmatory typing process. (Exhibit 8.2.2).

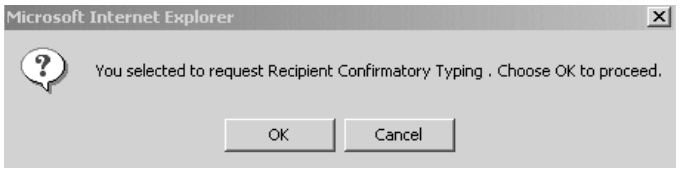


Exhibit 8.2.2

The Recipient Sample Shipping Notification (Figure 8.5A) should accompany the recipient sample when it is sent to the HLA laboratory. A copy should also be faxed to the MCC. It is recommended that recipient confirmatory HLA typing be completed before a patient can be registered. The recipient sample must be labeled with COBLT Recipient ID and name code.

Confirmatory typing data for both the recipient and the CBU(s) are transmitted to the MCC by the HLA reference laboratories for incorporation into the COBLT search databases. Confirmatory HLA typing for CBU(s) will be automatically updated. Confirmatory HLA typing for the recipient must be reviewed by the transplant center before the database is updated.

The MCC will compare recipient typing results provided by the transplant center to typing results provided by the HLA typing laboratory. In the event of typing discrepancies, a Typing Results-Recipient is generated (Figure 8.6). The transplant center must review the HLA typing data and enter the final HLA typing online. Discrepancies in the HLA typing between the transplant center and the reference laboratory must be resolved by indicating the consensus HLA typing on the Typing Results-Recipient (Figure 8.6) and submitting the updated report to the MCC.

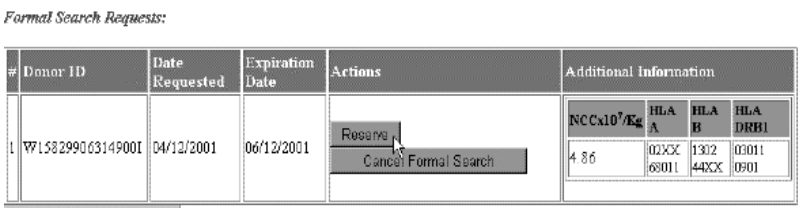
8.3 COBLT CBU RESERVATION

At this time, the transplant center has the option of reserving a CBU for a recipient or continuing the formal search process (see Figure 8.1). One COBLT CBU per recipient can be reserved for a maximum of four months with the possibility of an extension. Transplant centers requesting a reservation extension should contact the Search Coordinator at the MCC. All requests for extensions will be tracked by the MCC. Reserved units will not appear on other search reports. Reservation of a unit is initiated online (Exhibit 8.3.1 and 8.3.2).

Reservations:

#	Donor ID	Date Requested	Expiration Date	Actions	Additional Information			
					NCCx10⁷/Kg	HLA A	HLA B	HLA DRB1
1	W158200067402OC	04/12/2001	08/12/2001	Cancel	7.97	02XX 25XX	18XX 35XX	0701 1401

Exhibit 8.3.1



Formal Search Requests:

#	Donor ID	Date Requested	Expiration Date	Actions	Additional Information			
					NCCx10⁷/Kg	HLA A	HLA B	HLA DRB1
1	W158299063149001	04/12/2001	06/12/2001	Reserve Cancel Formal Search	4.86	02XX 6801	1302 44XX	0301 0901

Exhibit 8.3.2

After the CBU Reservation has been requested online, the Transplant Center Feedback Sheet will be produced and sent to the transplant center. The sheet contains updated CBU information and Maternal Sample infection disease test results. Notification of interest by a transplant center will also be sent to the appropriate CBB.

8.4 REQUEST FOR SHIPMENT OF A RESERVED COBLT UNIT

At the time a patient is registered on the COBLT Protocol, the MCC will produce a Confirmation of Registration / CBU Release Request (Figure 8.7). This sheet will provide the COBLT Recipient ID, the requested CBU ID, date registered, and the proposed start of conditioning date. Upon receipt, the transplant center will complete the middle portion of the Confirmation of Registration / CBU Release Request and provide the proposed shipment date, contact information, and a shipping address. Once the sheet has been completed and signed by the transplant center PI it is faxed to the CBB.

The Confirmation of Registration / COBLT CBU Release Request will serve as the written request for shipment of the reserved CBU. Note that shipments will be routinely scheduled for weekdays (i.e., Monday to Thursday shipment for Tuesday through Friday receipt), however, all efforts should be made to ship Tuesday and Wednesday. This will help to ensure optimal staffing for receipt and storage of the CBU.

The CBU will typically be requested 2-3 weeks prior to transplant (1-2 weeks prior to initiating conditioning). Note that once a CBU is shipped, it will not be returned to the bank inventory if the intended recipient does not proceed to transplant. Thus, the storage time of the unit should be minimized at the transplant center to reduce the chances of discarding CBUs.

The CBB will notify the MCC when a shipment request has been received by completing the final portion of the Confirmation of Registration / CBU Release Request. The MCC will prepare and send the Investigators Brochure (Appendix B) including the Transplant Center Feedback Sheet to the CBB. The CBB will include the Investigators Brochure with the CBU shipment. At the time of shipment, the CBB completes the CBU Disposition Form and the unit is removed from the search registry.

8.5 CONFIRMATION OF RECEIPT OF CORD BLOOD UNIT

Accompanying all shipped CBUs is a Transplant Center Feedback Sheet. The lower portion of this report is completed at the time of receipt of the CBU to document the adequacy of the condition of the shipping container and the CBU upon receipt at the transplant center. After completion of the lower portion, the report is sent by facsimile to the originating CBB.

After thawing of the CBU which is performed shortly before the transplant, the post-thaw total nucleated cell count and cell viability are recorded on the report. The report is sent to both the originating CBB and the MCC by facsimile on the day of transplant.

8.6 MULTIPLE SEARCHES FOR A RECIPIENT AND TRANSFERRING SEARCHES

More than one center may perform a preliminary search for the same recipient. During the search process, the MCC attempts to identify multiple recipient searches from different centers for the same recipient. This information will be stored and tracked by the MCC.

Patients searched at one center can be transferred to a second center after completion of the Search Transfer Form. This form should be completed by the original searching center and submitted to the Search Coordinator at the MCC.

8.7 CORD BLOOD UNITS FROM NON-COBLT BANKS

A patient may still be transplanted with a non-COBLT cord blood unit and participate in the COBLT study. However, non-COBLT units must come from the New York Blood Center, NMDP-approved banks, or U.S. banks meeting NetCord-FAHCT standards. In addition, the transplant center must follow the COBLT protocol, which specifies conditioning regimens, GvHD prophylaxis, and standard operating procedures for handling units. It is recommended that all units from non-COBLT cord blood banks be confirmatory typed. Samples must be obtained from the wash during the thawing process for retrospective allele level DNA-based typing by the COBLT HLA laboratories. The Non-COBLT Cord Blood Unit Sample Shipping Notification (Figure 8.5B) should accompany the cord blood unit sample when it is sent to the COBLT HLA laboratory.

Figure 8.1
COBLT CBU Searching and Reserving

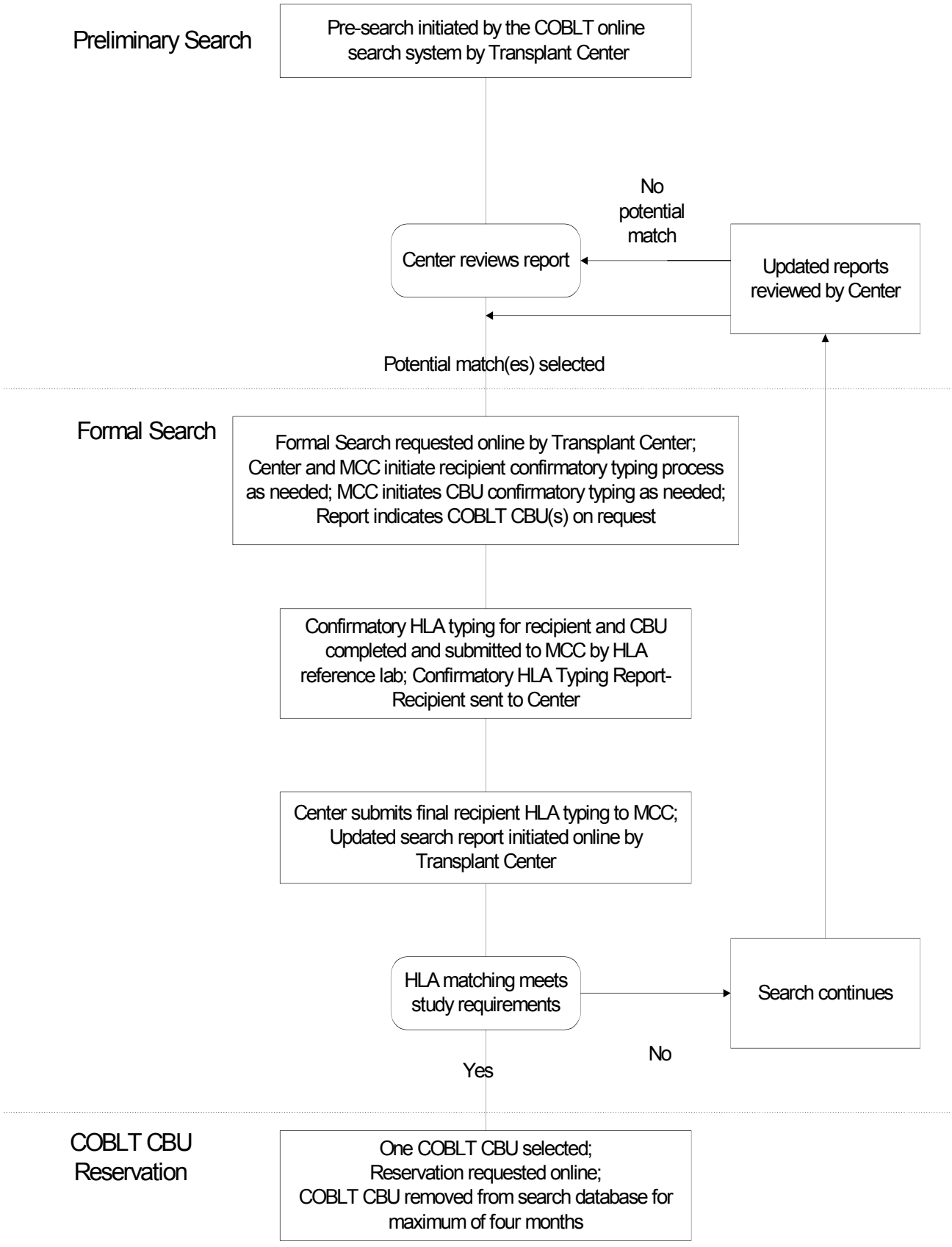


Figure 8.2
Confirmatory HLA Typing Process by COBLT Laboratory

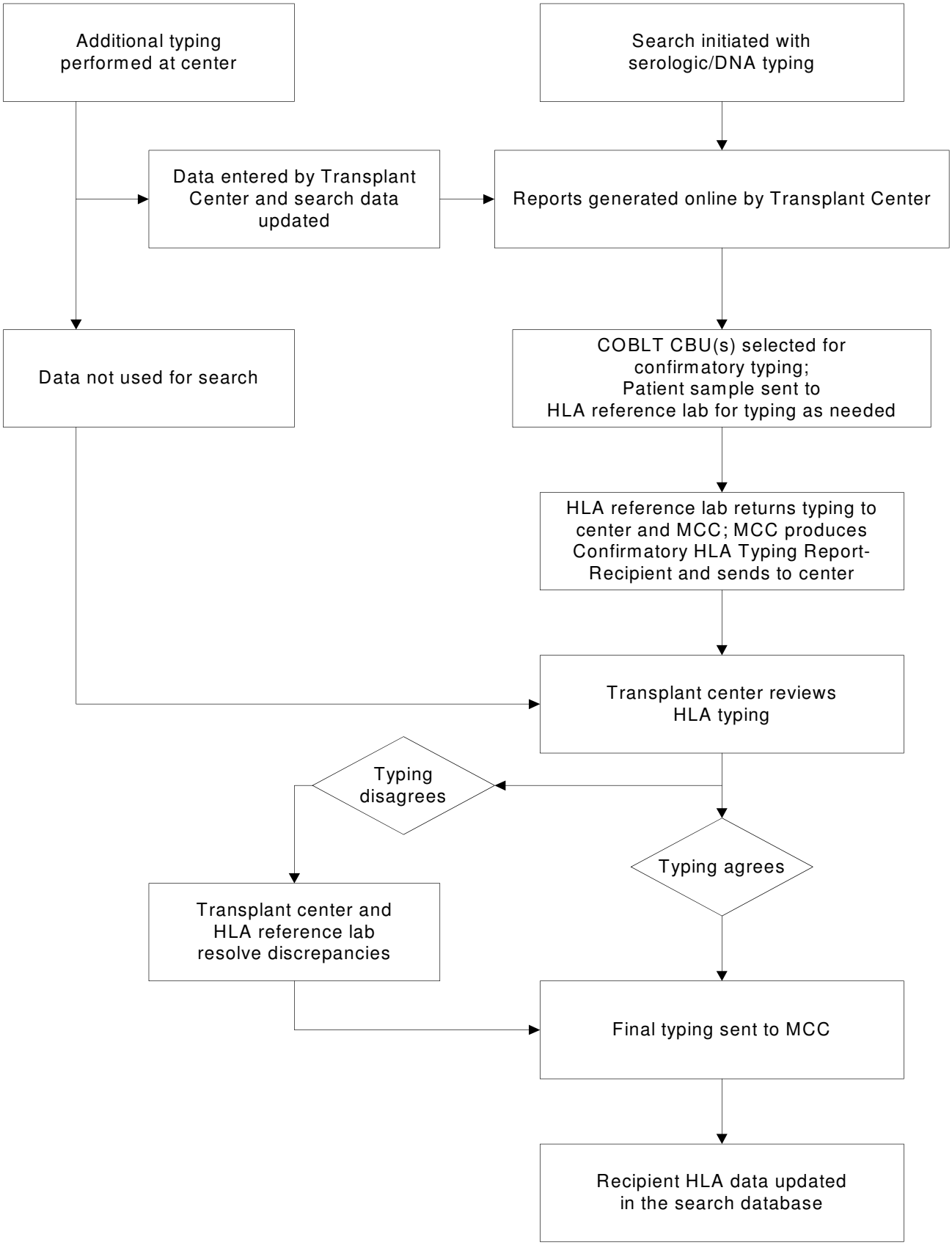


Figure 8.3

CONFIRMATORY TYPING REPORT - RECIPIENT

To: From: MCC, COBLT Study

Fax: Fax: 301-251-1355

This is a request from the Medical Coordinating Center to initiate confirmatory typing for recipient,_____.
A sample from this recipient will be sent by_____.
If you have any questions, please call the MCC at 301-251-1161.

Date:
☐ Check here and fax back to the MCC to confirm receipt or
Email confirmation to COBLTDM@emmes.com

(To be completed by the HLA reference laboratory.)

CONFIRMATORY TYPING RESULTS

Recipient: Namecode:

HLA-A: _____

HLA-B: _____

HLA-DRB1: _____

Optional HLAs:

HLA-C: _____

HLA-DQB1: _____

HLA-DRB2: _____

HLA-DRB3: _____

HLA-DRB4: _____

HLA-DRB5: _____

☐ Check here if additional information has been attached.

_____ _____
Signature Date

Fax this completed HLA typing report for the above recipient to the MCC.
To: MCC, COBLT Study Fax: 301-251-1355

Figure 8.4

CONFIRMATORY TYPING REPORT - COBLT CORD BLOOD UNIT

To: From: MCC, COBLT Study

Fax: Fax: 301-251-1355

This is a request from the Medical Coordinating Center to initiate confirmatory typing for CBU

Please contact the MCC at 301-251-1161 if you have any questions.
Date:

☐ Check here and fax back to the MCC to confirm receipt or Email confirmation to COBLTDM@emmes.com

---

(To be completed by the HLA reference laboratory)

CONFIRMATORY TYPING RESULTS

HLA-A: _____

HLA-B: _____

HLA-DRB1: _____

Optional HLAs:

HLA-C: _____

HLA-DQB1: _____

HLA-DRB2: _____

HLA-DRB3: _____

HLA-DRB4: _____

HLA-DRB5: _____

☐ Check here if additional information has been attached.

_____ _____
Signature Date

Send HLA typing results for the above unit to the MCC in electronic form for inclusion into the HLA typing database, and fax this completed report to the MCC.

To: MCC, COBLT Study Fax: 301-251-1355

Figure 8.5A

COBLT
CORD BLOOD TRANSPLANTATION STUDY

RECIPIENT SAMPLE SHIPPING NOTIFICATION

COBLT Recipient ID: ☐☐☐ ☐☐☐☐

COBLT Name Code: ☐☐☐

Center Code: ☐☐☐

Recipient sample shipped on: ☐☐/☐☐/☐☐

**This completed sheet must accompany the sample at the time of shipment to the HLA Reference Laboratory and the COBLT Recipient ID number MUST be recorded on the label of the recipient sample.*

(Optional) Hospital ID: ☐☐☐☐☐☐☐☐☐☐☐☐

Please select one: ☐ Confirmatory Typing Sample ☐ Retrospective HLA Typing Sample

Specify type of buffer:_____

(Optional) Date results due:_____

Name of person shipping sample:_____ Phone #:_____

_____ _____
Signature of shipper Date

**Fax this completed sheet to the MCC at the time the recipient sample is shipped.*

To: COBLT MCC
Fax: 301-251-1355

From:_____
Fax:_____

Recipient Confirmatory Typing and Retrospective HLA Typing - Specimen Shipping Instructions

What to send:

- For patients with normal WBC, 7 mL peripheral blood (yellow top-ACD or purple top-EDTA). Note that in smaller patients, 2mL of peripheral blood is usually sufficient if acquisition of 7 mL is problematic.
- For patients with low WBC, 20 mL peripheral blood (yellow top-ACD or purple top-EDTA) or a minimum of 5 mL peripheral blood PLUS 2 buccal swabs.
- For heterozygous HLA, 4 buccal swabs should be obtained. Additional sample may be required if homozygosity must be confirmed.
- Study-approved buccal swab kits must be used to collect samples. Kits can be obtained from the COBLT Medical Coordinating Center. All buccal swab samples should be sent to Dr. Baxter-Lowe's lab.
- For blood samples, send the samples in two tubes if possible.
- For alternative specimens, contact the Medical Coordinating Center at 301-251-1161.

How to send:

- Samples may be stored at room temperature up to a week prior to shipping
- Ship next day delivery, Monday thru Thursday for delivery at the labs Tuesday - Friday
- Label outside of container with: SHIP AT ROOM TEMPERATURE - DO NOT REFRIGERATE - HUMAN BLOOD SPECIMENS

Where to send:

Transplant Center	COBLT HLA Laboratory
Children's Hospital of L.A. Children's Hospital of Orange County City of Hope Duke University Fred Hutchinson CRC Hackensack University North Texas Hospital for Children UCLA UCSF	Dr. LeeAnn Baxter-Lowe UCSF Immunogenetic and Transplant Laboratory 45 Castro Street Main Hospital Level B San Francisco, CA 94114 Phone: 415-476-3883, 415-476-3886 FAX: 415-476-0379
Dana Farber Cancer Institute Indiana University University of Minnesota Cardinal Glennon Case Western Reserve University All other centers not listed	Dr. Marcelo Fernandez-Vina Navy Medical Research Institute GU-BMR Nicholson Research Building A, 4th Floor 5516 Nicholson Lane Kensington, MD 20895 Phone: 301-998-8904 FAX: 301-998-8946

V03, 04/03 Fax this form to the COBLT MCC at 301-251-1355. Page 1 of 1

Figure 8.5B

COBLT
ORD BLOOD TRANSPLANTATION STUDY

NON-COBLT CORD BLOOD UNIT SAMPLE SHIPPING NOTIFICATION

COBLT Transplant Center Information:

Center Name:_____Contact Person:_____

Phone:_____Fax:_____

COBLT Recipient ID: ☐☐☐☐☐☐☐

CBU ID: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Source of CBU Sample: G New York Blood Center
G NMDP-approved CBB. Specify:_____
G Transplant Center - Post-thaw sample
G Other, Specify:_____

Transplant Center should fax this form to the Non-COBLT cord blood bank to complete shipping information. If this is a post-thaw sample, the transplant center should complete the entire form and send with the CBU sample to the COBLT HLA reference laboratory. A copy of the completed form should also be faxed to the MCC.

Shipping Information:
Cord Blood Bank should complete the shipping information below and include a copy of this form when shipping the CBU sample to the COBLT HLA reference laboratory. A copy of this completed form should also be faxed to the COBLT Transplant Center contact person noted above.

Note: The CBU identification number must be recorded on the CBU sample label prior to shipping.

Date CBU sample shipped: ☐☐/☐☐/☐☐

Specify type of buffer: _____

Shipped by:_____ Institution:_____

Phone:_____ FAX:_____

Where to send CBU sample:

Transplant Center	**COBLT HLA Laboratory**
Children's Hospital of L.A. Children's Hospital of Orange County City of Hope Duke University Fred Hutchinson CRC Hackensack University North Texas Hospital for Children UCLA	Dr. LeeAnn Baxter-Lowe UCSF Immunogenetic and Transplant Laboratory 45 Castro Street Main Hospital Level B San Francisco, CA 94114 Phone: 415-476-3883, 415-476-3886 FAX: 415-476-0379
Dana Farber Cancer Institute Indiana University University of Minnesota Cardinal Glennon Case Western Reserve University All other centers not listed	Dr. Marcelo Fernandez-Vina Navy Medical Research Institute GU-BMR Nicholson Research Building A, 4th Floor 5516 Nicholson Lane Kensington, MD 20895 Phone: 301-998-8904 FAX: 301-998-8946

Note: Upon completion of the Shipping Information, the Transplant Center should fax this form to the MCC (301-251-1355) and the COBLT HLA Reference Laboratory.
V02, 04/03

Figure 8.6

COBLT CORD BLOOD TRANSPLANTATION STUDY

DISCREPANT TYPING RESULTS - RECIPIENT

The following are the most recent HLA typing results provided by the Transplant Center and the HLA reference laboratory.

Recipient: _____ **Namecode:_____**

Transplant Center typing results:
HLA-A: _____
HLA-B: _____
HLA-DRB1: _____

HLA reference laboratory typing results:
HLA-A: _____
HLA-B: _____
HLA-DRB1: _____

Please check the appropriate box and follow the instructions:

☐ **Typing provided by the HLA reference laboratory should be used as the final typing for the above recipient.** Complete this sheet ***and*** the Search Update Form with the final typing and fax both to the MCC.

☐ **There is a discrepancy between the typing reported by the Transplant Center and the HLA Reference Laboratory.** Contact the HLA Reference Laboratory. Once final typing has been determined, complete this sheet ***and*** the Search Update Form with the final typing and fax both to the MCC. Fax this sheet to the HLA Reference Laboratory with instructions to sign and date sheet and fax to the MCC.

Final typing results:
HLA-A: _____
HLA-B: _____
HLA-DRB1: _____

_____ _____
Signature (Transplant Center) Date

_____ _____
Signature (HLA Reference Lab) Date

The EMMES Corporation • 401 North Washington Street, Suite 700, Rockville, Maryland 20850 • (301) 251-1161 • FAX (301) 251-1355

Figure 8.7

COBLT - CORD BLOOD TRANSPLANTATION STUDY
CONFIRMATION OF REGISTRATION / CBU RELEASE REQUEST
1 page

TO: _____ FAX:_____

FROM: The COBLT Medical Coordinating Center
Phone 301-251-1161 Fax 301-251-1355

DATE:

COBLT Recipient ID: Requested CBU ID:

Date Registered: Proposed start of conditioning:

To be completed by the Transplant Center and faxed to the COBLT Cord Blood Bank

TO: _____ Fax:_____

FROM: _____ Fax:_____

DATE: _____

Proposed CBU shipment date:_____ Proposed transplant date: _____

Name of Person Receiving Unit:_____
Hospital:_____
Address:_____
City, State, Zip Code:_____
Telephone Number:_____
Fax number:_____

_____ _____ _____
Signature Certification # Date

To be completed by the Cord Blood Bank and faxed to the COBLT MCC

TO: COBLT MCC FROM: _____
Fax: 301-251-1355 FAX: _____

This request has been received at Cord Blood Bank #_____. The above CBU will be shipped on _____. Please send an Investigators Brochure to the CBB.

_____ _____ _____
Signature Certification # Date

8.8 SEARCH FORMS

8.8.1 Preliminary Search Form

This form is designed to identify CBUs with a suitable cell dose and HLA type for a recipient. Recipient HLA typing for a preliminary search may be performed by serology for Class I (HLA-A and HLA-B) and Class II (DRB1) alleles. However, for DRB1, DNA typing is highly recommended. Preliminary searches are performed and an initial search report is generated within one business day from receipt of the form.

Note: The COBLT Name Code is the first 3 letters of the recipient's name.

Note: If "Other" is used for any data item, then the corresponding "Specify" text must be filled.

Note: Following a preliminary search, a search report is generated at the MCC and transmitted to the transplant center. The recipient is uniquely identified by the COBLT Recipient ID assigned at the time of the preliminary search.

Note: A preliminary search is active for 6 months or until a request to discontinue the search is received at the Medical Coordinating Center (MCC). Searches can be discontinued or extended beyond six months by submitting a search update form.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE PRELIMINARY SEARCH FORM.

1. Record the recipient's date of birth and gender.

2. Record the recipient's blood type ABO and Rh. This data is not required to initiate a preliminary search. The form should be updated and sent to the MCC when ABO and Rh are known.

3. Record the recipient's most recent weight (kg) rounded to the nearest decimal. Search reports cannot be generated without recipient weight.

4. Indicate the recipient's Primary Disease.

5. Indicate the ethnicity of the recipient's mother and father.

6. Indicate the recipient's HLA typing. Search reports cannot be generated without HLA typing results.

Note:

- *'Typing Method' and 'Antigens/alleles provided' MUST be completed.*
- *If the recipient is <u>known</u> to be homozygous (from familial typing), 'Antigens/alleles provided' should be recorded as 'Two' and the comments should reflect that the patient is known to be homozygous for the locus.*
- *If the recipient is <u>presumed</u> to be homozygous, 'Antigens/alleles provided' should be recorded as 'One' and the comments should reflect that the patient is presumed to be homozygous for the locus.*

OPTIONAL: Record recipient's first name, middle initial, and last name.

7. Report transplant center data by indicating first initial, last name, and e-mail address.

8.8.2 **Formal Search Form**

This form is designed to place up to 3 COBLT units on hold per recipient. Submission of this form also activates requests for confirmatory HLA typing for the recipient and CBU(s). COBLT CBUs are placed on hold for a maximum of 60 days.

Note: The COBLT Name Code is the first 3 letters of the recipient's last name.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE FORMAL SEARCH FORM.

1. Indicate up to 3 COBLT CBU ID number(s) to be placed on hold per recipient.

2. Indicate if recipient confirmatory typing should be initiated.

3a. Record date recipient sample sent to the COBLT contract laboratory. The recipient sample must be labeled with COBLT Recipient ID and name code.

3b. Indicate to which COBLT contract laboratory the sample was sent.

Note: If the information for Questions 3a and 3b is not provided at the time the form is initially submitted, update this information and fax to the MCC when the sample is shipped.

4. Report fax confirmation of formal search status by indicating first initial, last name, and fax number.

8.8.3 **CBU Reservation Form**

This form is designed to reserve a COBLT CBU. One CBU per recipient can be reserved for a maximum of 4 months.

Note: The COBLT Name Code is the first 3 letters of the patient's name.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE CBU RESERVATION FORM.

1. Indicate the COBLT CBU ID number to be reserved for a recipient.

2. Report fax confirmation of COBLT CBU reservation by indicating the first initial, last name, and fax number.

8.8.4 **Search Update Form**

This form is designed to report the status of a COBLT search. This form can be submitted at any time during the course of the search.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE SEARCH UPDATE FORM.

1. Indicate the planned course of action for the search.

   If the answer to Question 1 is "Continue COBLT search following 6-month automatic search period", update HLA's in Question 3, if necessary, and sign and fax form.

   If the answer to Question 1 is "Cancel COBLT search", continue with Question 2.

   If the answer to Question 1 is "Update recipient HLA typing", continue with Question 3.

2. Provide <u>one</u> primary reason for search cancellation. Only one primary reason can be recorded. Indicate for the remaining reasons whether they were contributing or non-contributing reasons for search cancellation.

3. Provide the updated recipient HLA typing data.

   Note:
   - *'Typing Method' and 'Antigens/alleles provided' MUST be completed.*
   - *If the recipient is <u>known</u> to be homozygous (from familial typing), 'Antigens/alleles provided' should be recorded as 'Two' and the comments should reflect that the patient is known to be homozygous for the locus.*
   - *If the recipient is <u>presumed</u> to be homozygous, 'Antigens/alleles provided' should be recorded as 'One' and the comments should reflect that the patient is presumed to be homozygous for the locus.*

8.8.5 **Search Transfer Form**

This form is designed to transfer control of search activity from one transplant center to a second center. After submission of this form, future search reports will only be sent to the "new" transplant center.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE SEARCH TRANSFER FORM.

Note: The top portion of this form should be completed by Search Coordinator initiating transfer.

1. Record date of transfer.

2. Record center code at new center.

Note: The bottom portion of this form should be completed by Search Coordinator at the final center.

3. Indicate COBLT ID to be used for future searches. The COBLT ID should either be the Recipient ID indicated at the top of the form or the Recipient ID which has been used by the "new" center's preliminary searches.

4. Report fax confirmation of transfer by indicating the first initial, last name, and fax number.

CHAPTER 9

TRANSPLANT CENTER LABORATORY PROCEDURES

CHAPTER 9

TRANSPLANT CENTER LABORATORY PROCEDURES

9.1 IMMUNE RECONSTITUTION ASSAYS

9.1.1 Introduction and Objectives

Two of the principal problems that occur following allogeneic transplantation are graft versus host disease (GVHD) and post-transplant immunodeficiency. After marrow transplantation, the severity of acute GVHD increases as the difference in HLA antigens between donors and recipients increases. Recipients of unrelated-donor marrow have an immunodeficiency of greater severity compared to recipients of related marrow than can be explained by the increased severity and frequency of their acute GVHD. Thus, other factors beside GVHD may contribute to the prolonged immunodeficiency observed in recipients of unrelated marrow. Among the reasons hypothesized for the increased immunodeficiency are the effects of GVHD on the thymus (4), defects in differentiation of donor T cells in the recipient, and histoincompatibility between donor-derived T cells and patient antigen presenting cells. It is of interest to determine the extent to which this prolonged immunodeficiency occurs following cord blood transplantation.

There is no permanent carry over of antigen specific T lymphocyte or B lymphocyte functions. Antigen specific immune function after transplantation depends on the development of new antigen specific T lymphocytes through the recipient thymus and on subsequent development and maturation of new functional B cells. Most of the patients in the post transplant period are receiving IVIG. Therefore, development of B lymphocyte function can only be assessed by immunization of the patients with neo-antigens. For this reason, the primary objectives of this study are to characterize the regulation of the production of new T cells in the recipient, evaluate the antigen specific T cell response to infectious antigens (herpes simplex, HSV; varicella, VZV; cytomegalovirus, CMV) and following immunization (tetanus toxoid, TT), determine the role of cytokines (IL-2 and IL-7) in antigen specific function, and to investigate the capacity of recipient T cells to interact with B cells to induce specific antibody production. Data will be analyzed considering patient age at transplant, primary disease, and degree of HLA mismatch. Each assay will be performed in a single laboratory to eliminate inter-site variation.

9.1.2 Background

Previous studies demonstrated that there was no significant carry over of antigen specific T cells following transplantation. Thus, antigen specific T cell function in recipients following marrow transplant is provided by T cells that differentiated in the recipient's thymus. Immunophenotypic analyses were undertaken to determine if the T cells present in the peripheral blood of recipients early following transplant had immunophenotypic characteristics similar to those of lymphocytes present in the cord blood of newborn infants and the peripheral blood of fetuses. Early following transplantation, CD3+ T cells co-expressed CD4 and CD8, and CD1-expressing T cells were detected in some patients (1), much like neonates.

The phenotypic evaluation of transplant recipients was confounded by the fact that the marrow used for allogeneic transplantation was contaminated by a significant number of T cells. The evaluation of patients receiving T cell-depleted marrow represented a more accurate assessment of post-transplant T cell ontogeny. When patients with severe combined immune deficiency (SCID) were evaluated following T-cell depleted transplant, no T cells were identified by flow cytometry for the first 8-12 weeks following transplantation. The appearance of phenotypic T cells at 12 weeks parallels normal fetal lymphoid development in which phenotypic T cells first exit from the thymus at 12 weeks of gestation (2). Longitudinal analyses revealed that the first detectable CD3+ cells in the peripheral blood of transplant recipients were $CD3^{dim}$ and did not express either CD4 or CD 8 (i.e. double negative cells.) Within a week to ten days of the initial appearance of $CD3^{dim}$ cells, $CD3^{bright}$ cells, some of which co-expressed CD4 and CD8, were detectable. These findings are consistent with the fact that lymphocytes that are normally only found in the thymus in post-natal life ($CD3^{dim}$ and $CD3^{bright}$, double positive cells) are found in the peripheral blood of recipients early following transplantation.

Recent thymic immigrants expressing CD3 and CD4 also express the high molecular weight isoform of CD45, CD45RA. Normal cord blood CD4+ T cells express CD45RA but not the low molecular weight isoform, CD45RO which is found on "memory" T cells. A cross sectional analysis of histocompatible recipients without GVHD showed an age dependent decline in the number of CD45RA-expressing CD4 T cells/mm^3 more than one year post-transplant. This is similar to the age dependent decline in the production of new CD4 T cells observed in normal individuals and patients receiving chemotherapy (3,4.)

Histocompatible recipients who had chronic GVHD or received unrelated marrow had reduced numbers of CD45RA-expressing CD4 T cells. This was not age dependent and suggested that recipients of unrelated marrow had a decreased capacity to generate new CD4 T cells regardless of age. The inability to generate new CD4 T cells may play a central role in the post-transplant immune deficiency seen in the recipients of unrelated transplants.

When histocompatible recipients with GVHD were evaluated for their antigen specific response to the antigen tetanus toxoid following immunization, the only recipients with chronic GVHD who were able to generate an antigen specific response were those who were also capable of producing new CD45RA-expressing CD4 T cells. Thus, the capacity of recipients with GVHD to generate new T cells was predictive of their antigen specific T cell f unction. Conversely, those recipients, regardless of age, who were unable to produce significant numbers of new CD4 T cells did not develop antigen specific responses following immunization with tetanus toxoid.

During development, the capacity of T cells to respond to the mitogen phytohemagglutin (PHA) can be detected first at 12 weeks of gestation, whereas antigen specific responses are not detected until 20 weeks. In histocompatible recipients without GVHD, the immunization of transplant recipients (like that of normal individuals) resulted in the detection of antigen specific function in 75% of patients after one immunization and 95% of patients after two immunizations. However, if patients were receiving significant immunosuppression and/or had ongoing GVHD, the rate of successful immunization following initial tetanus toxoid immunization was markedly lower (5).

In vitro antigen specific immune function was evaluated with and without exogenous interleukin-2 (IL-2.) The longitudinal evaluation of antigen specific proliferation *in vitro* following tetanus toxoid immunization has shown that antigen specific, IL-2 dependent T cells appear in the peripheral blood approximately 2-4 weeks prior to the appearance of antigen specific IL-2 producing T cells in normal histocompatible transplant recipients. In histocompatible recipients with GVHD or recipients of unrelated marrow, the appearance of the antigen specific IL-2 producing subpopulation can be significantly delayed. Thus the basis for the lack of *in vivo* antigen specific immune function seen in some patients may be caused by a selective delay in the ontogeny of antigen specific IL-2 producing cells or defects in antigen presentation resulting in an absence of antigen specific T cells.

Similar studies have been performed in transplant recipients suffering from infections with herpes viruses (CMV and VZV.) Whereas patients without GVHD rapidly developed antigen specific proliferation in the absence of exogenous IL-2, many recipients of unrelated marrow or histocompatible recipients with chronic GVHD had the presence of antigen specific T cells detected only in the presence of added IL-2. This implied that there was a delay in the development of the antigen specific IL-2 producing cells but that antigen specific IL-2 dependent T cells had developed normally (6). Clinically, patients suffered from recurrent herpes virus infections until they had detectable *in vitro* proliferative responses without the addition of IL-2. Thus the ability to clinically control herpes virus infections correlated with the development of antigen specific IL-2 producing T cells.

IL-7 is a lymphokine with a central role in T cell development in the thymus. Preliminary analysis of IL-7 levels in sera of transplant recipients showed that SCID recipients (who are young) had higher levels of IL-7 following transplantation than older patients with leukemia or aplastic anemia (7). The relationship between IL-7 and the ability to produce new CD45RA T cells is an area of intense study.

Several investigators have studied changes in the immunophenotype of peripheral lymphocytes over time for histocompatible transplant patients with or without GVHD as well as recipients of unrelated marrow. Recipients without GVHD developed normal immunophenotypic T cells by 6-12 months following transplantation whereas recipients with GVHD or the recipients of unrelated marrow had significant delays in the development of normal numbers of CD4+ T cells and B cells (8).

Other investigators have reported that SCID recipients of haploidentical marrow depleted of T cells had no T cells identifiable by flow cytometry during the first three months following transplantation. However, once phenotypic T cells were present, the proliferative response to PHA also developed and was normal by one year (9).

The induction of the cell surface protein CD40 ligand on T cells is central to cooperation between T cells and B cells. Cord blood T cells have reduced CD40 ligand expression following polyclonal stimulation. This might contribute to the defects in antibody production against carbohydrate antigens seen in infants.

9.1.3 **Specific Aim 1 - Production of New Lymphocytes**

The hypothesis for this aim is that following cord blood transplant, the patients without GVHD will develop antigen specific T lymphocytes within 9 months, and that the development of antigen specific T lymphocytes is delayed in patients with GVHD.

Peripheral blood samples will be obtained to evaluate immunological responses according to the schedule in Table 9.1.3.1.

Table 9.1.3.1
SCHEDULE OF IMMUNE EVALUATION

Forms	Months Post-Transplant																			
	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	30	36	42	48
Immunophenotyping [1]	X	X	X			X			X			X		X		X		X		X
PHA Response [2]	X		X			X			X			X		X		X		X		X
Antigen Specific Blastogenesis [3]			X			X			X			X		X		X		X		X
Tetanus Toxoid Immunization			X			X						X								
ΦX174 Stimulation												X				X		X		X
CD40 Ligand Expression [4]												X				X		X		X

[1] CD3, 4, 8, 56, 19/20, 4/8, RA/RO/4
[2] 3 doses of PHA ± IL-2
[3] Tetanus toxoid, varicella zoster, CMV, herpes simplex, ± IL-2, IL-7
[4] After PHA/PMA stimulation

Specimens will be prepared as below and analyzed by two color immunofluorescence using the monoclonal antibody combinations displayed in Table 9.1.3.2. Three color immunofluorescence will be used for CD4/CD45RA/CD45RO.

Table 9.1.3.2
MONOCLONAL ANTIBODY PANEL FOR IMMUNOPHENOTYPING-
IMMUNE RECONSTITUTION

FITC Antibody	PE Antibody	Detects
IgG1	IgG2a	Non-specific Binding
IgG2a	IgG1[1]	Non-specific Binding
Anti-CD3[2]	Anti-CD4	Helper T Cell Subset
Anti-CD3	Anti-CD8	Cytotoxic T Cell Subset
Anti-CD4	Anti-CD8	Double Positive T Cells
Anti-CD45RA[3]	Anti-CD45RO	Naive vs Memory T Cells
Anti-CD16	Anti-CD3	NK Cells
Anti-CD3	Anti-CD19	B Cells

[1] Plus additional isotype controls as required
[2] CD3+ cells will be characterized as $CD3^{dim}$ or $CD3^{bright}$
[3] Three-color immunofluorescence using CD4

9.1.4 **Specific Aim 2 - Antigen Specific T Cell Function**

The hypothesis for this aim is that cord blood transplant patients will develop a proliferative response to the mitogen PHA by three months post transplant, a response to tetanus toxoid immunization by six months, and a response to herpes viral antigens by 6 months. The secondary hypotheses that exogenous IL-2 and IL-7 will hasten the antigen specific responses and occurrence of GVHD will delay the antigen specific responses will be evaluated. The antigen specific response will be correlated with the appearance of T cells as determined in specific aim 1.

Peripheral blood mononuclear cells from patients will be tested according to the schedule in Table 9.1.3.1. Cells will be stimulated with both PHA and specific antigens (tetanus toxoid, varicella zoster virus, cytomegalovirus, and herpes simplex virus) in a microtiter culture system as described below. When adequate numbers of cells area available, the mitogen and antigen specific studies will be done in the presence of exogenous IL-2 and IL-7.

9.1.5 **Specific Aim 3 - T and B Cell Cooperation**

The hypothesis for Aim 3 is that cord blood transplant recipients produce antibodies to ΦX 174 antigen synchronously with development of expression of CD40 ligand.

Immunizations will be performed and peripheral blood mononuclear cells isolated from patients will be tested according to the schedule in Table 9.1.3.1. Procedures for immunization, antibody analysis and CD40 ligand induction are specified below. Use of the phage antigen ΦX174 allows assessment of a specific antibody response in patients receiving immune globulin. Antibody isotype, avidity, and class switching will be studied.

9.1.6 **Collecting and Shipping of Peripheral Blood Samples**

1. 10 cc heparinized blood (green top) at room temperature delivered within 24 hours.

2. Samples should be delivered Monday through Thursday from 7:30 AM to 6:30 PM (Pacific Time), and on Friday from 7:30 AM to 2:00 PM.

3. Samples should be delivered to :

   Robertson Parkman, M.D.
   Children's Hospital of Los Angeles
   4650 Sunset Boulevard, Mail Stop #62
   Los Angeles, CA 90027
   Telephone: 323-669-2196 Fax: 323-660-1904

9.1.7 **References**

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8. Keever CA, Small TN, Flomenberg N, et al.1989. Immune reconstitution following bone marrow transplantation: comparison of recipients of T-cell depleted marrow with recipients of conventional marrow grafts. Blood 73:1340-1350.

9. O'Reilly RJ, Keever CA, Small TN, Brochstein J. 1989. The use of HLA-non-identical T cell-depleted marrow transplants for correction of severe immunodeficiency disease. Immunodeficiency 1:273-309.

9.2 THAWING COBLT CRYOPRESERVED CORD BLOOD UNITS FOR TRANSPLANTATION

The COBLT Study requires certification of Transplant Centers in receiving and thawing CBUs prior to shipment of a COBLT CBU for transplant.

9.2.1 CBU Thawing Procedures

COBLT CBUs are cryopreserved in 10% DMSO and 1% Dextran. Cells cryopreserved in DMSO have limited viability upon thawing, resulting in significant losses of cells available for transplantation. DMSO, the cryopreservant used to maintain cell viability at ultra low temperatures, is toxic to cells when warmed to 37° C. Intracellular DMSO creates a hypertonic environment which leads to sudden fluid shifts and cell death upon warming. Lysis of red blood cells leads to accumulation of extracellular free hemoglobin which can be nephrotoxic if infused intravenously. In addition, DMSO causes adverse side effects in vivo after reinfusion, including blood pressure instability, fever, chills, and nausea. These problems can be ameliorated by mixing the thawed cells with a hypertonic solution, Dextran 40 + 5% albumin, immediately upon thawing. Cells can then be washed and further manipulated to remove DMSO, free hemoglobin, and other cellular products, as well as to perform other procedures before reinfusion to the patient.

The COBLT CBU thawing procedure is designed to enable the technologist to sterilely thaw cryopreserved cord blood within a closed system while maximizing viable cell recovery. The final product can be resuspended in a variable amount of Dextran 40/albumin solution, allowing for adjustment to a suitable volume for reinfusion into patients of varying sizes. The final product is stable for at least six hours. COBLT CBU thawing procedures are included in the Investigators Brochure shipped with each COBLT CBU for transplant. A copy of the Investigators Brochure can be found in Appendix B of the Transplant Center Manual of Procedures (MOP) and Appendix F of the CBB SOP.

9.2.2 **CBU Thawing Certification Requirements for Transplant Centers**

Certification will be granted to a center if at least one staff member completes the following steps:

- Attends a COBLT thawing wet workshop training session or visit a COBLT CBB for on-site training.

- Receives three CBUs from a COBLT CBB, thaw all three CBUs using the COBLT thawing procedure, and report data to the CBB and Medical Coordinating Center (MCC).

- Meets the COBLT Study requirements of:
  - ≥ 75% cell viability
  - ≥ 60% viable nucleated cell recovery.

Certification will be granted to a non-COBLT Transplant Center if at least one staff member:

- Visits a COBLT CBB or Transplant Center to watch and perform the COBLT CBU thawing procedure.

- Receives three CBUs from a COBLT CBB, thaw all three CBUs using the COBLT thawing procedure, and report data to the CBB and the MCC.

- Meets the COBLT Study requirements of:
  - ≥ 75% cell viability
  - ≥ 60% viable nucleated cell recovery.

9.2.3 **Requesting CBUs for Thawing Certification**

Transplant centers may request CBUs for thawing certification from COBLT CBBs at Duke University and University of California – Los Angeles. Each center is assigned to a specific CBB by the MCC. Centers should contact the Data Coordinator at the MCC to determine their assignment. To request COBLT CBUs for thawing certification, the Transplant Center Thawing Coordinator should contact the COBLT CBB Coordinator at their assigned CBB using the CBU Request for Thawing Certification. A maximum of four CBUs may be requested at one time. The request should be faxed to the CBB Coordinator at the appropriate CBB as designated below.

The CBB Coordinator will confirm shipment of the certification CBUs by completing and faxing the CBU Request for Thawing Certification to the Thawing Coordinator requesting the CBUs at the time of shipment. A copy of the fax will be sent to the Data Coordinator at the MCC.

The CBB Coordinator will complete and include the Thawing Certification CBU Packing Information for all CBUs included in the shipment. The CBUs will be shipped to the Transplant Center in a 'dry shipper' or on dry ice.

9.2.4 **Obtaining Certification to Thaw COBLT CBUs**

Upon receipt, the Transplant Center staff should store and thaw CBUs according to current COBLT Thawing Procedures as described in the Investigators Brochure (Appendix B of the Transplant Center MOP, Appendix F of the CBB SOP). For each COBLT CBU thawed, a CBU Thawing Form should be submitted to the MCC to confirm that COBLT Study requirements on cell viability and recovery are met. Upon completion of all study requirements, the MCC will issue certification numbers to Transplant Center staff. Instructions for completing the CBU Thawing Form can be found in Chapter 10 of the Transplant Center MOP.

9.2.5 **Maintaining Certification**

To maintain certification, staff members from both COBLT and non-COBLT Transplant Centers will be required to thaw and report data to the MCC on a minimum of one COBLT CBU every six months. This requirement may be met by performing a minimum of one transplant every six months. Centers can request practice CBUs from their designated COBLT CBB to maintain certification.

9.2.6 **Requesting Cell Wash/Infusion Bag Sets**

Thawing Coordinators should order Cell Wash/Infusion Bag Sets from the MCC using the COBLT Bag Order Form located in Chapter 10 of the Transplant Center Manual of Procedures (MOP). A log documenting the use of each bag set must be kept at each Transplant Center.

CBU REQUEST FOR THAWING CERTIFICATION

(Fax request to CBB Coordinator.)

TO:		**FROM:**	
COBLT CBB		Center	
Phone #		Phone #	
Fax #		Fax #	
	Date:		# of Pages:

Number of CBU(s) Requested: _____ For Receipt the Week of: _____
(A maximum of 4 CBU(s) can be requested at one time.)

Name of Person Receiving CBU(s): _____

Shipping Address: _____

_____

_____

_____

Contact Phone Number: _____

CONFIRMATION

(Fax confirmation to the Transplant Center staff requesting the CBUs and to the Medical Coordinating Center (MCC), 301-299-3991 FAX, at the time of shipment.)

TO:		**FROM:**	
Center		COBLT CBB	
Phone #		Phone #	
Fax #		Fax #	
	Date:		# of Pages:

Date CBU(s) Shipped: ____/____/____

Shipped CBU(s) ISBT Number(s): W __ __ __ __ __ __ __ __ __ __ __ __ __ __ 00 __

W __ __ __ __ __ __ __ __ __ __ __ __ __ __ 00 __

W __ __ __ __ __ __ __ __ __ __ __ __ __ __ 00 __

W __ __ __ __ __ __ __ __ __ __ __ __ __ __ 00 __

CBB Contact Name and Phone Number: _____ _____

THAWING CERTIFICATION CBU PACKING INFORMATION

Complete information below for all CBUs included in the shipment to the Transplant Center.

CBU ID#: W _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ 00 _

Cryopreserved CBU Information

% Viability	
% Mononuclear cells	
Total viable nucleated cell count x 10^8	
Total viable mononuclear cell count x 10^8	

Microbial Culture	

Maternal Infectious Disease Results

CMV	
Anti-HBc	
Syphilis	
Anti-HCV	
HBsAg	
HIV-1/2	
HIV p-24 Antigen	
HTLV I/II	

CBU ID#: W _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ 00 _

Cryopreserved CBU Information

% Viability	
% Mononuclear cells	
Total viable nucleated cell count x 10^8	
Total viable mononuclear cell count x 10^8	

Microbial Culture	

Maternal Infectious Disease Results

CMV	
Anti-HBc	
Syphilis	
Anti-HCV	
HBsAg	
HIV-1/2	
HIV p-24 Antigen	
HTLV I/II	

Comments: _____

Shipped By: _____

Shipped To: _____ Date Sent: _____

9.3 METHODS FOR BUSULFAN DOSE ADJUSTMENT

Nursing Instructions

1. Complete the enclosed pink charge slip form. Use an addressograph, if available, for patient's name and ID code in upper left corner. Also include age, actual weight and weight used for busulfan dose, if different, and the actual amount of busulfan administered (mg q 6 hr). Write the actual draw times on this slip.

2. In the comment space, include disease and the number of busulfan doses planned per protocol.

3. In the result section, indicate the target CSS (ng/mL) given by the protocol.

4. Draw 1-3 mL of blood into green top tubes. Label with patient name, ID code, sample number, date, and actual time of draw.

5. Place labeled samples immediately on wet ice and refrigerate as soon as possible.

6. **Draw schedule for Test Dose and Dose 1:** (all items post-dose): (suspension only, 15 minutes) 30 minutes, 1, 1.5, 2, 3, 4, 5, and 6 hours.

7. **Draw schedule for Dose 5 and 9:** pre-dose, 1, 2, 4, and 6 hour post.

8. Send the pink charge slip to the send-out laboratory so it may accompany the samples to Seattle.

Sample Processing

1. Use a capped 3 mL plastic tube for the plasma.

2. Use appropriate labels for identification.

3. Spin samples as soon as possible at 4°C. Separate plasma from RBCs and freeze plasma immediately at -20°C.

4. Plasma samples are to be shipped on dry ice using an overnight carrier.

5. Send to:
   Linda Risler
   Fred Hutchinson Cancer Research Center
   1100 Fairview Avenue North, D2-245
   Seattle, WA 98109

6. Enclose a pink charge slip and any other pertinent information with the samples.

9.4 PRE- AND POST-TRANSPLANT SAMPLES

9.4.1 Blood Draws for Chimerism Studies

Principle

A peripheral blood sample is required for chimerism studies: pre-transplant and post-transplant between Days 28 and 42, Day 100, and 1 year.

Specimen

Draw 3 mL peripheral blood in a EDTA (purple top) at the specified time periods.

Procedure

Ficoll cells to isolate mononuclear cell fraction, wash and pellet mononuclear cell layer, transfer to 1 labeled nunc vial and store at -20 °C at the home institution.

Label the vial with the following identifying information: COBLT ID, COBLT name code, date drawn, and type of sample.

File laboratory worksheet in laboratory manual and patient file.

9.4.2 CBU Sample for Retrospective HLA Typing

Principle

All non-COBLT cord blood units must have samples made available for retrospective allele level DNA based typing by a COBLT reference HLA laboratory.

Specimen

Samples form all non-COBLT units must be obtained from the wash during the thawing process.

Procedure

Remove 50 mL of the (usually 2nd) supernatant and place in a 50 mL (Falcon) conical tube.
Spin at 3000 rpm for 5 minutes to pellet cells
Remove supernatant and discard
Resuspend cells in approximately 600 µL dextran albumin
Add approximately 200 µL into 3 microfuge tubes
Spin at 14,000 rpm for 4 minutes to pellet cells
Remove supernatant, using a pipette
Freeze in -20 C freezer
Mail on dry ice

Label the sample with the following identifying information: CBU ID, date obtained, and type of sample.

Complete Non-COBLT CBU Sample Shipping Notification form. Fax form to the designated COBLT HLA laboratory and the Medical Coordinating Center. The form must accompany the sample at the time of shipment.

9.4.3 **Blood Draws for Retrospective HLA Typing**

Principle

A pre-transplant peripheral blood sample is required for retrospective HLA typing for all recipients.

Specimen
For patients with normal WBC, 7 mL peripheral blood (yellow top-ACD or purple top-EDTA). Note that in smaller patients, 2mL of peripheral blood is usually sufficient if acquisition of 7 mL is problematic.

For patients with low WBC, 20 mL peripheral blood (yellow top-ACD or purple top-EDTA) or a minimum of 5 mL peripheral blood PLUS 2 buccal swabs.

For heterozygous HLA, 4 buccal swabs should be obtained. Additional sample may be required if homozygosity must be confirmed.

Study-approved buccal swab kits must be used to collect samples. Kits can be obtained from the COBLT Medical Coordinating Center. All buccal swab samples should be sent to Dr. Baxter-Lowe's lab.

Procedure

Label the sample with the following identifying information: COBLT ID, COBLT name code, date drawn, and type of sample.

Complete Recipient Sample Shipping Notification form. Instructions for shipping samples are provided on the form.

Fax form to the designated COBLT HLA laboratory and the Medical Coordinating Center. The form must accompany the sample at the time of shipment.

CHAPTER 10

DATA COLLECTION

CHAPTER 10

DATA COLLECTION

10.1 DATA COLLECTION PROCEDURES

Data for the Cord Blood Transplantation (COBLT) Study will be submitted on forms supplied by the National Marrow Donor Program (NMDP), the International Bone Marrow Transplant Registry (IBMTR), and on supplementary forms supplied by the Medical Coordinating Center (MCC).

10.1.1 Training and Certification

COBLT requires training and certification of COBLT Clinic Coordinators in forms completion and submission. Clinic Coordinators who attend a data management training session at a COBLT Clinic Coordinators Meeting will be considered certified in forms completion and submission. Clinic Coordinators who have not attended a data management training session can be granted certification by the Data Coordinator at the MCC.

On completion of the training requirements, Clinic Coordinators will be assigned a certification number by the Data Coordinator. The certification number will be unique for each Clinic Coordinator and must be recorded on all study forms submitted to the MCC. COBLT does not require that certified personnel complete forms. However, COBLT does require that all forms be reviewed and submitted by a certified Clinic Coordinator.

10.1.2 Forms Completion

The COBLT Recipient ID and the COBLT Name Code, the first 3 letters of the patient's last name, will be used to identify individual patients participating in the COBLT Study. Patient names, social security numbers, and any other patient identifiers must be removed from all NMDP and IBMTR forms before submission to the MCC.

All reported data items should be legibly completed. Illegible data items cannot be entered into the master database and will be reported as missing values. If data for a required item are not available, a line must be drawn through the data box and "Not Tested" written in the margin beside the box. On questions that state "check all that apply," all appropriate data items should be marked, as the computer system will set any unmarked item to a negative response.

Corrections to COBLT data should be made on the form by placing a line through the incorrect number(s) or word(s), recording and circling the correct response, and dating and initialing the correction. All corrections should be done with an ink pen; correction fluid should never be used.

10.1.3 Forms Submission and Missing Forms

Supplementary forms and copies of NMDP and IBMTR forms should be mailed to the Data Coordinator at the MCC using COBLT mailing labels. A copy of every form submitted to the MCC

should be retained at the clinic in a patient's COBLT file. Each mailing must include a completed Forms Mail Log (Section 10.4.1). The Forms Mail Log is used by the MCC to confirm receipt of forms and can assist in tracking forms that were sent by the Clinical Centers.

Only current versions of NMDP forms, IBMTR insert, and COBLT supplementary forms will be accepted by the MCC. Forms with old version numbers will be returned to the Clinic and a completed current version of the form requested. Clinic Coordinators will be supplied with new forms whenever the date printed on the form's lower left corner is changed. Clinic Coordinators should discard old forms when new forms are received.

Table 10.1.1 summarizes the timing of submission of the COBLT supplementary forms, the NMDP forms, and the IBMTR insert. Table 10.1.2 details the criteria for forms submission. Forms that are not received at the MCC within the submission criteria are considered delinquent. Delinquent forms will be identified by the MCC on a bi-monthly basis and a Missing Forms Report will be distributed to the Clinical Centers. A missing form will continue to be requested either until the data for the form are sent and integrated into the MCC's master database or until an exception is granted and entered into the Missing Forms Exception File. Exceptions should be requested by indicating on the Missing Forms Report that no data are available. The report should then be mailed or faxed to the Data Coordinator at the MCC.

10.1.4 **Missing and Incorrectly Coded Data**

Missing data, incorrectly coded data, questionable data, and inconsistent coding between data items on and within forms will be detected by the MCC database quality system during each database update. All probable errors and inconsistencies detected by the database quality system generate a query message. Query reports will be mailed to COBLT Clinical Centers within the first week of each month.

10.1.5 **Ordering Forms**

A packet consisting of the following forms will be mailed after each patient registration:

- 17 Acute GVHD Assessment Forms
- 6 Post-Transplant Infection Forms
- 3 Re-Admission Forms
- 3 Hematopoiesis Assessment Forms - Neutrophils
- 3 Hematopoiesis Assessment Forms - Red Cell
- 2 Toxicity Forms
- 1 Relapse Form
- 1 Infusion Form
- 10 Specimen Submission Forms

The COBLT Supplementary Forms Request (Section 10.4.2) should be used to order additional supplementary patient data forms and laboratory forms. Mailing labels can also be ordered using the Supplementary Forms Request. The order may be mailed or faxed to the COBLT Administrator at the MCC.

10.1.6 **Additional Reporting Requirements**

COBLT clinics are required to provide information on all patients receiving cord blood, unrelated-donor marrow, and haplo-identical transplants at their centers, both on and off protocol. Clinic Coordinators should complete and fax to the MCC, on the first working day of each month, a Monthly Recruitment Report (Section 10.4.3). The report should reflect the previous month's activities.

Table 10.1.1
Forms Submission Schedule

FORM	Prior to Transplant	Days Post-Transplant						Months Post-Transplant						
		1-28	29-42	43-99	100	120	150	6	9	12	18	24	36	48
Eligibility	X													
CBU Thawing and Infusion Form		X												
Acute GVHD Weekly Assessment		Submit weekly				X	X							
NMDP 120: Baseline + Insert		X												
IBMTR Cord Blood Transplant Insert		X												
Toxicity		X	X											
Hematopoiesis Assessment - Neutrophils			X[1]		X[1]									
Hematopoiesis Assessment - Red Cells					X			X[2]		X[2]				
NMDP 130: 100-Day Visit					X									
Specimen Submission Form - Immune Reconstitution[3]		X	X	X				X	X[4]	X	X[4]	X	X	X
NMDP 140: Follow-Up Visit								X		X		X	X	
Post-Transplant Infection		Submit after each infectious episode or at follow-up visits if no infection has occurred												
Re-Admission		Submit for each hospitalization after the initial discharge												
Relapse		Submit at time of relapse												
Adverse Experience		Submit for each unexpected serious adverse experience												

1. Or at time of graft failure.
2. Due if Red Cell Engraftment not previously documented.
3. Only required for patients with malignant diseases.
4. Optional.

Table 10.1.2
Criteria for Forms Submission

Supplementary Forms:

Form	Submission Criteria
CBU Thawing and Infusion	≤ 15 days after CBT
Acute GVHD	≤ 14 days after GVHD staging date
Post-Transplant Infection	≤ 14 days after infection starting date or ≤ 45 days after follow-up visit target date
Re-Admission	≤ 14 days after discharge date
Toxicity	≤ 14 days after end of assessment period
Relapse	≤ 7 days after date of relapse
Hematopoiesis Assessment-Neutrophils	≤ 7 days after end of assessment period
Hematopoiesis Assessment-Red Cell	≤ 7 days after end of assessment period
Adverse Experience	≤ 24 hours after adverse experience
Specimen Submission	≤ 14 days after visit target date

NMDP and IBMTR Forms:

Form	Submission Criteria
120: Baseline + Insert	≤ 28 days after registration
IBMTR Insert	≤ 28 days after registration
130: 100-Day	≤ 45 days after 100-day target date
140: Follow-up	≤ 45 days after visit target date
190: Death	≤ 7 days after death

10.2 FORMS AND INSTRUCTIONS

10.2.1 Eligibility Form

This form is designed to ensure that patients registered onto the COBLT Study meet the eligibility criteria. The Eligibility Form should be faxed to the Data Coordinator at the Medical Coordinating Center (MCC) for eligibility confirmation prior to registration.

Note: All dates on this form must be earlier than the date the form is received at the MCC.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: If "Other" is used for any data item, then the corresponding "Specify" text must be filled in.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE ELIGIBILITY FORM.

1. Indicate the source of the cord blood unit (CBU) selected for transplant.

   - ! If the unit is from a COBLT Cord Blood Bank, record the COBLT Cord Blood Bank unit I.D. number and proceed to Question 5.
   - ! If the unit is from a source <u>other than</u> a COBLT Cord Blood Bank, continue with Question 2.

2a-c. Record CBU I.D. number, the post-processing/pre-cryopreservation total nucleated cell count, and the patient weight used when selecting the CBU for transplant.

3. Indicate whether or not a sample of the CBU has been sent to a COBLT HLA Typing Lab.

4. Record the CBU HLA Typing.

Note:
- *'Typing Method' and 'Antigens/alleles provided' MUST be completed.*
- *If the recipient is <u>known</u> to be homozygous (from familial typing), 'Antigens/alleles provided' should be recorded as 'Two' and the comments should reflect that the patient is known to be homozygous for the locus.*
- *If the recipient is <u>presumed</u> to be homozygous, 'Antigens/alleles provided' should be recorded as 'One' and the comments should reflect that the patient is presumed to be homozygous for the locus.*

5. Indicate if the confirmatory HLA-Typing Report – Recipient from the COBLT HLA Typing Lab has been received at the Transplant Center.

6. Record the proposed starting date for conditioning therapy.

7. Record the patient's date of birth

8. Indicate the patient's sex.

9. If the patient is female, indicate whether or not she is currently pregnant or breastfeeding.

10. Indicate whether or not the patient had a previous allogeneic stem cell transplant with cytoreductive preparative therapy.

11. If the answer to Question 10 is "Yes", indicate the date of allogeneic stem cell transplant.

12. Indicate whether or not the patient has had a previous autologous stem cell transplant.

13. If the answer to Question 12 is "Yes", indicate the date of autologous stem cell transplant.

14. Indicate whether the patient has a consenting, 5 of 6 or 6 of 6 HLA-matched related donor.

15. Record the date the patient signed the informed consent form to receive the cord blood transplant.

16. Indicate whether or not the primary disease includes active CNS leukemia involvement.

17. If the answer to Question 16 is "Yes", indicate whether or not the cerebrospinal fluid contains > 5 WBC/μL.

18. If the answer to Question 16 is "Yes", indicate whether or not malignant cells have been found as a result of cytospin.

19. Record the functional status of the patient by indicating the current Karnofsky score for patients aged 16 or older or the current Lansky score for patients under 16 years of age.

20. Indicate whether or not the patient has an uncontrolled viral, bacterial, or fungal infection at the time of enrollment.

21. Indicate whether or not the patient is seropositive for HIV.

22. Indicate whether or not the patient has myelofibrosis.

23. If the answer to Question 22 is "Yes", record grade of myelofibrosis.

24. If the answer to Question 22 is "Yes", indicate whether or not the recipient has primary myelofibrosis.

25. Indicate whether or not the patient has been diagnosed with dyskeratosis congenita.

26. Indicate whether or not the patient has symptomatic cardiac disease.

27a,b. If the answer to Question 26 is "Yes", record the left ventricular ejection fraction at rest or record the shortening fraction at rest.

28. If the answer to Question 26 is "Yes" and left ventricular ejection fraction was measured, indicate whether or not it improves with exercise.

29. Indicate whether or not the patient has any pulmonary disease symptoms.

30a,b. If the answer to Question 29 is "Yes", record DLCO, FEVI or FEC (Diffusion capacity) or record O_2 saturation on room air.

31. Record the most recent serum creatinine, SGOT, and total serum bilirubin values. Also indicate the serum creatinine upper limit of normal and lower limit of normal for your institution, and the SGOT upper limit of normal for your institution.

32. Indicate whether or not the serum creatinine value is greater than the institution's ULN.

33. If the answer to Question 32 is "Yes", record creatinine clearance value and LLN for your institution.

34. If the answer to Question 32 is "Yes", record glomerular filtration rate (GFR) and LLN for your institution.

35. Record the patients primary disease.

36. If the patient has Acute Myelogenous Leukemia (AML) with translocation t(8;21) and inv (16), indicate whether or not the patient is in complete remission. Complete remission is defined as $\leq$ 5 % blasts in marrow.

37. If the answer to Question 36 is "Yes", indicate whether or not the patient has failed first line induction therapy.

38. Indicate whether or not the patient is in first complete remission with translocation t(15;17). Complete remission is defined as $\leq$ 5 % blasts in marrow.

39. If the answer to Question 38 is "Yes", indicate whether or not the patient has failed first-line induction therapy.

40. If the answer to Question 38 is "Yes", indicate whether or not the patient has molecular evidence of persistent disease.

41-43. Indicate whether or not the patient has Down Syndrome and is in first complete remission. Indicate whether or not the patient is in ≥ 3 medullary relapse. Indicate whether or not the patient has refractory disease (other than primary induction failure).

44. If the patient has Acute Lymphoblastic Leukemia (ALL), indicate whether or not the patient is in first complete remission. Complete remission is defined as ≤ 5 % blasts in marrow.

45-48. If the answer to Question 44 is "Yes", indicate whether or not the patient has hypoploidy or pseudodiploidy with translocation t(9;22), 11q23, or t(8;14) or +MLL gene rearrangement. Record the white blood cell count in μL at presentation and indicate whether or not the patient achieved a complete remission after 4 weeks of induction therapy.

49. Indicate whether or not the patient has been diagnosed with B-ALL.

50-52. If the answer to Question 49 is "Yes", indicate whether or not the patient has translocation t(8;14). Indicate whether or not the blasts have surface immunoglobulins. Indicate whether or not the patient is CD10+.

53-54. Indicate whether or not the patient is in ≥ 3 medullary relapse. Indicate whether or not the patient has refractory disease (other than primary induction failure).

55. If the patient has Chronic Myelogenous Leukemia (CML), record the date of diagnosis.

56. Record the phase of CML.

57-59. If the answer to Question 56 is "Chronic" phase, indicate whether or not the patient has an adequately matched unrelated bone marrow donor identified. Indicate whether or not the patient has been unresponsive to interferon. Indicate whether or not the patient is unable to tolerate interferon.

60-61. If the patient has Undifferentiated or Bi-Phenotypic Leukemia, indicate whether or not the patient is in ≥ 3 medullary relapse. Indicate whether or not the patient has refractory disease (other than primary induction failure).

62-69. If the patient has Juvenile Myelomonocytic Leukemia (JMML), indicate whether or not the Philadelphia chromosome is present. Record % marrow blasts and peripheral blood monocytes. Indicate whether or not there is spontaneous growth of peripheral blood and/or GM-CSF hypersensitivity. Indicate whether or not the patient has an increased hemoglobin F for his/her age. Indicate whether or not the patient has clonal abnormalities present and myeloid precursors present in the peripheral blood. Record the white blood cell count at diagnosis.

70. If the patient has Myelodysplastic Syndrome (MDS), indicate the patient's disease using the disease definitions in COBLT Protocol, Section 2.2.1.

71-74. If the patient has Hodgkins Disease, Non-Lymphoblastic Non-Hodgkins Lymphomas or Lymphoblastic Non-Hodgkins Lymphomas, indicate whether or not the patient is in first complete remission. Indicate whether or not the patient was a primary induction failure. Indicate whether or not tumors demonstrated chemosensitivity. Tumors have demonstrated chemosensitivity (defined as > 50 % reduction in mass size). Indicate whether or not the patient has a history of bone marrow involvement.

75-78. If the patient has Acquired Severe Aplastic Anemia, record the granulocyte, platelet and absolute reticulocyte count. Indicate whether or not the patient is unresponsive to medical therapy with anti-thymocyte globulin and/or cyclosporine.

79.a,b. If the patient has Hurler's Syndrome, Adrenoleukodystrophy, Maroteaux-Lamy Syndrome, Globoid Cell Leukodystrophy, Metachromatic Leukodystrophy, Fucosidosis, Mannosidosis or other Metabolic Disorder, and the patient is greater than 5 years of age, record the patient's IQ. If the patient is less than or equal to 5 years of age, indicate whether or not the patient's neurodevelopmental exam demonstrates potential for stabilization at a level of functioning where continuous life support would not be predicted to be required in the year following transplantation.

80-81. If the patient has Fanconi Anemia, indicate whether or not increased chromosomal fragility assays to mitomycin C and DEB have been documented. Indicate whether or not the patient has been diagnosed with severe pancytopenia, myelodysplastic syndrome with clonal chromosomal abnormalities and/or leukemic transformation.

82. If the patient has a combined immunodeficiency disorder, indicate whether or not the patient requires cytoreduction.

83. If the patient has Familial Erythrophagocytic Lymphohistiocytosis (FEL), indicate whether or not the cerebrospinal fluid is currently positive for disease as defined by abnormal brain MRI or neurologic symptoms or > 7/mm^3 lymphocytes plus monocytes.

84. If the patient has Langerhans Cell Histiocytosis, Blackfan-Diamond, Kostmann's Congenital Agranulocytosis, indicate whether or not the disease is unresponsive to medical therapy.

85. Indicate the patient's COBLT strata.

86. Indicate the patient's planned conditioning regimen.

- ! If the patient's planned conditioning regimen are choices 1, 2, or 4, sign, date, and provide your 5-digit COBLT study I.D. on the form. Fax the form to 301-299-3991 to expedite the registration process, and notify search coordinator at the MCC of its submission.

- ! If the patient's planned conditioning regimen is Busulfan (Busulfex)/Melphalan, proceed to Question 87.

87. Indicate whether or not the patient was diagnosed with infant acute leukemia when less than 2 years old.

88. If the answer to Question 87 is "Yes", record date of diagnosis.

89. Indicate whether or not the patient has a malignant disease and is unable to tolerate TBI.

90. If the answer to Question 89 is "Yes", record the reason the patient is unable to tolerate TBI.

- If the patient received prior dose-limiting radiation, record prior dose.
- If other reason, specify.

91. Indicate whether or not the patient has been diagnosed with leukemia or myelodysplastic syndrome due to prior therapy.

Note: Sign, date, and provide your 5-digit COBLT Study I.D. on the form. Fax the form to 301-251-1355 to expedite the registration process, and notify search coordinator at the MCC of its submission.

10.2.2A **CBU Thawing Form**

This form is designed to obtain data on COBLT Cord Blood Units (CBU's) thawed for transplant or Transplant Center certification. The CBU Thawing Form should be completed at the time a CBU is thawed. All data items should be completed. Comments documenting unusual circumstances should be added at the end of the form.

Note: Thawing Procedures can be found in the Investigator's Brochure that accompanies every CBU used for transplant and in the COBLT MOP, Appendix B.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: Center Code is the center's NMDP ID.

Note: When recording data for CBU's thawed for Transplant Center certification, record 999 999 6 *for the COBLT Recipient ID and* CRT *for COBLT Name Code.*

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE CBU THAWING FORM.

1. Record the date and starting time of the CBU thaw.

2. Record the total viable nucleated cell count of the CBU recorded on the Transplant Center Feedback Sheet or Thawing Certification CBU packing information.

3. Record the reagent and supply data.
   - Record the lot number of the cell wash/infusion bag set.
   - Record the lot number, expiration date and manufacturer for the Dextran 40.
   - Record the lot number, expiration date and manufacturer for the stock albumin.

4. Record the weight of washed and resuspended cells in the Transplant Bag from tared scale. The bag should be weighed after re-suspending the cells and prior to removal of the QC sample. This value should be recorded in grams and rounded to one decimal place.

5. Record the cell count and viability of washed and resuspended CBU in Transplant Bag.
   - Record the volume for infusion. This value should be recorded in milliliters and reported to one decimal place.
   - Record the cell viability. This value should be reported as a percentage.
   - Record the automated nucleated cell count. This value should be recorded x 10^6 /mL and rounded to one decimal place.
   - Calculate the viable cell recovery to determine if recovery of additional cells is necessary (see thawing procedures for details).

Note: Total viable nucleated cells in the resuspended CBU is calculated by multiplying the volume for infusion, the cell viability, and the automated nucleated cell count. The calculated value should be x 10^8. The total viable nucleated cells in the pre-freeze CBU is the value recorded for Question 2.

6. Indicate whether or not cells from the waste-bag supernatant were recovered and infused. If the answer to Question 6 is "Yes", complete Question 7. If the answer to Question 6 is "No", skip to Question 9.

7. Indicate whether or not the recovered cells were added to the Transplant Bag for infusion.

8. If the answer to Question 7 is "Yes", complete Question 8 with the final volume infused, cell viability, and cell count from the Transplant Bag. If the answer to Question 7 is "No", complete Question 8 with the volume infused, cell viability, and cell count from the second bag.

9. Calculate the final infused viable cell recovery.
   - Record the total viable nucleated cell count. This value should be recorded $x10^8$ and rounded to two decimal places.

Note: If only 1 transplant bag is used for infusion, total viable nucleated cell count is calculated by multiplying the final volume for infusion, the final cell viability, and the final automated nucleated cell count. If 2 bags are used for infusion, add the total viable nucleated cell count for bag 2 (calculated for Question 8) to the total viable nucleated cell count for the first transplant bag (calculated for Question 5).

   - Record the viable cell recovery. This value should be recorded as a percentage and rounded to one decimal place.

Note: Viable cell recovery is calculated by dividing the FINAL total viable nucleated cell count recorded for Question 9 by the total viable nucleated cells in the pre-freeze CBU recorded for Question 2.

10. Record the recipient's actual body weight on the day of infusion.

11. Indicate if there were performance issues with the cryo bag or cell wash/infusion bag set. If Question 11 is "Yes", specify the problem. If "No", continue with Question 12.

12. Record your 5 digit Study ID(s). These Study ID's are issued by the Medical Coordinating Center.

13. Indicate the results of the sterility assay. Record as 'Pending' at the time of thaw. When sterility assay results are available, update the form and fax to the MCC. If Question 13 is "Yes", specify the type of bacteria. If the type of bacteria is unknown, write 'Unknown'.

10.2.2B **CBU Infusion Form**

This form is designed to obtain data on the infusion of the COBLT Cord Blood Unit (CBU). All data items should be completed. Comments documenting unusual circumstances should be added at the end of the form. The CBU Infusion Form should be faxed to the Data Coordinator at the Medical Coordinating Center (MCC) within 48 hours of transplant.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: Center Code is the center's NMDP ID.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE CBU INFUSION FORM.

1-2. Record the date, starting, and finishing time of the CBU infusion.

3. Indicate if any pre-infusion medications were administered within 2 hours of infusion

4. If the answer to Question 3 is "Yes", record the medication administered.

5. Indicate if emergency medications were administered during or within 2 hours of infusion.

6. If the answer to Question 5 is "Yes", record the emergency medications administered.

7. Record the highest grade of complication/toxicity the patient experienced within 24 hours of the infusion.

Note: A toxicity grade should be indicated for each category listed.

10.2.3 **Acute GVHD Weekly Assessment**

This form is designed to obtain information on acute GVHD within the first 100 days post-transplant. The first Acute GVHD Weekly Assessment Form should be completed between day 4 and day 10 post-CBT. Assessments should be made every 7 days from the previous assessment date up to day 100 post-CBT and at day 120 and day 150 post-CBT. All data items should be completed. Comments documenting unusual circumstances may be added at the end of the form.

Note:
- *The COBLT Name Code is the first 3 letters of the patient's last name.*
- *The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.*
- *For Assessments 1 - 14, number should be recorded as the week number post transplant. The 120 day visit should be recorded as Assessment Number 15 and the 150 day as Assessment Number 16.*
- *Center code should be completed using your center's 3-digit NMDP code.*
- *If "Other" is used for any data item, then the corresponding "Specify" text must be filled in.*

Note: The Rule of Nines is included on the back of the form to assist in estimating the percentage of body surface involved.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE ACUTE GVHD WEEKLY ASSESSMENT FORM.

1. Record the date on which the GVHD staging levels were determined.

2. Record the type of immunosuppressant received during the assessment period. If no immunosuppressant was received, record 'Not Given' during the assessment period.

3. Record the lowest immunosuppressant trough level determined during the assessment period and record the date this level was determined. If an immunosuppressant is given but the trough level is below detectable levels (e.g. < 25 or < 50, depending on assay used), record 25 and include comments.

*Note: **Assessment period** is defined as a 1-week period which encompasses the date of staging.*

4. Indicate the highest level of organ abnormalities for skin, intestinal tract, liver, and upper GI during the assessment period. Note that this should reflect <u>all symptoms</u>, not just symptoms attributed to GVHD.

5. Indicate for skin, intestinal tract (upper or lower), and liver the etiologies that contributed to the symptoms within the assessment period or within the subsequent 7-

day period. For day 120 post-CBT, the assessment period covers the previous 20 days and subsequent 7-day period. For day 150 post-CBT, the assessment period covers the previous 30 days and subsequent 7-day period.

6. Indicate the biopsy results pertaining to GVHD for skin, intestinal tract (upper or lower), and liver. If a biopsy was not taken, record 'Not Done.'

7. Indicate whether or not primary or secondary treatment for GVHD was initiated. If treatment was initiated, indicate the type of treatment in the comments section of the form.

Note:
- *The answer should be marked as "No" if only topical treatment was given.*
- *The answer should be marked as "No" if only cyclosporine or tacrolimus dose adjustments were made.*
- *The answer should be marked as "Yes" if steroid doses are increased.*
- *The answer should be marked as "Yes" for any new systemic treatment.*

□□□□□□ Toxicity Form

T□i□□orm i□d□i□□□d to o□t□i□i□orm□tio□o□r□□im□□□r□□t□d toxiciti□□x□ri□□c□d □y □□□□T □□ti□□t□□y □□y□□□□d □□ □o□t□□□T□Toxiciti□□□□o□d □□□r□d□d □i□□t□□□c□□□o□t□□□□c□o□ t□□□orm□

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

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10.2.5 **Hematopoiesis Assessment - Neutrophils**

This form is designed to collect data on engraftment and graft failure for all COBLT patients surviving at least 28 days post-CBT. The form should be completed at the following times:

Day 42 post-CBT:	All patients surviving to at least day 14 post-CBT.
Day 100 post-CBT:	All patients not experiencing secondary graft failure. Complete at day 100 or at time of death if patient dies between day 42 and day 100.
Secondary graft failure:	All patients experiencing secondary graft failure.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

Note: If "Other" is used for any data item, then the corresponding "Specify" text must be filled in.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE HEMATOPOIESIS ASSESSMENT FORM-NEUTROPHILS.

1. Indicate whether or not the patient engrafted as evidenced by an ANC $\geq$ 500/mm^3 on 3 consecutive days.

2. If the answer to Question 1 is "Yes", record the ANC values and the dates the values were obtained.

3. Indicate whether or not the patient had severe neutropenia (ANC < 500/mm^3) without subsequent improvement occurring either spontaneously or after growth factor therapy. Improvement is defined as ANC $\geq$ 500/mm^3 consistently.

4. If the answer to Question 3 is "Yes", then record percent of marrow cellularity. Check box if marrow cellularity is not quantifiable, but less than 25%.

5. If the answer to Question 3 is "Yes", then record the date the marrow sample was obtained.

6. Record the results of any chimerism assays performed on the marrow or blood. If an assay was performed, record the assay date, the primary method used, and the assay results.

7. Indicate whether or not the patient received stem cell reinfusion (marrow or peripheral blood) due to inadequate hematopoietic function.

8. If the answer to Question 7 is "Yes", then record the date of stem cell infusion. Record the first date if the patient received more than one.

10.2.6 **Hematopoiesis Assessment - Red Cells**

This form is designed to collect data on red cell engraftment for all COBLT patients surviving at least 28 days post-CBT. The form should be completed at the following times:

Day 100 post-CBT:	All patients surviving to at least day 14 post-CBT.
6 Month post-CBT:	All patients who have not achieved RBC engraftment by day 100 post-CBT.
12 Month post-CBT:	All patients who have not achieved RBC engraftment by 6 months post-CBT.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE HEMATOPOIESIS ASSESSMENT FORM-RED CELLS.

1. Indicate whether or not the patient engrafted as evidenced by an absolute reticulocyte count $\geq$ 30,000/mm^3 for 2 consecutive measurements. If this data was previously reported, check the appropriate box.

2. If the answer to Question 1 is "Yes", record the absolute reticulocyte count values and the dates the values were obtained.

3. Record the date of the most recent red cell transfusion, if known.

4. Record the date cyclosporine ended.

10.2.7 **Specimen Submission Form - Immune Reconstitution**

This form is designed to document collection and shipment of Immune Reconstitution samples for COBLT patients with **malignant** diseases. The immune reconstitution studies and submission of the Specimen Submission form are **not** required for patients with non-malignant diseases. Immune Reconstitution studies will be performed at 1 month post-CBT to 3 years post-CBT. A schedule of Immune Evaluation samples can be found in Table 9.1.3.1.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

Note: A copy of the Specimen Submission Form should be sent to the MCC at the time of shipment.

Note: Samples should be sent to:

Robertson Parkman, M.D.
Children's Hospital, Los Angeles
4650 Sunset Boulevard, Mail Stop #62
Los Angeles, CA 90027

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE SPECIMEN SUBMISSION FORM.

1. Record the date that the blood sample was drawn.

2. Record the date that the sample was shipped to the laboratory for processing.

3. Record the date of the most recent tetanus immunization.

4. If this is the first assessment, provide infectious disease testing results.

10.2.8 **Post-Transplant Infection Form**

This form is designed to obtain information on all infections occurring after recipient registration . A Post-Transplant Infection Form should be completed for each infection and submitted to the Medical Coordinating Center (MCC) within 14 days of the reported infection being resolved. If the patient has not had an infection between 2 COBLT follow-up visits (e.g., between the 6-month and the 1-year visit), complete Questions 1 and 2, sign, and submit the form to the MCC within 45 days of the visit target date. Comments documenting unusual circumstances may be added at the end of the form.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

Note: If "Other" is used for any data item, then the corresponding "Specify" text must be filled in.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE POST-TRANSPLANT INFECTION FORM.

1. Record the starting date of the infection, or, if no infection has occurred between 2 COBLT follow-up visits, record the date of the visit confirming the infection-free period.

2. Indicate whether or not the form documents an infection episode.

3. Report all clinically important infections present at the start of the infection episode. Use the codes listed on page 2 of the form to record the site(s) of infection, the organism(s) causing the infection, and the infection severity scale.

4. Indicate whether or not the only diagnosis for this infection episode was "Fever of Undetermined Origin."

5. Indicate whether or not the infection was treated in addition to ongoing prophylaxis.

10.2.9 **Re-Admission Form**

This form is designed to obtain information on COBLT patients re-hospitalized following their initial hospital discharge. A Re-Admission Form should be submitted to the Medical Coordinating Center (MCC) within 14 days of the discharge date recorded on the form. All data items should be completed. Comments documenting unusual circumstances may be added at the end of the form.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

Note: If "Other" is checked as the primary or secondary cause, then the corresponding "Specify" text must be filled in.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE RE-ADMISSION FORM.

1. Record the date of discharge for this hospitalization period. If the patient dies in the hospital, the date of discharge is the date of death.

2. Indicate the patient's status at discharge.

3. Indicate the primary reason for re-admission. Only one primary reason can be recorded. Indicate for the remaining reasons whether they were contributing or non-contributing reasons for hospitalization.

4. Record the number of days the patient was on a ventilator for this hospitalization period. Record 0 if the patient had no days on a ventilator.

10.2.10 **Relapse Form**

This form is designed to obtain data on the recurrence of disease in COBLT patients after cord blood transplantation. The form should be submitted as soon as all the information required to document relapse is complete. Relapse is defined and described in the COBLT Protocol, Section, 2.1.8All data items should be completed. Comments documenting unusual circumstances should be added at the end of the form.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: Center Code is the center's NMDP ID.

Note: If "Other" is used for any data item, then the corresponding "Specify"text must be completed.

Note: Answer Question 51 for all patients.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE RELAPSE FORM.

1. Indicate the patient's primary diagnosis.

   Note: Answer Questions 2-14 if the primary diagnosis is CML.

2. Indicate if immature hematopoietic cells have been documented in the peripheral blood.

3. If the answer to Question 2 is "Yes", record the date first documented.

4. Indicate if myeloid hyperplasia in the bone marrow has been documented in the absence of infection of growth factor.

5. If the answer to Question 4 is "Yes", record the date first documented.

6. Indicate if host cells have reappeared.

7. If the answer to Question 6 is "Yes", record the method(s) used. Check either "Yes" or "No" as appropriate for each method.

8. Indicate if the 9;22 translocation has reappeared.

9. If the answer to Question 8 is "Yes", record the date of cytogenetic analysis.

10. Record the number of metaphases analyzed.

11. Record the number of metaphases exhibiting the 9;22 translocation.

12. Indicate molecular (BCR/ABL) examinations of blood or bone marrow post-transplant.

13. Record the date of second cytogenetic analysis.

14. Record the number of metaphases exhibiting the 9;22 translocation.

    Note: Answer Questions 15-27 if the primary diagnosis is AML, ALL, Undifferentiated Leukemia, Bi-phenotypic Leukemia, Hodgkins Disease, Non-Lymphoblastic Non-Hodgkins Lymphoma, Lymphoblastic Non-Hodgkins Lymphoma, or Lymphoblastic Lymphoma.

15. Indicate if the leukemic blasts were documented in the marrow or peripheral blood. Record the % of Leukemic Blasts and the date the blasts were first observed. If % blasts are $\leq$ 25%, repeat test.

16. Indicate if host cells have reappeared.

17. Indicate if cytogenetic abnormalities have reappeared.

18. If the answer to Question 17 is "Yes", record the method(s) used. Check either "Yes" or "No" as appropriate for each method.

19. Record the date the disease was first detected.

20. Indicate if the disease was detected at an extramedullary site. If the answer is "Yes", continue with Questions 21-27.

21. Record the date the disease was first detected.

22. Indicate if the disease was confirmed by pathology.

23. Indicate if a new extramedullary mass had been documented.

24. Indicate if the previous masses have demonstrated an increase in size.

25. Indicate if the blasts were present in the cerebrospinal fluid.

26. If the answer to Question 25 is "Yes", record the % of the white blood cell count in the cerebrospinal fluid.

27. Record the date the WBC was recorded.

    Note: Answer Questions 28-41 if the primary diagnosis is Non-Lymphoblastic Non-Hodgkin's Lymphoma, Lymphoblastic Non-Hodgkins Lymphoma, or Hodgkin's Disease.

28. Indicate if there has been a progression more than 25% in the product of the 2 largest diameters of any measurable lesion. If the answer is "Yes", answer Questions 29-36.

29. Record the method(s) used. Check either "Yes" or "No" as appropriate for each method.

30. Record the diameter of lesion 1 pre-transplant.

31. Record the diameter of lesion 2 pre-transplant.

32. Record the date of the measurements.

33. Record the method(s) used to determine the diameter of the lesion. Check either "Yes" or "No" as appropriate for each method.

34. Record the current diameter of lesion 1.

35. Record the current diameter of lesion 2.

36. Record the date of the measurement.

37. Indicate if new definitive lesions have appeared.

38. If the answer to Question 37 is "Yes", Indicate if the lesions have been confirmed by biopsy. If the answer is "Yes", record the date of the biopsy.

39. Indicate if bone marrow specimens have been obtained.

40. If the answer to Question 39 is "Yes", record the method used.

41. Indicate if there has been and appearance of lymphoma, if the answer is "Yes", indicate the date of the appearance.

Note: Answer Questions 42-46 if the primary diagnosis is JMML.

42. Indicate if host cells have reappeared.

43. If the answer to Question 42 is "Yes", record the method(s) used. Check either "Yes" or "No" as appropriate for each method.

44. Indicate if there are any clinical and laboratory features present which are consistent with the patient's original disease.

45. Indicate if there has been a reappearance of an abnormal cytogenetic marker which was present at diagnosis.

46. Indicate if the patient has a GM-CSF hypersensitivity or spontaneous growth of CFU-GM in peripheral blood.

Note: Answer Questions 47-49 if the primary diagnosis is MDS.

47. Indicate if any MDS-associated morphologic abnormalities have reappeared.

48. If the answer to Question 47 is "Yes", record the dates of 2 consecutive marrow specimens and % cells of host origin.

49. Indicate if there has been a reappearance of an abnormal cytogenetic marker which was present at diagnosis.

Note: Answer Questions 50 and 51 if the primary diagnosis is FEL or LCH.

50. Indicate if erythrophagocytosis has been documented by biopsy or is infiltrative disease consistent with FEL or LCH.

51. Indicate if host hematopoiesis has reappeared.

Note: Answer Question 52 for all patients.

52. Indicate whether or not specific therapies were initiated for relapse reversal. If a therapy was initiated, record the first date of initiation.

10.2.11 **Adverse Experience Form**

This form is designed to report a COBLT patient unexpected adverse experience. An adverse experience is defined as some unplanned, unwanted event which may or may not be related to the use of protocol therapy. Expected adverse experiences (i.e., those listed in the informed consent, product inserts, or study materials) need not be reported to the Medical Coordinating Center (MCC). Unexpected serious adverse experiences (i.e., adverse experiences NOT listed in the COBLT Protocol or the Informed Consent) must be reported to the MCC as indicated in the COBLT MOP Chapter 3, Section 3.2.

Note: The COBLT Name Code is the first 3 letters of the patient's last name.

Note: The COBLT Recipient ID is assigned by the MCC at the time a preliminary search form is submitted.

Note: Center code should be completed using your center's 3-digit NMDP code.

Note: Summarize the adverse experience on the form, attach a narrative description of the event, and include a description of the patient status. If an IRB notification has been prepared, that notice may serve as the narrative description.

Note: If "Other" is used for any data item, then the corresponding "Specify" text must be filled in.

Note: Principal Investigator must review adverse experience form and narrative description before submission to the MCC.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE ADVERSE EXPERIENCE FORM.

1. Document the adverse experience.

2. Indicate whether or not this is an unexpected serious adverse experience.

3. Indicate the severity of the adverse experience.

4. Indicate the suspected relationship to the study therapy using the definitions below:

   Definite: Clear-cut temporal association with a positive rechallenge test or laboratory confirmation

   Probable: Clear-cut temporal association not reasonably explained by the subject's known clinical state

   Possible: Less clear temporal association; other etiologies are also possible

   Remote: Less clear temporal association; other etiologies are probable

None: No temporal association; related to other etiologies such as concomitant medications/conditions or subject's known clinical state

5. Indicate the effect of the adverse experience on study therapy.

6. Indicate whether or not treatment for the adverse effect was required.

7. Indicate the status of the adverse experience.

8. Record the date of resolution of the adverse experience, if known.

9. Indicate whether or not the adverse experience has been reported to your Institutional Review Board.

10.3 NMDP/IBMTR FORMS AND INSTRUCTIONS

10.3.1A Form 120: Recipient Baseline and Transplant Data

10.3.1B **Form 120 Insert I – Acute Myelogenous Leukemia**

10.3.1C **Form 120 Insert II – Acute Lymphoblastic Leukemia**

10.3.1D **Form 120 Insert III – Chronic Myelogenous Leukemia (CML)**

10.3.1E **Form 120 Insert IV – Other Leukemias**

10.3.1F **Form 120 Insert V – Myelodysplasia/Myeloproliferative Disorders**

10.3.1G **Form 120 Insert VI – Multiple Myeloma**

10.3.1H **Form 120 Insert VII – Other Malignancy**

10.3.1I **Form 120 Insert VIII – Aplastic Anemia**

10.3.1J **Form 120 Insert IX – Hodgkin and Non-Hodgkin Lymphoma**

10.3.1K **Form 120 Insert X – Severe Combined Immunodeficiency (SCID)**

10.3.1L **Form 120 Insert XI – Wiskott Aldrich Syndrome (WAS)**

10.3.1M **Form 120 Insert XIII – Leukodystrophies**

10.3.1N **Form 120 Insert XIV – Mucopolysaccharidoses and Other Storage Diseases**

10.3.2 **IBMTR Cord Blood Transplant Insert**

10.3.3A **Form 130: 100-Day Follow-Up Visit of Recipient**

10.3.3B **Form 130 Post Transplant Follow-up Form Insert I – Severe Combined Immunodeficiency (SCIDS)**

10.3.3C **Form 130 Post Transplant Follow-up Form Insert II – Wiscott Aldrich Syndrome (WAS)**

10.3.3D **Form 130 Post Transplant Follow-up Form Insert III – Information for Hodgkin and Non-Hodgkin Lymphoma**

10.3.4A **Form 140: 6-Month to 2-Year Follow-Up Visit of Recipient**

10.3.4B **Form 140 Post Transplant Follow-up Form Insert I – Severe Combined Immunodeficiency (SCIDS)**

10.3.4C **Form 140 Post Transplant Follow-up Form Insert II – Wiscott Aldrich Syndrome (WAS)**

10.3.4D **Form 140 Post Transplant Follow-up Form Insert III – Information for Hodgkin and Non-Hodgkin Lymphoma**

10.3.5 **Form 150: Yearly Follow-Up for Greater Than Two Years Post-Transplant**

10.3.6 **Form 160: Leukemia and MDS Yearly Follow-up for Relapse Post-Stem Cell Transplant**

10.3.7 **Form 190: Recipient Death Information**

10.4 DATA MANAGEMENT AND REPORTING

10.4.1 Forms Mail Log

The Forms Mail Log is designed to confirm receipt of all COBLT forms at the Medical Coordinating Center (MCC) and to assist in tracking forms sent to the MCC by the COBLT Clinical Centers. A completed Forms Mail Log must accompany each batch of forms mailed to the MCC. Clinic Coordinators should keep copies of logs submitted to the MCC.

10.4.2 **Supplementary Forms Request**

The Supplementary Forms Request should be used to order additional supplementary patient data forms, and mailing labels. The order may be mailed or faxed to the COBLT Administrator at the Medical Coordinating Center (MCC).

10.4.3 **Monthly Recruitment Report**

The Monthly Recruitment Report is designed to provide information on all patients receiving cord blood, unrelated-donor marrow, or haplo-identical transplants at a COBLT Center. The report should reflect the previous month's activities.

Note: Fax a completed report to the Medical Coordinating Center (MCC) at 301-251-1355 on the first working day of each month.

Note: Center code should be completed using your center's 3-digit NMDP code.

THE FOLLOWING NUMBERS REFER TO THE QUESTION NUMBERS ON THE MONTHLY RECRUITMENT REPORT.

1. Record the report month and year. *The report should reflect the previous month's activities.*

2. Indicate whether or not any clinically eligible patients who were NOT enrolled on the COBLT Study Protocol received a cord blood transplant during the report month.

   If the answer to Question 2 is "Yes", then record the number of patients who received a cord blood transplant and the source of the cord blood unit (CBU) for the following categories:

   - The number of non-enrolled clinically eligible patients who received a cord blood transplant after an unsuccessful search of the COBLT registry or unsuccessful search of COBLT approved non-COBLT cord blood banks (CBBs) for a suitable cord blood unit (CBU).

Note: An unsuccessful search is defined as a search performed at the COBLT registry which results in a CBU that does not meet the COBLT HLA matching criteria (see Protocol 2.2.1, #12).

   - The number of non-enrolled clinically eligible patients who received a cord blood transplant because a unit with a better HLA match was available from a non-COBLT approved bank.

   - The number of non-enrolled clinically eligible patients who received a cord blood transplant because a unit with a higher cell count was available from a non-COBLT approved bank.

   - The number of non-enrolled clinically eligible patients who received a cord blood transplant for any other reason not mentioned above. Specify reason(s).
   - The number of non-enrolled clinically eligible patients who received a cord blood transplant for whom no search was made at the COBLT registry or COBLT approved registries for a suitable CBU. Specify the reason(s) why the search was not initiated.

3. Indicate total number of patients NOT meeting the COBLT Protocol eligibility criteria, regardless of COBLT CBU availability, received a cord blood transplant during the report month. Document CBU source and reason(s) for ineligibility.

4. Record the number of haplo-identical transplants performed during the report month.

Note: A haplo-identical transplant is defined as a related donor with a 4/6 or 3/6 HLA match.

5. Record the number of unrelated donor marrow transplants performed during the report month.

6. Record the number of unrelated peripheral blood stem cell transplants performed during the report month.

10.4.4 **COBLT Bag Order Form**

The COBLT Bag Order Form should be used to order COBLT collection bag sets and transfer/freezing bag sets for cord blood banks (CBBs) and COBLT cell wash/infusion bag sets for transplant centers. Orders should be faxed to the COBLT Administrator at the Medical Coordinating Center (MCC) no more than once per month. The MCC submits bag orders to Pall Medical, the bag manufacturer, within 48 hours of receipt of the COBLT Bag Order Form.

APPENDIX A

ROSTER

(updated 6/7/05)

TABLE OF CONTENTS

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KEY
BC = Blood Bank Coordinator; **CC** = Clinic Coordinator; **CI** = Co-Investigator; **CN** = Consultant; **CO** = Contracting Officer; **DC** = Data Coordinator; **DSMB** = Data Safety and Monitoring Board Member; **FLO** = Flow Cytometry Personnel; **LAB** = Laboratory Personnel; **LC** = Laboratory Coordinator; **PI** = Principal Investigator; **PO** = Project Officer; **RO** = Radiation Oncologist; **SC** = Search Coordinator; **TC** = Transplant Coordinator;

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BC = Blood Bank Coordinator; **CC** = Clinic Coordinator; **CI** = Co-Investigator; **CN** = Consultant; **CO** = Contracting Officer; **DC** = Data Coordinator; **DSMB** = Data Safety and Monitoring Board Member; **FLO** = Flow Cytometry Personnel; **LAB** = Laboratory Personnel; **LC** = Laboratory Coordinator; **PI** = Principal Investigator; **PO** = Project Officer; **RO** = Radiation Oncologist; **SC** = Search Coordinator; **TC** = Transplant Coordinator;

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PACKING INFORMATION

Cord Blood Bank (CBB) Instructions: Complete all information below. Then fax this sheet to the requesting Transplant Center AND include a copy with the shipped cord blood unit (CBU).

Shipping to: _____ FAX: _____

This dry shipper contains **a frozen cryopreserved human placental umbilical cord blood unit (CBU)** for COBLT Recipient ID: _____

Contents of Dry Shipper:

COBLT CBU ID: _____

Accompanying Paperwork:
Transplant Center Feedback Sheet
Receipt Procedures
Procedure for Thawing Cryopreserved Cord Blood Unit (CBU) for Transplantation
Product Information
COBLT Bar Code Labels

Name of CBB Supplying the CBU: _____

CBB Shipper Number: _____

Federal Express Tracking Number: _____

For questions, contact:

CBB Contact Person: _____

Phone #: _____ Fax #: _____

Alternate CBB Contact:_____

Phone #: _____ Fax #: _____

Transplant Center Instructions: Upon receipt of this information, call the CBB contact person listed above for the combination of the dry shipper lock or if you have questions/concerns.

TRANSPLANT CENTER FEEDBACK SHEET

CBU ID #: _____ Recipient ID #: _____

CBU Information:

Volume (mL) - 25:
ABO Rh Type:
HLA A:
HLA B:
HLA DRB1:
CBU Collection Weight (gm):
Total Viable NCC x 10^8:
CFU-GM x 10^5:
CD 34+ x 10^6:
CD 3+ x 10^6:
Infant gender:

Maternal Sample Test Results:

CMV IgM Antibody:
Anti-HBc:
Syphilis:
Anti-HCV:
HbsAg:
Microbial Culture:
HIV-1/2:
HIV p-24 Ag:
HTLV-I/II:
Hemoglobinopathy Screen:

Complete the following information prior to packing the CBU in the dry shipper

Charged Weight of Unpacked Dry Shipper: _____ _____ _____ lb.

Complete the following information upon receipt of the CBU and fax to:
Name and FAX Number of CBB and MCC - Computer Generated

Transplant Center Code: ___ ___ ___ _____ Time Zone (ET, CT, MT, PT)

Date and Time of Receipt: ___/___/___ ___:___ (24 hour clock)

Confirm Label Checks:
CBU ID and Recipient ID on Packing Information / Transplant Feedback Sheet / CBU Registration _____
CBU ID on Unit / Transplant Feedback Sheet _____
Transplant Feedback Sheet / Accompanying Labels _____

Weight of Unpacked Dry Shipper: _____ _____ _____ lb.

Condition of CBU at Receipt: 1 G Satisfactory 2 G Unsatisfactory, *specify*:_____

Condition of Dry Shipper: 1 G Satisfactory 2 G Unsatisfactory, *specify*:_____

Did shipper temperature monitoring device indicate temperature > -120°C? 1 G Yes 2 G No

Please specify conditioning regimen intended for Recipient ID_____
_____

Information Completed By:_____ Study ID: __ __ __ __ Date: __/__/__

RECEIPT PROCEDURES

1. Verifying and Storing the Cord Blood Unit (CBU)

1.1 Open the top of the dry shipper using the combination lock number supplied by the CBB contact person. Locate the Transplant Center Feedback Sheet included in the packing information. Verify that the COBLT CBU ID and the COBLT Recipient ID recorded in the packing information, on the Transplant Center Feedback Sheet, and on the COBLT Confirmation of Registration/CBU Release Request match.

If there is a discrepancy, DO NOT PROCEED. Immediately call the designated CBB contact person listed in the packing information.

1.2 Open the main storage compartment of the dry shipper and locate the plastic bag containing the CBU canister. Transfer the CBU from the dry shipper into the vapor phase of liquid nitrogen in a liquid nitrogen freezer at ≤ -120°C. Verify that the identification number on the CBU matches the CBU ID number on the Transplant Center Feedback Sheet. **THESE STEPS MUST BE COMPLETED AS QUICKLY AS POSSIBLE TO MINIMIZE THE TIME THE CANISTER CONTAINING THE CBU IS EXPOSED TO THE AMBIENT TEMPERATURE.**

If there is a discrepancy, proceed. After safely storing the CBU canister, immediately call the designated CBB contact person listed in the packing materials.

1.3 After the CBU is safely stored, inspect the condition of the dry shipper and locate the temperature monitoring device packed with the CBU canister. Contact the CBB immediately if there is any indication that the CBU was damaged or exposed to temperatures > -120°C.

1.4 After all checks have been performed and any discrepancies resolved, notify the appropriate individuals at your institution that the CBU has arrived, and complete the receipt information on the Transplant Center Feedback Sheet. Fax the sheet to the CBB responsible person listed in the packing materials and to the MCC.

2. Returning the Dry Shipper (Contract Centers Only)

2.1 Make arrangements to return the dry shipper to the CBB immediately following storage of the CBU. Return the dry shipper via Federal Express using the enclosed return shipping label. Pack the Styrofoam packing, bubble paper, and the shipper lid. Lock the lid with the combination lock.

2.2 On the day the shipper is sent, inform the CBB designated contact person so that they can expect its arrival.

Immediate return of the shipper is essential because it is needed for another patient's product. If there are any questions, please call the designated CBB contact person.

THAWING CRYOPRESERVED CORD BLOOD UNIT (CBU) CELLS FOR TRANSPLANTATION

Principle

Cells cryopreserved in DMSO have limited viability upon thawing, resulting in significant losses of cells available for transplantation. DMSO, the cryopreservant used to maintain cell viability at ultra low temperatures, is toxic to cells when warmed to 37° C. Intracellular DMSO creates a hypertonic environment which leads to sudden fluid shifts and cell death upon warming. Lysis of red blood cells leads to accumulation of extracellular free hemoglobin which can be nephrotoxic if infused intravenously. In addition, DMSO causes adverse effects in vivo after reinfusion, including blood pressure instability, fever, chills, and nausea. These problems can be ameliorated by mixing the thawed cells with a hypertonic solution, Dextran 40 + 5% albumin, immediately upon thawing. Cells can then be washed and further manipulated to remove DMSO, free hemoglobin, and other cellular products, as well as to perform other procedures before infusion to the patient.

NB: This procedure is designed to enable the technologist to sterilely thaw cryopreserved cord blood within a closed system while maximizing viable cell recovery. The final product can be resuspended in a variable amount of dextran/albumin solution, allowing for adjustment to a suitable volume for reinfusion into patients of varying sizes. The final product is stable for at least 6 hours and time should be taken to work carefully and calmly.

Specimen

Frozen CBU within a metal canister maintained in the vapor phase of liquid nitrogen in a liquid nitrogen freezer at -120° C. The cryo bag containing the CBU may be overwrapped with plastic and may have 1-2 sealed tubing segments attached.

Equipment

Laminar Flow Hood	
Refrigerated Blood Bank Centrifuge	Sorvall
Plasma Expressor	Baxter 4R4414
Coupler	Baxter 4C2405
Transfer Packs with Spike (#2, 300 mL)	Baxter 4R2014
Sterile Docker	Haemonetics SCD 312
Balance	Sartorius or Mettler
Heat Sealer	Sebra
Hemocytometer with Coverslip	Hausser Scientific, Bright-Line 1492
Instrument to Count WBCs	Coulter
BacT/Alert 120	Organon Teknika
Glass Microscope Slides (2)	
Nunc Tube	
Sterile Gloves	
Protective Freezer Gloves	
COBLT Bar Code Labels	From CBB
CBU Thawing Form	

Reagents

Albumin 25% Human UPS (12.5 grams in 50 mL)	Baxter
Dextran 40 (10% Gentran 40 in 0.9% NaCl, USP)	Baxter
Trypan Blue Vital Stain, 1% Solution	Gibco

Supplies

12 x 75 mm Tubes, Non-sterile	Falcon 2052/Fisher 149-596
12 x 75 mm Sterile Culture Tubes with Snap Caps	Labcon 3336-335-000/Port City, Inc.
Syringes: Sterile 1 cc, 20 cc	Becton-Dickinson: (1 cc) 309623, (20 cc) 309661
Injection Needles: Sterile 16 g, 19 g	Becton-Dickinson: (16 g) 305198, (19 g) 305187
Cell Wash/Infusion Bag Set	Pall Medical (791–03)
Hemoset (optional)	Abbott Labs #8948

Or

Y-Type Blood/Solution Set with Large Standard Blood Filter (170-260 micron filter)	Baxter
Hemostats (optional)	
Insul - Ice Mat (optional)	POLYFOAM Packers #970362
Cup of Regular Ice	
Bucket of Dry Ice	
Small Plastic Zipper-locked Bags* *Gas sterilize in house	
Alcohol Prep Pads	Baxter Healthcare #40000-110
Iodine Swabsticks	Baxter Healthcare #40000-040

Procedure

1. Begin preparations.

    a. Verify that the water bath temperature is 37° C.

    b. Prepare and label QC materials: counting vials, glass slide(s) for Wright's stain, tubes for viability, nunc tube to refreeze cryo bag segment(s), and bacterial culture bottles. Nunc tubes should be labeled using one of the cryogenic ISBT-128 bar code labels supplied with the CBU. OPTIONAL: Tubes for immunophenotyping and sterile tubes for progenitor assays.

    c. Assemble and bar code the necessary paperwork, completing as much as possible.

d. Mark transfer and label packs at 150 cc, 50 cc, and 25 cc with a permanent marker using a template prepared in the laboratory.

e. Place dry ice in bucket.

f. Place regular ice in cup, then inside the hood for QC.

g. Label the transplant bag and waste bag of the Cell Wash/Infusion Bag Set (Figure 1) and put 100, 125, 150, and 175 mL marks to the outsides of the transplant bag, using a template prepared in the laboratory, to aid in adding the correct volume of Dextran/albumin solution (Illustration 1). Additional marks for 50, 200, and 250 mL may also be added. Tare the scale and use the same tared scale to weigh the transplant bag and residual cells in Step 6d.

NB: To obtain accurate weights, always position the transplant bag and attached tubing identically. To do this, obtain a plexiglass tray with pins which fit into the holes in the transplant bag. Also place a block next to the scale to rest the tubing attached to the transplant bag. Always rest the tubing on the block at the same distance from the bag. It is suggested that marking the tubing 15 cm from the top of the transplant bag will help in positioning the tubing.

2. Prepare Dextran 40 + 5% albumin solution.

a. With sterile technique, add 25 gm (100 mL from 2 bottles) of stock albumin (25% Human UPS, 12.5 gm/50 mL) to a UPS bag containing 500 mL of Dextran 40. Final volume is 600 mL Dextran/albumin solution with a final concentration of approximately 5% albumin (actually 4%).

Or

From a UPS bag containing 500 mL of Dextran 40, drain 250 mL Dextran 40 and sterilely add 12.5 gm (50 mL from one bottle) of stock albumin (25% Human UPS, 12.5 gm/50 mL) to the remaining 250 mL of Dextran 40. Final volume will be 300 mL of Dextran/albumin solution with a final concentration of approximately 5% albumin (actually 4%).

b. Using sterile technique (sterile docking or spike), transfer 300 mL of Dextran/albumin solution into the labeled 300 mL sterile transfer pack. Heat seal the tubing and remove the transfer bag.

c. If 600 mL of solution is prepared, using sterile technique (either sterile docking or spiking), transfer the remaining 300 mL of Dextran/albumin solution into a second marked 300 mL sterile transfer pack. Label bag with a 24 hour expiration date and time and save for another thaw procedure.

3. Set up a closed system.

   a. Sterile dock the 300 mL Dextran/albumin transfer bag to the Cell Wash/Infusion Bag Set (Illustration 2). Using the volume marks on the transplant bag, allow 125 mL of Dextran/albumin to flow into the transplant bag (see Step 1g).

   b. Clamp off the tubing. Surround the bag with an ice mat to allow the solution to cool and place in hood (Illustration 3).

4. Thaw the cord blood and transfer to transplant bag.

   a. Remove the cryopreserved cord blood from the freezer carefully. Two technicians will perform label checks as per institution SOP.

   b. Working in vapor phase of liquid nitrogen, open the cassette, remove cryo bag plastic overwrap if present, and quickly separate segment(s) from the cryo bag. Place segment(s) in labeled nunc tube and put nunc tube in vapor phase of liquid nitrogen immediately to prevent thawing of the cord blood in the segment(s). Nunc tubes should be placed in a permanent storage location at a later time.

   c. Remove the frozen CBU from the cassette. Wipe down outside of cryo bag quickly and carefully place into a sterile zipper-locked bag. Thaw the CBU in the zipper-locked bag in the water bath until the product reaches a slushy/liquid consistency. Remove the zipper-locked bag containing the CBU from water bath, dry outside of zipper-locked bag, and place under the hood.

   d. Under the hood, remove CBU cryo bag from zipper-locked bag and, if necessary, dry the outside of the cryo bag. Clean the cryo bag port covers with iodine solution, cut the covers over the ports, and clean the cut and inner surfaces again with alcohol.

      NB: The ports on the cryo bag are covered with a plastic seal. In addition, there is an internal seal that the spikes will break as they enter the bag.

      Use sterile gauze to dry the ports. Spike into the cleaned ports with the spike lines attached to the Cell Wash/Infusion Set. Envelope the cryo bag with an ice mat. **Open the connection to the Dextran/albumin bag, but do not begin mixing the cells with the dextran/albumin until you read through Steps e and f below.**

   e. Hold the cold pack-wrapped cryo bag in one hand and the cold pack-wrapped transplant bag in the other hand, lower the cryo bag, and raise the transplant bag to allow the Dextran/albumin solution to run into the cryo bag (Illustration 4). (Approximately 25 mL of Dextran/albumin solution should flow into the bag by gravity over 1-2 minutes.) Adjust the cold pack to allow the cryo bag to expand to accommodate this additional volume (Illustration 5). Massage the cryo bag by hand to thoroughly mix the 50 mL of cells plus Dextran/albumin solution.

f. Continue to **gently mix** the cells in the cryo bag with the Dextran/albumin solution by alternatively raising the cryo bag (with ice mat) relative to the transplant bag (with ice mat) and then the transplant bag relative to the cryo bag. Allow gravity to facilitate mixing of the cells and remaining Dextran/albumin solution. Gradually and completely mix cells with Dextran/albumin over a minimum of 4-5 additional minutes. After complete mixing, lower the ice pack-wrapped transplant bag and raise the ice packed-wrapped cryo bag to allow the cells to run into the transplant bag (Illustration 6). A small amount of residual fluid and cells will remain in the cryo bag and tubing. Clamp off the lines between the cryo bag and transplant bag in preparation for the rinsing procedure.

g. To rinse the cryo bag, unclamp the tubing between the Dextran/albumin bag and the cryo bag. Allow approximately 25 mL of Dextran/albumin solution to run into the cryo bag. Close the clamp on the tubing between the Dextran/albumin bag and the cryo bag. Swirl the solution around the cryo bag to mix any remaining cells with the Dextran/albumin solution. Open the tubing between the cryo bag and the transplant bag and allow the rinse solution with cells to run from the cryo bag into the transplant bag (Illustrations 7a-c). Repeat this process a second time. The total volume in the transplant bag should now be approximately 200 mL. [125 mL Dextran/albumin + 25 mL cells in DMSO + 25 mL (rinse 1) + 25 mL (rinse 2)]. CAUTION: Do not add more than 250 mL to the bag. Overfilled bags may break when centrifuged.

Note: To enhance flow during rinsing, add air from the transplant bag to the cryo bag. Sometimes the liquid in the 5 mL section of the cryo bag will not drain out of the bag. If this happens, close the clamp between the 20 mL section of the cryo bag and transplant bag. The fluid will then run out of the 5 mL compartment. CAUTION, do not add more than 250 mL to the bag. Overfilled bags may break when centrifuged. Allow a few mLs of well-mixed Dextran/Albumin + cells to enter back into the cryo bag. Drain back into Transplant bag.

5. Centrifuge the cord blood to pellet the cells.

a. Place the Cell Wash/Infusion Bag Set and Dextran/albumin transfer bag into a centrifuge bucket. It is suggested that the bags be placed in a sterile zipper-locked bag prior to placement in the centrifuge bucket. The assembly must be supported and cushioned and all bags must be standing upright with ports facing up (Illustration 8). Bags can be cushioned by placing two 250 mL bags filled with water or saline placed on either side of the transplant bag. Weigh and tare the balance. Balance with a second bucket.

b. Pellet the cells at 880 G for 20 minutes at 4° C via centrifugation. On their Sorvall model, personnel at Duke University spin at 1800 rpm to achieve 880 G . Each center should validate its centrifuge prior to thawing a COBLT CBU.

6. Express supernatant and prepare cells for transplantation.

   a. After centrifugation, gently remove the Cell Wash Infusion Bag Set and Dextran/albumin bag, taking care not to disrupt the cell pellet at the bottom of the transplant bag.

   b. Hang the transplant bag on the plasma expressor without disturbing the pellet at the bottom of the bag.

   c. Express the majority of the supernatant from the transplant bag into the waste bag. Continue to apply pressure until the cells in the pellet at the bottom of the transplant bag start to move or when the net remaining cell solution reaches a volume of approximately 25 mL.

      Note: Clear the tubing between the transplant bag and the waste bag by adding air from the waste bag.

   d. After completion of expression of the supernatant, move the transplant bag to the tared scale (see Step 1g). The transplant bag and tubing must be placed in the same position used to tare the scale.

   e. Carefully open the tubing between the Dextran/albumin bag and transplant bag. Resuspend cells in 50 mL (or desired volume between 30-150 mL) of fresh Dextran/albumin. Record the weight from the tared scale of the washed and resuspended CBU on the CBU Thawing Form. Heat seal and remove the waste and Dextran/albumin bags.

      Note: If patient weight is $\leq$ 20 kg, use approximately 30 mL. If patient weight is $\leq$ 40 kg, use approximately 40 mL.

   f. Using sterile technique, remove a 0.5 mL sample of the cells for QC. Obtain a cell count and viability on the final product. Record values on the CBU Thawing Form.

      Calculate viable cell recovery using the following formula:

$$\frac{\text{Total viable nucleated cells in washed and resuspended CBU}}{\text{Total viable nucleated cells of cryo-preserved CBU}}$$

      Note: To standardize viability reporting, viability should be performed by Trypan Blue dye exclusion within 5 minutes of taking the QC sample. See Procedure Notes: Viability counts using Trypan Blue.

      If < 75% of total viable nucleated cells are recovered (calculated above), re-spin supernatant in waste bag to recover additional cells, as detailed in Procedure Note 1.

      OPTIONAL: Calculate the amounts needed for progenitor cell assays and immunophenotyping.

g. If the final cord blood product contains clumps, filter using a burette filter (100 mL burette hemoset, Abbott Labs #8948) or Fenwal Y-type filter set (blood component filter set). Do not use any filter small enough to deplete leukocytes (e.g. < 60 microns). A pore size 60 - 270 microns is recommended. Do not irradiate product.

h. Label the transplant bag with information per institutional SOP.

i. Remove 15 mL from the waste bag and add to sterility testing tubes.

Procedure Note

1. To attempt to recover additional cells from the waste bag, follow the procedure below.

   a. Heat seal the tubing between the transplant bag and the waste bag proximal to the transplant bag. The transplant bag can be transported to the transplant unit for infusion into the patient.

   b. Using sterile technique, attach the tubing on the waste bag to a new transfer bag. Pellet the residual cells in the waste bag. Centrifuge the bag at 880 G at 4 degrees centigrade x 15 minutes. Remove the bag from the centrifuge carefully without disrupting the cell pellet.

   c. Express the supernatant into the transfer bag, leaving a residual volume of approximately 10-20 mL.

   d. Resuspend the cell pellet in the remaining supernatant and remove an aliquot of 0.1 mL. Perform cell count and viability.

   e. If $\geq 1 \times 10^6$ cells/kg of patient body weight are recovered from the waste bag and if patient received a cell dose of $1\text{-}5 \times 10^7$ cells/kg in the initial transplant bag, infuse these additional cells. These cells may be added to the original transplant bag or may be given as a boost later on Day 0. Transport residual cells to the patient's room for reinfusion. If $< 1 \times 10^6$ but $> 1 \times 10^5$ cells/kg are recovered, cells should be cryopreserved in 10% DMSO for future testing or other uses. These cells can be stored in a nunc vial or small cryo bag at the discretion of the transplant center lab.

Quality Control

Cell count

Viability

Smear for Wright's stain

Progenitor assay (Optional) * Do not remove more than 0.5% of total cells.

CD34+ Procount (Optional) * Do not remove more than 0.5% of total cells.

Procedure Notes

Viability Counts using Trypan Blue

1. Add 10λ of post-thaw cells and 10λ of trypan blue, 1% solution, to a sterile tube.

2. Mix thoroughly and incubate for 5 minutes.

3. Remove 10λ and place under a coverslip on a hemacytometer.

4. Allow to settle.

5. Count 200 cells, scoring live versus dead cells.

NOTE: The live cells are NOT blue, the dead cells are blue. Results are expresses as percent of cells that exclude the dye (i.e., are alive).

References

Pablo Rubinstein, M.D., Director of Placental Blood Bank, New York Blood Center, New York (personal training and communications).

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Cell Wash/Infusion Bag Set

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Illustration for COBLT CBU Thawing SOP - Page 1 of 3

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Illustration for COBLT CBU Thawing SOP - Page 2 of 3

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Illustration for COBLT CBU Thawing SOP - Page 3 of 3

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PROCEDURE FOR INFUSING THAWED CBU

Principle

Unrelated cord blood, banked for public use, can substitute for bone marrow as the source of reconstituting stem cells after marrow ablative therapy used to treat patients with cancer, bone marrow and immunodeficiency diseases, and selective genetic diseases. After selection for transplantation, the designated unit is shipped from the bank to the transplant center in a dry shipper before the patient begins cytoreductive therapy. At the transplant center, the unit is stored in the vapor phase of liquid nitrogen until the day of transplant, when it is thawed and washed in dextran/albumin, a process which increases cell viability and removes approximately 90% of the DMSO cryoprotectant. The washed cells are resuspended in dextran/albumin and transported to the patient's bedside in a labeled transplant bag for infusion.

The unit is infused into the patient's blood via the central venous catheter over 2-30 minutes. Every effort should be made to be sure that all the cells in the transplant bag and IV tubing are delivered to the patient, maintaining a closed system during the infusion procedure.

Materials

Labeled transplant bag
Y-infusion set
IV extension tubing
500 mL bag of Normal Saline
Blood filter, 170-260 microns

Procedure

1. Verify that the patient is stable and has received scheduled premeds for transplant.

2. Verify that the transplant bag label matches patient identifiers via institutional procedures.

3. Examine the transplant bag to be sure that cells are in solution and that large clumps are not present in the bag. If clumps are present, prepare to use blood filter in infusion set-up.

4. Close all clamps on the tubing on the Y-infusion set and blood filter.

5. Spike one arm of the Y-infusion set into the bag of normal saline.

6. Connect extension tubing to the distal arm of the Y-infusion set.

7. Prime all tubing with normal saline.

8. Spike the other arm of the Y-infusion set into the transplant bag.

9. Connect the distal end of the extension tubing to the patient's central venous catheter.

10. Open the clamps between the transplant bag, the extension tubing, and the patient's central line and allow cells to infuse into the patient's blood.

11. Rinse residual cells in the transplant bag and tubing. After all cells have dripped out of the transplant bag, close the clamps on the extension tubing and Y-set connected to the transplant bag. Open the clamps between the normal saline bag and transplant bag and allow approximately 25 cc of saline to run into the transplant bag. Close the clamps between the saline bag and transplant bag and open the clamps between the transplant bag and patient and infuse this saline to the patient. Repeat rinse x 1.

12. Monitor the patient's vital signs before, during, and after infusion per institutional practices.

PRODUCT INFORMATION

General Information

Bone marrow transplantation (BMT) from human leukocyte antigen (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. 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 (1 - 21).

As of June 2000, umbilical cord blood from sibling and unrelated donors has been used to reconstitute hematopoiesis in approximately 1200 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. The purpose of the Cord Blood Transplantation (COBLT) Study is to accurately describe 180-Day survival and other events after cord blood transplantation.

Drug Description

Umbilical cord blood is collected from the delivered placenta by insertion of a sterile transfusion set needle into the umbilical vein. Gravity causes the blood to drain into the collection bag, which is part of a sterile closed system. The anticoagulant citrate-phosphate-dextrose (CPD) is included in the bag. Collection volumes range from 40-300 mL. Informed consent is obtained from every mother and samples of the mother's blood are screened for CMV, Hepatitis B, Hepatitis C, HIV-1/2, HTLV-I/II, and syphilis. A sample of the cord blood unit is tested for microbial contamination and HLA type. Results from newborn sickle cell disease screening are obtained. A maternal medical history is obtained, and a six month follow-up of the baby is requested. A nucleated cell count, a CD34+ cell count, and a colony forming unit assay are performed on cells from the unit. Units are cryopreserved using a solution of 10% dimethyl sulfoxide (DMSO) and 1% dextran. Cryopreserved CBUs are permanently stored in liquid phase of liquid nitrogen. Small aliquots for additional testing and unit identification are also frozen. The collection bag, cryobag, test samples, and data forms are labeled with a study bar code. When selected for transplant, the unit is shipped to the transplant center using an express carrier. It is thawed in the laboratory at 37°C, washed with 10% dextran 40 and 5% human albumin to remove cryoprotectant, resuspended in fresh 10% dextran 40 and 5% human albumin, and infused into a patient who has received an appropriate conditioning regimen.

Pharmacological/Toxicological Effects

In early studies, there were reports of reactions to the cryoprotectant used for freezing the cord blood unit. A change in the thawing procedure (22) has reduced or eliminated that problem and improved viability of the infused cells. Reported graft versus host disease, even in patients who received two and three HLA antigen mismatched cord blood units, appears to have been less than would have been expected with marrow from an unrelated donor (16).

Pharmacokinetics

The median time to engraftment (ANC >500 on the first of three days) for patients who receive cord blood stem cell transplants has been reported to vary from 17 to 26 days (17). Hematopoietic recovery may have been related to the use of growth factors in this study. Others have suggested it may also be related to cell dose per kg of patient weight, and perhaps to other unidentified factors. Platelet engraftment is significantly delayed in recipients of cord blood compared to other types of stem cell transplants (median time to platelets >50,000 = 67 days in the Wagner study and 82 days in the Kurtzberg study).

Safety and Effectiveness

Nearly 375 unrelated donor UCB transplants have been performed at Duke University and University of Minnesota. In July 2000 (21), a detailed analysis of their combined data sets was performed to determine the potential influence of various factors (e.g., graft cell dose and donor/recipient HLA disparity) on rate of hematopoietic recovery and probabilities of engraftment, acute GVHD, chronic GVHD, non relapse mortality, relapse and overall survival. In comparison to prior reports on unrelated donor UCB transplantation, the present study benefits from standardized HLA typing with high resolution typing of HLA-DR, greater homogeneity in supportive care treatments between two centers, and the ability to internally verify data accuracy.

The results from the analysis demonstrated that cryopreserved UCB from HLA 0-3 antigen mismatched unrelated donors contains sufficient numbers of transplantable hematopoietic stem and progenitor cells for most small patients. The data presented indicated that the probabilities of grade III-IV acute GVHD and extensive chronic GVHD are low. Please see the reference list for complete citation and additional studies.

Risks and Toxicities

Recipients of cord blood transplants, like recipients of allogeneic marrow transplants, incur risks from pre-transplant conditioning and graft versus host disease (GVHD) prophylaxis which must be weighed against the risk of malignancy or other disease for which they are receiving a transplant. Compared to other forms of transplantation, the following risks may be increased in recipients of cord blood.

1. Failure to engraft or secondary graft failure can occur. It appears that both white cell and platelet engraftment are slower compared to other sources of stem cells. Graft failure is of special concern in larger patients. Additional stem cells will not be available from the same donor to treat graft failure.

2. Relapse of the underlying disease may occur, especially in patients with advanced disease at the time of transplant. Because of the naive nature of the cord blood cells, relapse may be an increased problem in this kind of transplant. Additional stem cells will not be available from the same donor to treat graft failure.

3. GVHD may be increased compared to marrow transplants, especially in patients with two or three HLA antigen disparity.

4. Infections can be life threatening in the transplant patient population, especially patients receiving immunosuppressive therapy for GVHD.

5. Unknown toxicity from residual cryoprotectant or other agents in the cord blood infusion is a theoretical possibility.

Despite these potential risks and toxicities, the published data to date suggest that cord blood transplants are an acceptable alternative to other forms of stem cell transplantation and prompted this study.

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