

CHAPTER 1

STUDY ORGANIZATION

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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.

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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

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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.

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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.

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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.

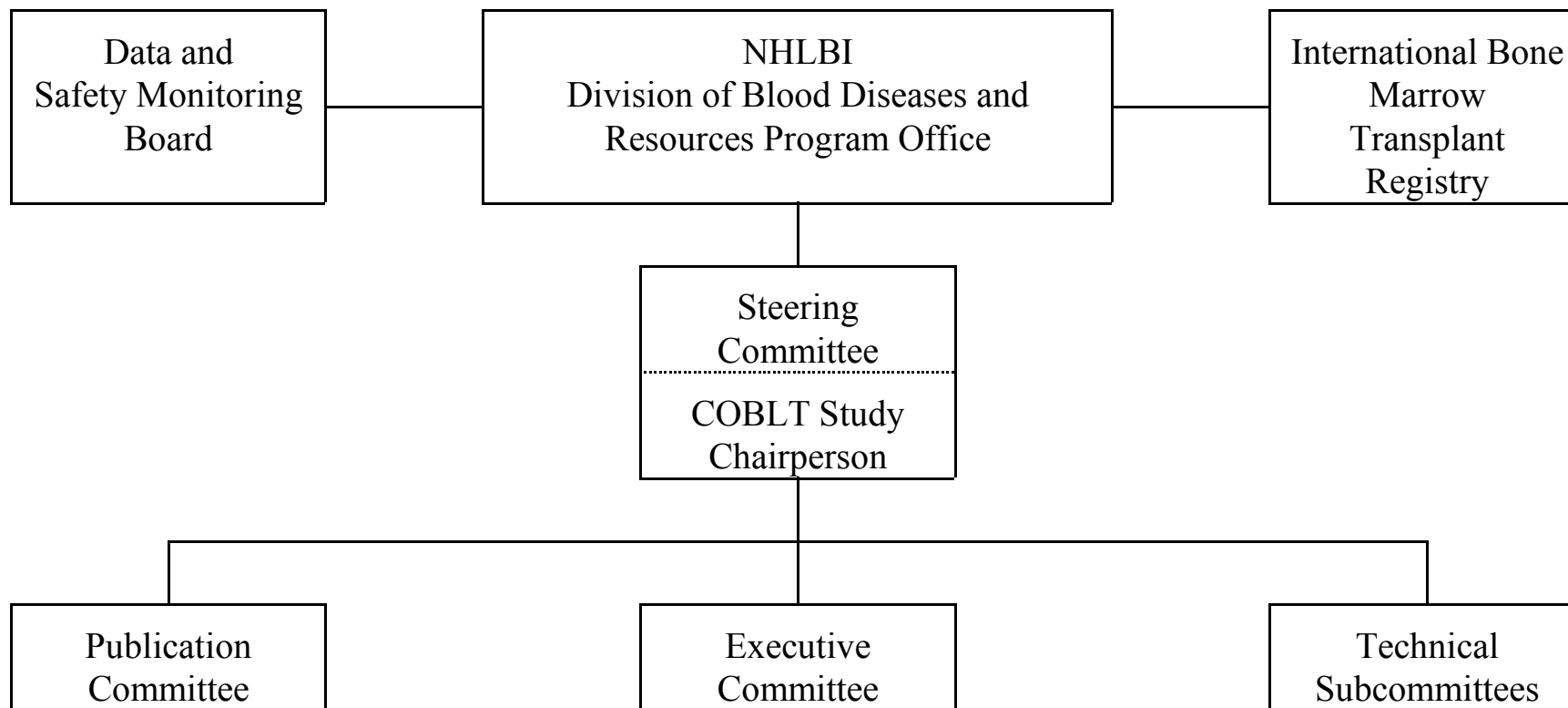
1.2.1 Study Chairperson

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



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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

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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

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- ! 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

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- ! 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.

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- ! 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.

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! 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.