

CHAPTER 5

QUALITY ENHANCEMENT

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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 studies¹⁻⁴ 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}

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- 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.

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

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

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

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

The number of unrelated cord blood transplants is increasing each year. The number of minority cord blood transplants is expected to increase faster than the number of Caucasian cord blood transplants. This is due to the emphasis and contract requirements placed on the COBLT blood banks to recruit specified numbers of donors from all the minority groups.

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

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

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 bias 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.

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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.

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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.

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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

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5.5 REFERENCES

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