

CHAPTER 4

DATA ANALYSIS AND REPORTING

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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.

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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.

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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

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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

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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.