

CHAPTER 7
QUALITY ASSESSMENT

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7.1 OVERVIEW OF CBB-SPECIFIC QUALITY ASSURANCE/QUALITY CONTROL PROGRAM

An extensive, site-specific Quality Assurance/Quality Control (QA/QC) program must be established and maintained by each collection facility under the direction and supervision of designated personnel. This program must verify the quality and integrity of cord blood units (CBUs) collected under this NHLBI project, as well as equipment used in the collection, processing, storage, and shipping of the units. In addition, there must be a review and approval process for policies and procedures, and documentation of compliance with regulatory requirements and standards.

Quality audits must be performed on a routine basis. It is the immediate obligation of the investigators, and by extension of the NHLBI, to assure conformity to Standard Operating Procedure (SOP) requirements relative to the eligibility or ineligibility of harvested CBUs for permanent storage.

As identified in the SOPs, the Steering Committee has established well-defined criteria for determining the integrity of potential CBUs for permanent CBB storage. Compliance with standards itemized in the SOPs is crucial for the welfare of cord blood donors and recipients, as well as for investigators and the NHLBI. To facilitate compliance and promote congruity between sites, the SOPs identify the functions and responsibilities of specific personnel, and provide detailed logs and flow sheets.

Adherence to the SOPs is more likely to be assured by instituting internal and external inspections, and uniform data forms completion standards. Inspection of completed data forms, including their audit against source records, is a recognized method of assuring the quality of research data. Internal and external audits provide quantitative and qualitative information relative to site compliance within established parameters. Internal audits of randomly selected patient records every 3 months by cross-trained personnel will provide direction for internal correction of any noted deficiencies. External verification of data forms against source records by an MCC monitoring team strengthens the integrity of data and the project, and provides sites with specific performance evaluations. Site monitoring is of particular value immediately following the initiation of a new research project. In the start-up phase, a monitoring team can be a critical communication link regarding application of the SOPs to the daily operations of the program. It encourages accountability and conformity between personnel as well as between sites.

External oversight by the MCC for the study will be instituted to inspect data collection forms and verify them against source documents. Within 6 months of a collection site's start-up, the monitoring team will review all data forms for randomly selected units. If the data audited satisfactorily demonstrates adherence to the SOPs, monitoring visits will occur every year. In the event of major breaches of protocol, the NHLBI may impose additional conditions on an investigator or, if necessary, potentially terminate the site's participation in the project.

The MCC and/or NHLBI will conduct external laboratory audits to inspect and certify the performance

of all CBU processing and storage laboratories. External audits will be completed, at a minimum, at 1 year intervals. Again, in the event of major breaches of protocol, the NHLBI may impose additional conditions on an investigator or, if necessary, potentially terminate the site's participation in the project.

In order to remain in compliance with federal regulatory requirements, principal investigators at each NHLBI banking site are held accountable for implementing and managing all regulatory responsibilities of the research project at both their immediate site and all satellite collection facilities. Those responsibilities are recognized to include the following:

- ! Promote the rights of research subjects
- ! Adhere to the NHLBI Cord Blood Bank SOPs
- ! Maintain all IRB administrative obligations
- ! Support monitoring audits of the sponsoring agency
- ! Source document the initiation, maintenance, and closure of the study
- ! Comply with quality assurance criteria

In turn, by virtue of holding an IND for the project, the NHLBI is charged with accountability for each of its sites. If the sites are not compliant to NHLBI directives, then NHLBI is liable and placed at risk of breaching federal regulations. In order to most effectively protect patients, investigators, sponsoring agencies, and the general research community, it is essential that layers of accountability, with documented adherence and oversight, be structured into the generic research process and its application in this project.

These issues are of particular clinical import for the COBLT Study in that the banked product is intended for use in human transplants. The increased inherent risks involved in representing the rights of two research subjects, the donor and recipient, and the clinical imperative of ensuring product integrity for transplant, intensify the need for regulatory scrutiny. Implementing universal, regulatory quality control standards for all participating collection sites will serve to protect patients and ultimately the project. Some of those standards are suggested below.

At the local level, the SOPs and customized informed consents will be submitted for initial review and approval to an IRB which satisfies federal and state requirements for IRB committee composition and function. No site will initiate collections without providing the MCC, as the NHLBI representative, with notification of such IRB approval. Sites will inform their IRBs of any major SOP amendments and any consent revisions, and will receive IRB approval prior to implementation. Annual progress reports will be supplied to the NHLBI, initial and updated Form FDA 1572s, laboratory accreditation and normal values, investigator and sub-investigator CVs will be sent to the MCC, and records of all correspondence will be retained.

Strict adherence to the elements of informed consent will be maintained at all points in the consenting process, in compliance with the approved consent, and COBLT and institutional SOPs. The rights of the recipient patient can best be met by pursuing an intensive, documented informed consent process, and by insuring the clinical integrity of the product. Confidentiality and linkage will be issues at all sites which require internal audits as well as external oversight by the MCC and/or NHLBI.

Follow up for infectious and genetic disease tracking will be maintained by each collection facility per SOP criteria, as well as records of neonatal follow up contact. Quarterly reports tracking screening, quarantine, permanent storage, and shipping of cord blood units (including demographic profiles) are integral quality assurance components to be maintained by each site. Similarly, data must be managed in common, universal formats that allow for confidentiality, linkage, verifiable results and accurate transmission. Laboratory quality control issues are of particular significance and are addressed specifically in the policies and procedures identified in each site's COBLT QA/QC Manual.

Though these particular guidelines may not be collectively acceptable, at this point, the records for any finalized, acceptable standards will be audited at regular intervals (every year) by the MCC and/or NHLBI for accuracy, compliance, and follow up. The financial implications of such requirements can be significant.

The design of the COBLT Study has been engineered by a dedicated, multidisciplinary team. The successful implementation of the project demands strict adherence to the SOPs, federal regulations, and accepted industry standards. Any collection site that gains authorization to contribute cord blood units to the project (i.e. contract and non-contract banks), must be required to meet ALL itemized standards in the SOPs without exception, and within quality control guidelines.

7.2 ASSESSING QUALITY

7.2.1 Purpose

To define the policies, tasks, and responsibilities related to quality assessment and help ensure the provision of high quality products and service.

7.2.2 Scope

Assessment tasks are designed to monitor whether personnel, procedures, reagents, equipment, supplies, cord blood product, and record keeping meet their expected functions in a reliable, reproducible manner.

7.2.3 Policies

7.2.3.1 a. This program shall support the goals and mission statements of the medical centers and hospitals associated with each Umbilical Cord Blood Bank.

- b. The primary goal of the Cord Blood Banks is to provide a safe, reliable and efficient source of umbilical cord blood stem and progenitor cells for transplant in an environment that supports and fosters research and continuing development and quality improvement.

7.2.3.2 This program shall incorporate the principles of continuous quality improvement when assessing umbilical cord blood processes.

- a. Assign responsibility.
- b. Delineate scope of responsibility.
- c. Identify important aspects of responsibility.
- d. Identify key indicators.
- e. Establish thresholds for evaluation.
- f. Collect and organize data.
- g. Evaluate care.
- h. Take action.
- I. Assess the effectiveness of the action.
- j. Communicate findings.

7.2.3.3 Quality assessment requirements shall be based on appropriate State regulatory bodies and on the following agencies and their current documents:

- a. FDA: Code of Federal Regulations, Title 21.
- b. AABB: Standards for Blood Banks and Transfusion Services; Accreditation Requirements Manual.
- c. CAP: Transfusion Medicine Inspection Booklet.
- d. JCAHO: Accreditation Manual for Hospitals.
- e. CLIA: Clinical Laboratory Improvement Act, 1988, Title 42, Part 493.
- f. FAHCT: Standards for Hematopoietic Progenitor Cell Collection Processing and Transplantation.

7.2.3.4 Each bank should have a designated quality team consisting of directorial and supervisory staff. This team shall audit, on an ongoing basis, key systems and critical control points related to the quality and safety of cord blood collection, processing, handling, testing, and distribution.

7.2.3.5 The quality control program shall be under the surveillance of the quality team. Items evaluated on a daily or weekly basis shall be reviewed by a trained individual at least weekly. Secondary review should occur at least monthly by another trained, designated individual. Items evaluated monthly shall have secondary review completed quarterly. Items evaluated quarterly or at a less often interval shall have a secondary review annually.

7.2.4 **Elements to be Assessed**

Personnel training and competency, as well as the quality assessment of procedures, equipment, supplies, and records, are integral parts of assuring component quality.

7.2.4.1 Personnel

- a. New employees are oriented to the Umbilical Cord Blood Bank policies pertinent to their sections and are trained for their assigned job functions.
- b. Job competency is assessed annually in accordance with institutional competency testing.
- c. Personnel are expected to confirm data and identification as they perform procedures and computer entries.
- d. Personnel are expected to record data/test results promptly at the time the results are determined or read.

- e. Employee performance and test results are reviewed for completeness and accuracy as part of regular supervisory reviews.
- f. Performance evaluation is discussed with employees at least annually.

7.2.4.2 Procedures

- a. Procedures are written, reviewed, and implemented as required. Changes and revisions are documented.
- b. Before new or revised procedures are implemented, they must be validated and staff must be trained.
- c. Procedures will be reviewed annually by the Director and Medical Director.
- d. Procedures retired from use must be archived and retained.

7.2.4.3 Reagents and Specimens

- a. Reagents used for routine donor testing must meet appropriate FDA criteria (see CFR Title 21, Part 660). Licensed reagents (when available) must be used and in-date.
- b. When a reagent/solution is not covered by FDA criteria or when the licensed reagent is not available or is rare, unlicensed or expired reagents may be used with proper documentation, quality control, and/or supervisor approval.
- c.
 - (1) New bottles of reagents shall be dated upon opening and tested for reactivity before being placed into use.
 - (2) Control specimens shall be tested in the same manner as patient samples.
 - (3) Control results must be verified as acceptable before reporting test results.
 - (4) Test results from procedures for which controls and calibration are not established or available shall be reviewed by the Medical Director before reporting.
- d. Reagents that appear to be contaminated (cloudy or turbid) shall not be used for testing or processing.
- e. Reagents shall be used as prescribed by the manufacturer.

- f. Any component of a reagent “kit” shall be used only within that kit lot unless otherwise specified by the manufacturer.

Coordinators shall establish intended use and performance specifications for all equipment items. These specifications and ranges of performance will be defined in the equipment procedure and/or checklist.

- g. Vendors should be selected based on their ability to provide equipment that meets these performance standards. Selection considerations might include equipment design, validation of intended use, training and service support, licenser, and the company’s commitment to quality.
- h. Before a piece of equipment is placed into service, it will be entered into inventory and validated in-house for its intended use.
- i. Equipment should be used as procedures and manufacturer’s directions dictate.
- j. Quality control and preventative maintenance shall be performed on all pieces of equipment as specified in procedures and/or checklists. These steps shall meet regulatory requirements and manufacturer’s recommendations.
- k. Thermometers or other temperature sensing devices shall be placed in each refrigerator, freezer, incubator, heat block, water bath, or other equipment used for testing or storage of cord blood, reagents, or samples.

7.2.4.4 Supplies

- a. Are units collected, processed, and stored according to procedure?
- b. Does the equipment used in the processing and storage of umbilical cord blood function properly?
- c. Do cord blood units meet quality control specifications?

7.2.4.5 Records

- a. All donor records are considered confidential and are subject to COBLT confidentiality policies. Computer access to data is limited by staff verification codes. Donor test results may be given only to the donor (or an individual designated by the donor with written authorization). Notifications shall be done only by the Medical Director or designated personnel.
- b. All records must carry facility identification and comply with regulatory standards. Records should have a title that designates intended use, observed test results and interpretations, test date, and personnel identities. They must be legible and corrections must be clearly identified.

- c. Test results and donor records must be reviewed for completeness and accuracy in a timely manner.
 - (1) Procedures and record systems are set up so that, whenever possible, current results can be compared to previous results. This allows staff to monitor accuracy of donor identification and detect significant changes during task performance.
 - (2) Computer procedures incorporate entry verification steps prior to data acceptance to help assure entry accuracy.
 - (3) Test results and critical documents are reviewed as specified in the section regarding supervisory review procedures and checklists.
 - (4) Significant abnormal results are flagged for medical review and action.
- d. Records shall be stored and retained as specified in each of the Cord Blood Bank's Quality Assurance Manuals.
- e. Records should be retrievable within a reasonable period of time.

7.2.4.6 Proficiency Testing

- a. Proficiency testing is performed on an ongoing basis to assess general division performance of policies and procedures, personnel, equipment, reagents, and supplies.

7.2.4.7 Facilities and Safety

- a. The environmental conditions in the laboratory shall provide a safe and adequate place to work while fulfilling all pertinent regulatory requirements.
- b. Each employee will participate in safety training programs as defined by the duties performed by that employee.

7.2.5 **Assessment Schedule**

Quality assessment tasks and the frequency with which they are performed will be specified in the section regarding procedures and on appropriate checklists.

7.2.6 **Variations and Corrective Action**

7.2.6.1 Variations and deviations noted in any of the elements listed in the above section should be immediately called to a supervisor's attention and documented on a "Continuous Improvement worksheet" and "Corrective Action Report" or Cord Blood Bank equivalent. This Variance report is forwarded to the Responsible Coordinator and Director.

7.2.6.2 Corrective action will be determined by the Laboratory Director.

7.2.6.3 Reagents, equipment, and supply items that do not meet performance specifications must be taken out of service for repair or removal.

7.2.6.4 Variance reports are compiled in a master log and reviewed quarterly by the QA unit for trend analysis.

7.2.7 **References**

1. FDA: Code of Federal Regulations, Title 21.
2. AABB: Standards for Blood Banks and Transfusion Services; Accreditation Requirements Manual.
3. CAP: Transfusion Medicine Inspection Booklet.
4. JCAHO: Accreditation Manual for Hospitals.
5. CLIA: Clinical Laboratory Improvement Act, 1988, Title 42, Part 493.
6. FAHCT: Standards for Hematopoietic Progenitor Cell Collection Processing and Transplantation.

7.2.8 **Quality Assessment Task and Frequency Summary**

Tables 7.2.8.1 and 7.2.8.2 provide examples for summarizing the framework and overview for each Cord Blood Bank.

1. Personnel
 - Training Prior to working independently
 - Competency Testing Annual
 - Continuing Education On-going
2. Procedures
 - Validation Prior to implementation and changes
 - Quality Assessment Review Annual
3. Records
 - Result Verification At computer entry
 - Supervisor Review Daily per procedures
 - File Rotation/Storage Annual or as specified

4. Reagents and Supplies

5. Equipment and Supplies

- Initial Validation Prior to use
- Preventative Maintenance See checklists

- Recertification After repairs or changes in use

- Cord Blood Collection Processing At the time of assembly of collection kits and again prior to use

- Centrifuges
 - Function Monthly
 - Speed and Timer Quarterly
 - Temperature Monthly
 - Function and Safety Check Annual

- Computer
 - Clean Screens As Needed
 - Vacuum Printers As Needed
 - Keyboard Covers Quarterly
 - Validation of Specific Activity Semi-annual

- Heating Blocks/Water Baths
 - Temperature Each day of use
 - Quadrant Checks Annual
 - Periodic Maintenance Annual

- Heat Sealers
 - Function Check Each use
 - Service/Cleaning Annual

- Microscopes
 - Cleaning As Needed
 - Function and Safety Annual
 - Service Check Every 5 years

- Pipetter Recalibration Annual

- Scales/Balances
 - Weight Check Each day of use
 - NIST Reference Weight Monthly

- Sterile Connecting Device
 - Weld Check Each use
 - Clean Daily
 - Function and Safety Check Annual

- Thermometers
 - Safe T Vue Upon receipt/annual

- Timers/Wall Clocks Upon receipt/annual

- Transport Coolers
 - Function Upon receipt
 - Shipping Temperatures Winter/Summer

- Water Baths/Heat Blocks
 - Temperature Each day of use
 - Quadrant Check Annual
 - Periodic Maintenance Annual

- Miscellaneous
 - Air Vents Clean/Inspect Quarterly
 - Electrical Safety Checks Annual
 - Eye Wash Weekly
 - Fire Drill Check Quarterly
 - Fire Extinguisher Service Check Monthly

- Internal Self-Assessment On-going

**Table 7.2.8.1
Quality Plan - Framework**

	Systems							
	Donor Suitability	Collection	Transport	Processing	Testing	Review and Labeling	Storage and Distribution	Investigation of Adverse Events
Critical Control Points								
Organization Issues								
Personnel Selection, Training, and Education								
Validation, Calibration, Preventative Maintenance, and Proficiency Testing								
Supplier Qualification								
Process Control								
Documentation/Record Keeping/Record Review								
Label Control								
Incident/Error Review								
Internal Assessment								
Process Improvement								

**Table 7.2.8.2
Quality Plan - Overview**

Organization Issues	Personnel Selection, Training, and Education	Validation, Calibration, Preventative Maintenance, and Proficiency Testing	Supplier Qualification	Process Control
<ul style="list-style-type: none"> • Description of Umbilical Cord Blood Bank • Organization Chart • Mission Statements • Management Responsibility • Quality Unit 	<ul style="list-style-type: none"> • Position Description • Performance Standards • Department Orientation • Training Program • Competence Assessment • Performance Appraisal • Continuing Education 	<ul style="list-style-type: none"> • Equipment Quality Standards • Equipment Specifications/Validation • Equipment Calibration • Equipment Preventative Maintenance 	<ul style="list-style-type: none"> • Reference Laboratories • Vendors • Reagent Receipt 	<ul style="list-style-type: none"> • Definition of Critical Control Points/Key Elements • SOPs for Critical Control Points/Key Elements • System Checks for Critical Control Points/Key Elements • Flow Charts • Change Control SOPs
Documentation/Record Keeping/Record Review	Label Control	Incident/Error Review	Internal Assessment	Process Improvement
<ul style="list-style-type: none"> • Revision of SOPs • SOP Index • SOP Archive • Record Review, Retention, and Storage 	<ul style="list-style-type: none"> • Label Control SOP • Label Storage/Destruction 	<ul style="list-style-type: none"> • Incident/Error SOP • Incident/Error Data Collection • Incident/Error Review • Corrective Action • Report to Quality Unit • Lookback 	<ul style="list-style-type: none"> • Audit SOP • Audit Schedule • Report to Quality Unit 	<ul style="list-style-type: none"> • Identification of Processes in Need of Improvement • Assessing Quality • Continuous Quality Improvement Policies and Processes

7.2.9 CBU Quality Assessment Program

The COBLT Study will use a Quality Assessment Program to monitor CBU processing activities at each CBB. The program will be initiated at each CBB following the start of CBU collections, and will continue until all collection and processing activities have been completed.

The quality of the processed CBU will be determined by comparing pre-freeze and post-thaw measurements on the following: viability, nucleated cell count, mononuclear cell count, CD34+ count, colony-forming units, and burst-forming units. This data will be submitted to the MCC using the CBU Processing QA Report which can be found in Chapter 8. Data on 10 CBUs will be required at the start of the collection and processing activities at each CBB. Following completion of this requirement, data on one CBU will be submitted to the MCC every three months.

7.3 **PROCESS IMPROVEMENT POLICY**

7.3.1 **Purpose**

To define a process by which opportunities for improvement detected by the Quality Plan are linked to selection and implementation of solutions in a continuous fashion.

7.3.2 **Scope**

Tasks are designed to move the program from identification of areas for improvement to realization of solutions.

7.3.3 **Policies**

7.3.3.1 On detection of error in a Corrective Action Report or through the activities of the Compliance Officer and the Quality Unit, the Responsible Coordinator shall collate all relevant data on patterns and influencing factors for presentation to the Quality Unit.

7.3.3.2 Based upon this report, the Quality Unit shall define potential solutions, obtain input from the Advisory Panel, select the most appropriate solution, and design a plan for its implementation.

7.3.3.3 The implementation shall be documented by changes in the relevant SOPs.

7.3.3.4 The Responsible Coordinator shall monitor the performance of the solution by personal observation and examination of data patterns and influencing factors as in Step 1.

7.3.3.5 The conclusions drawn from this monitoring shall be presented to the Quality Unit for consideration of the effectiveness of the solution.

- a. Where necessary, this process shall be repeated from Step 2 until satisfactory resolution is achieved.