

CHAPTER 2

PROTOCOL DESIGN

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2.1 ELIGIBILITY CRITERIA

Participants fulfilling the following criteria will be eligible for enrollment in the protocol:

1. Participant is diagnosed with a serious or life-threatening illness where umbilical cord blood transplantation is the only satisfactory treatment available.
2. Participant is not eligible for the Cord Blood Transplantation (COBLT) Study Transplant Protocol, but is eligible for treatment under another IRB-approved cord blood transplantation protocol.
3. Participant has an acceptably HLA matched COBLT CBU with a 3 of 6, 4 of 6, 5 of 6, or 6 of 6 match. The acceptable level of disparity is defined by the match criteria below:
 - a. At HLA-DRB1, a match is HLA DRB1 identity as determined by high resolution DNA typing.
 - b. At HLA-A and HLA-B, a match is HLA-A or HLA-B identity as determined by DNA typing at the “serologic level.”

If a single type is detected for a particular locus, the HLA type will be classified as homozygous. Homozygotes are treated as if the single type detected is present twice for that locus.

The “serologic level” equivalent for each allele designation is listed in the COBLT Study Manual of Procedures (MOP). This table is derived from the WHO definitions and is maintained by the COBLT Histocompatibility Subcommittee.

4. Participant provides informed consent for the cord blood transplant treatment protocol and for the COBLT Study Expanded Access Protocol.

Transplant Centers fulfilling the following criteria may enroll a participant in the Cord Blood Transplantation (COBLT) Study Expanded Access Protocol:

- Center has an IRB approval for the COBLT Study Transplant Protocol or IRB approval for an alternative cord blood transplant protocol.
- Center has an IRB approval for the COBLT Study Expanded Access Protocol.

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- Center agrees to submit documentation of IRB approval to the Medical Coordinating Center (MCC) for the treatment protocol and evidence that the subject has provided informed consent for treatment on the approved protocol prior to shipment of the COBLT CBU.
- Center agrees to send a blood sample from the subject to a COBLT HLA laboratory for confirmatory HLA typing.
- Center agrees to submit pre- and post-cord blood transplant data to the MCC using the schedule and forms described in this protocol.
- Prior to release of a COBLT CBU, due to the unique nature of the COBLT cryobag, center staff must demonstrate laboratory experience in receiving and thawing COBLT CBUs. Experience in thawing COBLT CBUs is demonstrated by providing data on 3 thawed CBUs with adequate viable nucleated cell recovery ($\geq 60\%$) and post-thaw cell viability ($\geq 75\%$). Details of these requirements are provided in Section 9.2, Thawing COBLT Cryopreserved Cord Blood Units for Transplantation, of the COBLT MOP. The MOP can be accessed on the Internet at <http://access.emmes.com/cobl>.

2.2 REGISTRATION PROCEDURES

To enter a patient on this protocol, the following procedure should be followed:

1. FAX the completed COBLT Study Eligibility Form to the Medical Coordinating Center (MCC) at (301) 251-1355.
2. The MCC will fax the Confirmation of Registration/CBU Release Request to the transplant center to confirm the registration and patient identification number.

If the COBLT Study Eligibility Form is received outside regular business hours (9:00 am - 5:00 pm Eastern Time, Monday - Friday), then the MCC will perform registration at the start of the next business day.

2.3 TREATMENT PLAN

The immediate pre-transplant evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study. Similarly, special orders and procedures will be those defined by the operations manuals of the Clinical Centers. All patients enrolled on this protocol will be hospitalized in accordance with isolation procedures for recipients of cord blood transplants as defined by the given institution.

The treatment plan will be carried out according to requirements of the IRB-approved cord blood transplantation protocol used to treat the subject. This plan will include the conditioning regimen, GVHD prophylaxis, GVHD treatment, use of growth factor(s), infection prophylaxis, blood product support, CNS prophylaxis and other supportive measures.

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2.3.1 Cord Blood Infusion

Procedures detailed in the COBLT Study MOP should be followed for requesting, receiving and characterizing the cord blood for infusion. Contingency plans for cord blood units which can not be infused will be made according to institutional policies. These plans may consist of autologous marrow back-up, obtaining marrow from a haploidentical relative, supportive care, or acquisition of another compatible cord blood unit, following local institutional practices.

The cord blood should be thawed and washed as described in the Investigators Brochure contained in the COBLT Study MOP. Infusion should begin within 1 hour of washing. The infusion should take no longer than 30 minutes. Pre-medications (if any) prior to cord blood infusion will be at the discretion of the center.

Under no circumstances is the cord blood to be irradiated. No in-line leukocyte filter should be used and no medications or fluids should be given piggyback through the catheter lumen that is being used for cord blood infusion. Vital signs should be monitored before beginning the infusion and periodically during administration.

Benadryl, epinephrine, and hydrocortisone should be available at the bedside for emergency use if necessary. Oxygen with nasal prongs for standby use should be present in the room.

2.4 STUDY MONITORING

Transplant Centers must complete the reporting requirements of the COBLT Expanded Access Protocol.

2.4.1 Required Reporting

Data on the thawing and infusion of the COBLT CBU will be provided to the COBLT MCC. A detailed description of the forms and the procedures required for forms completion and submission can be found in the COBLT MOP, Chapter 10.

The FDA requires that all unexpected fatal or life-threatening adverse experiences be reported 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. Transplant centers must report adverse experiences to the MCC with an Adverse Experience Form according to the above guidelines and the COBLT Study MOP.

A medical monitor associated with the MCC will review all adverse experience reports and assist the MCC in reporting these events to the FDA. Expected adverse experiences (i.e., those listed in the informed consent, product inserts, or study materials) not covered under the above requirements but which are reported elsewhere need not be reported using an Adverse Experience Form. Although death and graft failure are not considered unexpected experiences, they will be reported to the FDA via annual reports submitted according to FDA guidelines (21 CFR 312.33). The Data and Safety

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Monitoring Board will receive summary reports of all adverse experiences on at least an annual basis.

2.4.2 Follow-up Schedule

The scheduled study visits are outlined in Table 2.4.1 and required forms in Table 2.4.2. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the COBLT Study MOP, Chapter 10. The timing of follow-up visits is based on the date of cord blood infusion.

2.4.3 Criteria for Forms Submission

Criteria for timeliness of forms submission for all study forms are detailed in Chapter 10 of the COBLT Study MOP.

**Table 2.4.1
FOLLOW-UP SCHEDULE**

Study Visit	Target Day (Days Post-UCBT)
100 days	100 day
182 days	6 month
365 days	12 month
730 days	24 month
1,095 days	36 month

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**Table 2.4.2
FORMS SUBMISSION SCHEDULE**

FORM	Prior to Transplant	Days Post-Transplant			Months Post-Transplant			
		1-28	29-42	100	6	12	24	36
Eligibility	X							
CBU Thawing and Infusion Forms		X						
NMDP 120: Baseline		X						
IBMTR Cord Blood Transplant Insert		X						
Toxicity		X	X					
NMDP 130: 100-Day Visit				X				
NMDP 140: Follow-Up Visit					X	X	X	X
Re-Admission		Submit for each hospitalization after the initial discharge						
Adverse Experience		Submit for each unexpected serious adverse experience						
NMDP 190: Death		Submit at time of death						

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2.5 STATISTICAL CONSIDERATIONS

2.5.1 Accrual Objectives

It is anticipated that approximately 60 patients will be enrolled in the Expanded Access Protocol. These participants will be analyzed for 180-day survival, engraftment, GVHD, and survival.

2.5.2 Primary Analysis

The primary analysis will consist of estimating the Day 180 survival probability based on the Kaplan-Meier product limit estimator. The analysis will include the confidence interval for this probability. Similar calculations will be made for the secondary endpoints, e.g. neutrophil engraftment, red cell engraftment, platelet engraftment, survival, and acute GVHD.

Factors influencing time to event endpoints such as time to death or time to engraftment will be evaluated using Cox regression. Factors influencing binary endpoints such as engraftment will be evaluated using logistic regression. Factors to be evaluated include cell dose, degree of mismatch, age of recipient, race of donor and recipient, disease of recipient, and graft characteristics (e.g. number of T cells)

Methods for repeated measures data analysis, such as random effects models and GEE, will be used to describe the “natural history” of repeated cell counts, e.g. neutrophil counts, following transplantation.

Separate analyses may be performed by gender for each of these endpoints.

2.5.3 Secondary Analysis

A secondary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 28 days.

A secondary analysis will be performed on patients who fail to engraft. Incidence rates of both acute and chronic GVHD will be estimated using Kaplan-Meier product limit curves. Multivariate models will be employed to adjust for covariates.

The interaction of cell dose and degree of HLA mismatch on transplant outcomes will be examined using appropriate statistical models.

The secondary endpoint of infectious complications will be analyzed with respect to the number, the severity, and the subsequent complications of infectious episodes while controlling for important prognostic factors as previously described. Rates of other complications such as veno-occlusive disease and interstitial pneumonitis will be examined. Type and severity of adverse events will also be analyzed, including incidence of other malignancies, lymphoproliferative disorders, and post-transplant myelodysplasia.