IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 0903

1. Why conduct an allogeneic transplant trial in HIV-infected patients with acute leukemia in remission, lymphoma and myelodysplastic syndromes (MDS)?

The advent and wide-spread availability of highly-active anti-retroviral therapy (HAART) has dramatically changed the life expectancy and disease evolution of patients with HIV/AIDS. It has also permitted HIV-infected patients with hematological malignancies and MDS to receive aggressive therapeutic regimens that previously would not have been feasible. Trials at the City of Hope and in the AIDS Malignancy Consortium indicate that autologous hematopoietic cell transplantation (HCT) is feasible and safe in this patient population. There is also, a small body of literature that demonstrates the potential for the use of allogeneic stem cell transplantation in this patient population. Despite these encouraging data, HIV-infection is still considered an exclusion criterion for most allogeneic protocols and care plans. The goal of this trial is to demonstrate the feasibility and safety of allogeneic stem cell transplantation in HIV-infected patients with acute leukemia in remission, therapy-responsive lymphoma and MDS. The best means to achieve this goal is through the completion of a trial within the BMT CTN and performing transplants for this patient population in through a multi-center trial.

2. Why choose 100-day non-relapse mortality as the primary end-point?

One hundred-day non-relapse mortality was chosen as the primary end-point for this trial because the principle goal of this trial is to determine the safety of allogeneic HCT for patients with chemotherapy-sensitive hematological malignancies or MDS and coincident HIV-infection. One-hundred-day non-relapse mortality provides an objective end-point for comparing outcomes between HIV-infected patients undergoing allogeneic HCT transplantation vs. non-HIV-infected patients. One-hundred-day non-relapse mortality is a frequently-reported indicator for judging the risk of allogeneic HCT.

3. What is the importance of the secondary endpoints of the trial?

In addition to assessing the risk of 100-day non-relapse mortality, this trial will evaluate a number of endpoints related to allogeneic HCT including engraftment times, donor chimerism assays, hematological function and the incidence of acute and chronic graft-versus-host disease. More importantly, however, the trial will provide a key opportunity for analyzing a number of HIV-specific end-points. These include studies evaluating immunological reconstitution, risk of secondary infection and assessing the impact of transplant upon HIV viral load and viral reservoir. This trial will, for the first time, analyze those HIV-infected transplant patients with undetectable viral loads with the single copy assays in order to ascertain the extent of viral suppression post-allogeneic HCT.

4. What are selection criteria for related and unrelated donors? What is the role of donors who are homozygotes for the delta 32 mutation for CCR5?

For those patients who lack an appropriate HLA-compatible sibling donor, an unrelated donor will be identified through the NMDP. The donor must have no more than a single antigenic or allelic mismatch at HLA- A, -B, -C or –DRB1. Where feasible, we will attempt to identify a well-matched donor who is found to be a homozygote for the CCR5delta32 mutation. Homozygosity for this mutation may retard or prevent re-infection by HIV. Amongst donors of equivalent match quality, preference will be made for the donor who is a delta32 homozygote. HLA match quality will always, however, take precedence over a less suitably-matched donor who is a homozygote for the delta32 mutation.

5. Why was the age range of 15-70 chosen?

The lower age limit was chosen after considerable discussion with pediatric transplanters. It was agreed that the extreme rarity of AIDS-related acute leukemia, lymphoma or MDS in younger children would make it difficult, or impossible, to accrue any significant numbers of patients in this age group for the trial. The upper age range was chosen based upon the likely, physiologic limitations to transplantation in patients above this age range.

6. Is our accrual goal feasible?

Yes. We are projecting a modest accrual goal that appears feasible based on a survey of BMT CTN transplant centers based on current referral patterns. We will also be advertising this trial to HIV advocacy groups and research networks.

7. Is there a need for a multi-center network to meet the objectives?

Yes. One of the key goals of this trial is to demonstrate the safety and feasibility of this treatment modality. We believe that this can be accomplished only by performing the study in a multi-center network.

8. Accrual estimates – See separate summary of Accrual Estimates.

9. What are the recruitment strategies if applicable, and proposed plans for monitoring study accrual?

Core Clinical Centers and non-Core Centers will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies. Patient information and educational materials explaining this study will be prepared by the NMDP Office of Patient Advocacy and made available to centers in paper form and on the Web. As noted above, we will conduct an active outreach effort to publicize this study through existing AIDS research networks and advocacy groups.

Monthly accrual reports will be provided to the NIH. Additionally, recruitment reports based on the CIBMTR database will be provided every six months. The screening reports will summarize reasons for non-enrollment and reasons for ineligibility.

10. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted encrypted using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference and training of clinical research associates (CRAs).

Data collected on CIBMTR Initial and Follow-up Report Forms will be transferred electronically from the CIBMTR to EMMES on a regular basis. Any data relevant to real-time monitoring of safety or efficacy endpoints will be collected on BMT CTN supplemental forms, e.g. deaths.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in each protocol.

11. What is the monitoring and overall coordination of protocol management (e.g. brief summary of plans to run the study – initiation, coordination, data collection, and monitoring)?

A protocol coordinator is assigned to each BMT CTN protocol. The protocol coordinator is responsible for the daily operational needs of the study and of the participating transplant centers. The protocol coordinator oversees enrollment and data collection issues and is in regular communication with CRAs at participating transplant centers. The protocol coordinator also works closely with the protocol officer with respect to adverse event reporting and to medically-related protocol questions.

A form submission schedule is developed for each BMT CTN protocol and is included in these materials. A visit schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all expected visits and list of forms and/or samples required at each visit.

Initiation site visits will be conducted for all participating centers. These visits will either be in-person visits to the centers or be held via conference call with all transplant center personnel involved with this protocol.

DCC staff, including at minimum the protocol coordinator, will conduct periodic monitoring visits to the participating clinical centers and laboratories. The primary purpose of these visits is to conduct data audits. Other activities include those required to enhance data quality, ensure study integrity, satisfy regulatory requirements, and evaluate site performance. Site visits will

occur at variable frequency throughout the course of the studies, depending primarily upon the stage of the study, site performance, and sponsoring agency requirements.

There is an interm statistical monitoring plan for safety. If there are 4 or more non-relapse deaths observed within 100 days of transplant the study will stop because it will no longer be possible to reject the null hypothesis of 45% or worse non-relapse mortality at 100 days. The protocol statistician or other DCC statistical staff will ensure that programs are in place to conduct the interim monitoring in accordance with the statistical analysis plans in each protocol. Unexpected serious adverse experiences will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences. Expected transplant-related toxicities will be collected on each patient using the calendar-driven reporting system that has been previously reviewed and approved by the DSMB.

12. Are there any specific study training plans necessary to accomplish the research goals (e.g. workshops, study certification)?

CRAs will be certified for data submission by the DCC after participating in an in person meeting or in a training session conference call with the protocol coordinator. No other certifications or workshops will be required for this study.