**BMT CTN PROTOCOL #1202**

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic HCT

# FREQUENTLY ASKED QUESTIONS

## 1. Why create a multi-center repository of pre- and post-HCT research samples?

Serious complications following HCT, such as include graft-versus-host disease (GVHD), cancer recurrence, organ toxicity and opportunistic infection are major contributors to morbidity and mortality. Although some clinical variables (e.g., recipient age, donor-recipient human leukocyte antigen [HLA] mismatch) predict higher risk of some events (e.g., GVHD, infection), no diagnostic tests exist that reliably predict occurrence, severity or response to therapy of any of these complications. Recent compelling results from single center studies suggest that biomarkers can be identified that stratify patients into discrete risk groups for some outcomes and for overall mortality. However, these relatively small studies generally lack the statistical power or validation necessary to allow their results to be incorporated into practice. One key factor in the success of biomarker studies is the quality of clinical outcomes data that is linked to the specimens being analyzed. An adequate resource for these studies requires longitudinal sample collection integrated with longitudinal collection of comprehensive, standardized, high quality clinical data regarding complications, from onset to resolution, and regarding other clinical variables affecting risk of post-HCT outcomes.

The repository proposed in this study will address the important problem that no multicenter biospecimen collections exist that contain appropriate types and/or numbers of specimens, together with detailed, rigorously reviewed clinical data collected from adequate numbers of patients, for biomarker studies. This multi-center initiative will uniformly collect and store high quality biological specimens and high quality clinical data from a large, prospective cohort of patients and their donors. This repository will facilitate studies that will establish the utility of specific biomarkers for risk assessment, diagnosis and monitoring to allow more rational treatment strategies. These studies are also likely to provide mechanistic insights and to identify new therapeutic targets leading to development of more targeted and effective therapies.

## 2. Why limit sample collection to the first 100 days post-HCT?

Other than chronic GVHD and relapse, the majority of serious HCT complications develop within the first 100 days, even if their outcome does not become apparent until later. Therefore, the most informative research samples to predict the development of these complications and their response to treatment will be in the first 100 days.

This protocol collects a final sample around day 90-100. These samples will be available for the study of later occurring complications such as chronic GVHD.

**3. The study population will be heterogeneous. Why are the eligibility criteria not more restrictive?**

The goal of this protocol is to develop a repository that is highly reflective of the HCT recipient population. This approach will allow for maximal generalizability of the results of future studies using the repository and clinical data. Given the size of the repository, there will be sufficient samples from common populations to allow focused questions within subsets, when desired.

**4. Is our accrual goal feasible?**

Yes. Existing research repository studies, such as the NMDP research sample protocol, have very high rates of patient participation. Given the few restrictions on participation, accrual of 375 patients per year from the BMT CTN core centers and affiliates is very feasible. For comparison, 21 centers accrued 711 patients onto BMT CTN 0902 (a protocol with similar effort required on the part of the participating centers) in an 18 month period, or over 400 per year.

**5. How does this protocol take advantage of existing data and research sample collection efforts?**

This protocol utilizes the existing resources to the fullest extent possible. Centers will submit CIBMTR Comprehensive Report Forms for patients participating in this study and the data from these forms will be used to assess liver, kidney, and lung toxicity, as well as relapse/progression and transplant related death.

This protocol also leverages the existing NMDP research repository. Samples for future genomic research from donors and recipients are collected via this mechanism as are donor samples for future proteomic research.

**6. What is the volume of research blood samples on this study? Is it safe for children to participate?**

As noted above, recipients will have blood drawn for genomic research prior to admission (17 ml). An additional 80 mls of blood over a 3 month period will be drawn from all recipients for proteomic research. Thus, the repository will bank almost 100 ml of blood over a 3 month period. Good clinical research practice guidelines [http://www.med.umich.edu/irbmed/guidance/blood_draw.htm] indicate that a healthy person weighing at least 16 kg can provide this volume of blood for research purposes and this restriction has been routinely applied to hematology/oncology/BMT patients, who while not healthy, are closely monitored and treated for anemia as part of the care for their underlying condition.

Patients who are selected to provide research samples for gene expression will provide an additional 40 ml of blood over the same 3 month period for a total of 140 ml. This volume of blood can be safely removed from subjects who weigh at least 21 kg.

In order to provide an additional cushion of safety, patients must weigh at least 20 kg, which means that most children in the 5-6 year age range will be able to participate. However, to

provide the additional 40 ml of blood for gene expression, patients must weigh at least 30 kg, which does not typically occur until age 9-10 years old. Subjects who weigh less than 30 kg will not be asked to provide gene expression research samples.

As with all clinical research, the total research blood volume from all studies should be considered before co-enrolling subjects on more than one study.

**7. Why are donor samples not required in order to enroll recipients?**

It would be impractical to determine the availability and willingness of donors to provide the pre-donation sample before enrolling recipients onto this protocol. In order to maximize the number of donor samples registered into the repository, we only allow recipients to enroll if their donor (or cord blood) comes from a center participating in the NMDP research repository study. Our experience is that over 90% of donors from these centers provide samples to the repository. Related donors will be enrolled from the participating centers will be asked to provide research samples. Our experience is that the refusal rate from related donors is very low.

**8. Will research samples be obtained after patients relapse or experience graft failure?**

Research samples will not continue to be collected from recipients if they relapse or experience graft failure before day 100. Fortunately, these events are uncommon in the first 100 days after HCT. We anticipate fewer than 10% of patients will relapse or experience graft failure during the sample collection period. If more than 10% of the patients do experience one of these events in the first 100 days, replacement subjects will be recruited.

**9. How will the accuracy of the clinical data be assured?**

One of the key aspects to this protocol has been the development of a detailed Data Management Handbook which will assure uniformity of data collection across the multiple participating sites. In addition, a data adjudication committee will meet in real-time to adjudicate difficult or complex data soon after submission, when the issues are still fresh. This process of real-time data adjudication will resolve grey areas as they become apparent. Communication of how to resolve controversial issues to all participating centers will enhance the reliability of the data across the entire multi-site cohort.

Furthermore, this protocol collects raw data over interpreted data, whenever possible. For example, volume of diarrhea, rather than GI GVHD staging, will permit comparisons of proposed revised staging systems to existing ones using the already collected data.

**10. Patients often develop serious infections late after HCT, such as during chronic GVHD treatment. Why limit serious infections data collection to the first 100 days?**

Infection data collection is highly time consuming and requires detailed adjudication for quality assurance. Given the resources available to this protocol, for practical reasons, it was decided to limit the data collection for infections to the specified time frame.

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

Core Clinical Centers and Affiliate Centers will participate. Transplant centers will follow their local institutional practices for recruiting patients on research studies..

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.

**12. 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).

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.

**13. What is the monitoring and overall coordination of protocol management (eg. 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 the protocol. A follow up schedule will be provided to the transplant centers for every enrolled patient. This schedule will detail the dates of all follow-up time points and list of forms required at these time points.

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 a 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.

Unexpected serious adverse experiences will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences.

**14. Are there any specific study training plans necessary to accomplish the research goals (eg. workshops, study certification)?**

There is no specific training plan in this study.