FAQs for BMT CTN PROTOCOL 1704

Composite Health Assessment Model for Older Adults: Applying Pre-transplant Comorbidity, Geriatric Assessment, and Biomarkers to Predict Non-Relapse Mortality after Allogeneic Transplantation
(CHARM)

1. What is the rationale for developing a health assessment instrument for older adults undergoing allogeneic hematopoietic stem cell transplantation (HCT)?

We currently offer allogeneic HCT to more than 1000 older (defined here as those aged ≥60 years old) adults a year in the US and expect increasing use in the future given the aging of our population and increased frequency of most blood cancers among older patients. Although HCT is feasible in older adults, non-relapse mortality (NRM) rates are 20-25% and survival rates are ~60% at 1-year with little change in the past decade. It has become increasingly important to refine our tools for risk assessment to ensure 1) appropriate patient selection for the procedure and 2) pave the way to novel interventions targeting patient-specific poor overall health. Additionally, being able to accurately identify patients with low risks of NRM may increase the use of HCT in older adults who could benefit from the procedure, many of whom are still not being referred to HCT centers on the basis of their age alone.

This prospective observational study entails development and validation of a comprehensive composite health risk assessment model specific to older HCT recipients. The results will set the stage for risk-adapted studies based on the composite health assessment. This may include both more intensive therapies for older patients at low risk for NRM and, conversely, lower intensity approaches for those with intermediate to high-risk scores or perhaps other non-HCT cellular or other therapy. By facilitating better application of HCT, the risk model should improve HCT outcomes and the overall outcomes of this patient population whether HCT is pursued or not. Finally, we believe the validated study instruments will become the standard for pre-transplant assessment of older adults in BMT CTN and other clinical trials.

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

The 2014 BMT CTN State of the Science Symposia, which made recommendations on the highest priority studies to be considered by the BMT CTN and other networks, identified the present study as one of the highest priority key studies needed to address a critical unmet need.

A large, complex observational study such as the current proposal is best accomplished through a multi-center network like the BMT CTN to ensure generalizability of the model and adequate patient enrollment for rapid study completion. Other mechanisms for study design were considered. Embedding the health assessment tools in a single or even multiple interventional studies would not enroll an adequate number of subjects and would likely exclude patients representing the least fit population although such non-

robust patients are of highest interest for this study. However, co-enrollment with other studies is allowed. Embedding this study in a parent trial would also not include the broad array of HCT indications and HCT approaches used in the US. Adding tools to standard transplant center reporting through the CIBMTR would not be feasible because of the need for more granular outcomes data (e.g., cognitive or functional assessment). We are incorporating CIBMTR data in this study to increase efficiency and lower costs.

3. Why select NRM as the primary endpoint?

For older adults (and their physicians), the uncertainty and fear of mortality and life-threatening complications is the major factor limiting uptake of allogeneic HCT. Major advancements have clarified the risks of relapse after HCT and after conventional therapy (e.g. cytogenetic and molecular data, minimal residual disease, etc.). Similar efforts are needed to better understand risks of NRM, particularly among older patients who are more likely to suffer from NRM, possibly related to less resilience. We want here to provide clinicians and investigators with a novel and comprehensive tool to predict NRM that could be used alongside tools to predict relapse to make the best estimates for survival. However, although NRM represents the most widely used objective measure of life-limiting HCT related toxicity, we also plan to examine the ability of the CHARM to predict a broad range of endpoints including patient-centered outcomes, such as organ-specific toxicity, cognitive decline, development of frailty, graft-versus-host disease (GVHD), overall survival, disease-free survival and others.

4. Is this study feasible?

We have strong evidence that support study feasibility. First, we propose enrolling 880 HCT recipients over 24 months. By comparison, a previous similarly inclusive and minimally burdensome protocol, BMT CTN 0902, accrued 711 subjects over 18 months.

Based on CIBMTR data, the annual number of patients aged 60+ undergoing allogeneic HCT for hematologic malignancy was about ~900 over the period 2012-2016. With the consistent annual increase in number of older subjects undergoing allogeneic HCT (see Figure in the protocol), we anticipate that the actual annual number will be closer to 1000 subjects per year during the duration of this study. We expect the study to be open at all BMT CTN Core and many Affiliate Centers thus being available for ~90% of the 1000 subjects, for a total of 900 potential subjects annually. We require 880 patients receiving allogeneic HCT. Assuming 440 subjects enroll and undergo HCT per year, the study will require 24 months to recruit the target sample size of n=880 subjects or slightly less than 50% of eligible patients

More specifically, we estimate around 550 subjects per year will be consented and enrolled. Since enrollment occurs up to 21 days before HCT, we assume a conservative estimate of a 20% drop out rate, such that 440 per year would proceed to transplant and contribute to final model development.

5. How did you estimate the sample size?

Sample size calculation is based on the ratio of the number of NRM events divided by the number of potential predictors. This ratio is known as events per variable (EPV). An EPV in the range of 10-15 is widely advocated as a rule of thumb for Cox proportional hazards regression models, with higher EPV

recommended when there are predictors with low prevalence. Since we expect intermediate prevalence of our proposed predictors of 15-50%, we will use an EPV of 12. The NRM rate in our subject population is estimated at about 22% based on CIBMTR data. Per the equation: (N x 22%)/16 variables= 12 EPV, we will need a sample size around 880 subjects. Given a sample size of 880 patients, we will have 80% power to detect hazard ratios ranging from 1.63 (assuming the prevalence of the predictor in our cohort is ~40%) to 1.96 (assuming the prevalence of the predictor in our cohort is ~15%) using a two-sided test with a significance level of 0.05.

6. How much time does it take to complete study assessments?

The pre-transplant assessment will include a 30 minute assessment by the healthcare team, which includes a walk speed test, grip strength assessment, memory test (Montreal Orientation Memory Concentration (MoCA)) and blood work. Additionally, patients will complete a 13-20 minute self-report questionnaire. The questionnaire times vary based on method of delivery because computerized adaptive testing, used for participants who complete the survey online, has variable numbers of survey items given and time burden. The Day 100, Day 180, and Day 365 visits will include 10 minute assessments by the healthcare team to repeat the walk speed and grip strength tests. Self-report questionnaires will each take approximately 7-10 minutes at Day 100, and 11-17 minutes at both Day 180 and Day 365.

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

Standardized administration of these tools across sites will reduce measurement error and improve generalizability of results. Therefore, site staff administering these tests will be required to attend mandatory online training and will be required to pass the certification exam provided at the end of the online training. Video training will also be made available to view. Each site should have a "super-user" who can also train other staff to perform the testing.

8. Are you worried about patients who are enrolled but do not proceed to HCT as a potential source of selection bias?

The ultimate goal of the current study is to develop a HCT specific instrument that can optimally risk stratify older patients that *undergo allogeneic HCT*. However, we plan to capture reasons for not proceeding to HCT among the expected ~20% that get enrolled but then do not proceed to HCT. We expect that in a large proportion of them, the reason not to proceed will be disease progression prior to HCT. Finally, we also plan to compare their baseline demographics with the demographics of patients who do proceed to HCT to identify any major differences in their characteristics.

9. Why do you require 21 days for baseline assessments prior to proceeding with HCT?

While testing closer to conditioning may reduce the potential for changes in health and the proportion of subjects not proceeding to transplant, our experience shows that narrow windows for pretransplant testing are a major barrier to enrollment to BMT CTN trials. We created a 21 window to allow centers adequate time to coordinate testing and surveys prior to conditioning. Testing done outside of this window due to delays in transplant conditioning will need to be repeated. The benefit of measures accurately reflecting subject health outweighs the risks of learning effects of repeated measures.

10. Will patients 70+ be reasonably represented?

Per CIBMTR, the annual number of patients aged 70+ undergoing allogeneic HCT in Core + Affiliate centers is 170 patients and, if we assume conservatively that 60% will be enrolled and the drop-out rate is 20%, over 24 months we can enroll up to 160 patients, which would represent ~20% of the entire study cohort and should be reasonable representation of that age range.

11. Why restrict the study to hematologic malignancies and not consider benign disorders, such as aplastic anemia?

The frequency of allogeneic HCT for benign hematologic disorders among older adults is quite low, as shown by recent examination of CIBMTR data from all Core and Affiliate centers, which revealed that only 79 patients older than age 60 received a transplant for aplastic anemia from 2012-2016. Only 3 were 70 years and older. Additionally, the pre-HCT therapies and the natural history of these disorders are quite different from those undergoing HCT for hematologic malignancies and the small numbers will preclude adjusting for that heterogeneity.

12. Besides CRP and albumin, are you planning any other correlative/biomarkers studies?

The study will not collect additional correlative laboratory samples. However, the unique clinical data collected in this study forms a rich dataset for future exploration of correlative samples. Therefore, we will encourage the study team to offer the CIBMTR "Protocol for a Research Sample Repository for Allogeneic Hematopoietic Stem Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries."

13. Will primary data be collected on CIBMTR Forms?

Yes. All subjects enrolled on the study will be assigned to the Comprehensive Report Form (CRF) track. Additional study specific data will be collected through the Medidata Rave EDC and ePRO as described under FAQ #17.

14. Will the results of the baseline testing be shared with the clinical team?

Protocol submitted data will not be returned to the treating center. However, subjects and the team will not be blinded and may use information available. We recommend each institution follow their standard of care for such data.

15. Will the treating physician be notified of abnormal results found through the study tools?

No, we do require alerting the treating physician based on any survey result or test. Patients must be eligible for transplant based on institutional standards to enroll and will be aware of all routine testing including calculation of the HCT-CI score (which includes history of depression or anxiety) as this

information is required to be reported. No tool or survey in this study is diagnostic for a disease. We lack data on the independent prognostic value in this population, which forms the basis for this study.

However, for the subject surveys, we will include language at the footer of each survey page indicating these results will not be returned to the treating team and the patient should notify the treating team should they have any health concerns. The bedside testing will be performed at the center and can be utilized as per institutional standard of care. Nevertheless, to offer guidance, the protocol includes thresholds associated with heightened risks for the Montreal Cognitive Assessment (MoCA) based on other populations. Specifically, we suggested a MoCA < 23/30 may reflect mild cognitive impairment and a score < 18/30 may be associated with dementia.

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

The study will be widely publicized to participating BMT CTN and US CIBMTR centers. Subject enrollment and accrual among older adults will be monitored at each participating site. Through CIBMTR we will be able to capture data on patients older than age 60 undergoing allogeneic HCT for a hematologic malignancy that were not enrolled onto the protocol at the participating institutions after the protocol was activated at the sites. The goals are to accrue a high proportion of eligible subjects at each participating center, to meet overall accrual goals and to have a diverse representative population. Centers not enrolling a high proportion of eligible subjects will be contacted to determine whether there are barriers in approaching subjects.

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

Transplant outcomes data as well as some endpoint data (performance score, survival, relapse, NRM, GVHD, organ toxicities) will be collected on CIBMTR forms via the CIBMTR web-based platform FormsNet3. Additional study specific data (Eligibility, enrollment, MoCA, Frailty Phenotype) will be collected through a customized Medidata Rave database. Both FormsNet3 (CIBMTR's proprietary database) and Medidata Rave are 21 CFR Part 11 compliant, globally available application for collecting outcomes data electronically. Both are secure Web-based applications that are available wherever Web browser functionality is supported. Both platforms also support data collection, auditing, and event reporting; web services; and messaging. They offer real-time data validations; error messaging; and control of data entry flow, which includes enabling/disabling of questions and "smart navigation" between fields on a form. Queries will be developed in Oracle Business Intelligence Enterprise Edition (OBIEE) to check for missing and inconsistent data in both Medidata Rave and FormsNet3.

Patient reported data will be collected using Qualtrics online surveys, a component of the CIBMTR electronic Patient Reported Outcomes (ePRO) system. Qualtrics uses Transport Layer Security (TLS) encryption for all transmitted Internet data. TLS is a newer version of SSL. The CIBMTR Survey Research Group will track patient compliance with ePRO assessments, and provide completion/missing ePRO reports to the study chairs and coordinator at least monthly, and to centers on demand.

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.

18. 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.

Initiation site visits will be conducted for all participating centers. These visits will be held via conference call with all transplant center personnel involved with this protocol. Additional training and certification will be required for the Montreal Cognitive Assessment (MoCA) prior to center activation on the study.

Transplant outcome data will be collected on standard CIBMTR forms. Whether or not a patient participates in BMT CTN 1704, centers must register pre- and post-transplant clinical data on all consecutive HCTs done at their institution through the CIBMTR, which holds the contract for the US Stem Cell Therapeutic Outcomes Database charged with collecting data on US allogeneic HCTs.

Formulas for patient reported outcomes schedules will be built into the CIBMTR ePRO system. The CIBMTR Survey Research Group will use the ePRO system to track when PRO time points are due as patients enroll.

DCC staff including, at a minimum, the study monitor will conduct periodic monitoring visits to the participating clinical centers. Site monitoring visits will occur at variable frequency throughout the course of the study depending primarily upon the stage of the study, site performance, and data and process integrity.

Only adverse events related to the study consent process, study specific assessments (MoCA, Frailty Phenotype), or completing QOL surveys will be reported via study-specific supplemental forms in Medidata Rave and will be reported according to BMT CTN guidelines. A medical monitor will review all unexpected adverse events.

There is not an interim statistical monitoring plan for study primary or secondary endpoints.