



FAQs for BMT CTN PROTOCOL 1702

Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D)

1. Why is the study designed this way?

The primary goal of this study is to determine whether it is better to receive a transplant from a matched unrelated donor or an alternative donor such as haploidentical, cord blood or mismatched unrelated donor. Based on 2016 CIBMTR data, approximately 70% of alternative donors are haploidentical donors with 15% cord blood and 15% mismatched unrelated donors. There are several issues determining which is the right approach: (a) the likelihood of finding a matched unrelated donor; (b) the time it takes to either find that donor or decide that it is better to pursue a different alternative donor; (c) the patient's disease and disease status, if a delay in donor identification leads to either relapse/progression of the disease or co-morbidity from ongoing chemotherapy; and (d) whether donor type affects the success of transplant.

We will use each patient's likelihood of finding a matched unrelated donor as a **biologic assignment strategy** to prioritize a matched unrelated donor or a different alternate donor, anticipating that of the alternate donor cohort, more than 70% will receive haploidentical donors with the balance using mismatched unrelated donors or cord blood. Because the likelihood of finding a matched unrelated donor is unrelated to disease stage, we are eliminating a major potential bias where centers go immediately to haploidentical donors or cords for patients who are deemed to need a transplant quickly.

An **intent-to-treat** design to perform the analysis based on the donor search prognosis and not the donor actually used was chosen because it will best answer the primary question and allow us to understand the contribution of the above factors. By starting the clock early, before the decision is made that a suitable matched family member is not available, we will be able to track how the search progresses, and how key clinical data affect management decisions. We will collect survival for all patients, whether or not they undergo transplant. This information will tell us how many patients do not make it to transplant and whether pursuing more readily available donor types can improve the transplantation rate. This is a major gap in information about the barriers to successful transplantation.

We considered other study designs. A randomized trial would require a large sample size and was determined not to be feasible. An observation study that did not provide any guidance about donor search algorithm would also need a very large sample size and was deemed too biased to answer the primary research question.

2. Why are only patients who are Very Likely or Very Unlikely to find a matched unrelated donor part of the primary analysis?

Patients in the “less likely” group have a 26% chance of finding a matched unrelated donor and are excluded from the primary analysis because it is currently unclear which donor search strategy to pursue: matched unrelated donor or other alternative donor. The study team discussed randomizing this group but opted not to pursue this because of the difficulties of randomized trials and lack of certainty that centers would follow the protocol guidelines. Observing this cohort will provide important insights into the decisions transplant centers make in the real world regarding prioritization of donors.

3. Why are so many patients who are “Less Likely” to find a matched unrelated donor enrolled?

Because the likelihood of finding a matched unrelated donor may not be known at the time patients are enrolled, it is easiest to enroll all patients. In addition, this will allow us to monitor current practices and find the best approach for these patients. 200 patients who are Less Likely to find a matched unrelated donor will be funded by BMT CTN. The National Marrow Donor Program is funding data collection on the remainder of the Less Likely patients.

4. Is there guidance for what constitutes a “suitable HLA-matched family donor?”

We will let centers decide who they consider “suitable” as a matched family donor. Reasons for an HLA-matched and 1 allele or antigen mismatched family member not being considered a suitable donor include: failure of medical clearance, donor refusal, donor age, presence of 1 allele or antigen mismatch, and patient or center preference.

5. Have you looked at the CIBMTR data of the Very Unlikely to find a matched unrelated donor group to see how long, on average, it takes for that group to get to transplant?

We weren’t able to get that data because of data and database limitations in matching searches to transplant outcomes. We know that haploidentical donor recipients are more likely to be in the Very Unlikely group but we do not know how many patients did not make it to transplant because of delays in finding a donor. Once patients get to transplant, most studies suggest similar outcomes regardless of donor type. We have added additional information into the protocol showing comparable outcomes of matched unrelated and haploidentical donor transplantation. We have also added a table that shows the dismal chances of having a matched unrelated donor transplant for patients in the Very Unlikely group, regardless of whether they are racial/ethnic minorities or Caucasians.

6. What about centers whose current practice doesn't include a matched URD search?

In the last survey of transplant centers about 86% of respondents said they'd be willing to participate in the biologic assignment study design. Also, not all patients at a site need to enroll. Sites can choose to only enroll those patients that the study fits or that they can accommodate based on their current practices and research infrastructure. However, a few centers whose current practice is to proceed directly to haploidentical transplants and who are unwilling to alter that practice for this study have elected not to participate.

7. Would we talk to patients about this study only when it's determined no matched family member is available?

It is up to the center and their current practice when they approach patients. It is preferable to enroll and register patients once they are deemed transplant candidates, as early as when HLA typing is sent or the initial consultation, since this minimizes bias; however, if that is not possible, they can be enrolled up until or at the time no HLA matched related donor is identified. However, they are not considered evaluable until the centers declares that a suitable matched family member does not exist and other donor types are being pursued.

8. Will primary data be collected on CIBMTR Forms?

Yes. Patients enrolled on the main study will be assigned to Transplant Essential Data (TED)/Comprehensive Report Form (CRF) tracks per the standard CIBMTR algorithm. Both TED and CRF forms will capture the planned endpoints. Patients eligible for the QOL Substudy (about 16% of the total enrolled pre-transplant, or 32% of those transplanted) will be automatically assigned to the CRF track and also have patient-reported outcomes collected on separate forms.

9. Did you adjust for the possibility that the Very Unlikely group is due to race/ethnicity factors?

Yes, the plan is to stratify/statistically adjust for those factors since racial and ethnic minorities are more likely to be in the Very Unlikely group. Some studies show that minority status is associated with worse transplant outcomes. Hypotheses include fewer and less well matched available donors, lack of insurance, inadequate caregiver support, etc. that may also adversely affect outcomes. The study team acknowledges that statistical adjustment may not fully address this confounding. However, the fact that most of the patients in the Very Unlikely group and in this study are anticipated to be White somewhat mitigates this concern.

10. When would analyses of the primary and key secondary endpoints commence?

Analysis of overall survival according to likelihood of finding a matched unrelated donor will begin once the last enrolled evaluable patient reaches 18 month after enrollment. The analysis of cumulative incidence of receiving a transplant according to likelihood of finding a matched unrelated donor and barriers to achieving transplantation with different donor search strategies will start 6 months after the last evaluable patient is enrolled. These parameters are justified by the length of the enrollment period (three years), the inclusion criterion of intent to transplant within 6 months of enrollment, use of a time-to-event analysis for the primary endpoint of survival, and the fact that conclusions about transplant rates and barriers to transplant will not influence the primary endpoint of survival.

11. Could the sample size change?

Yes, the sample size could increase or decrease depending on the actual ratio of Very Likely to Very Unlikely patients. We estimated at 2.5:1 ratio but the ultimate sample size is dependent on the number of patients in the smaller (Very Unlikely) group.

12. How will the study results be interpreted?

The table below outlines how study results will be interpreted based on the difference in 2 year survival between the Very Likely and Very Unlikely groups, depending on a comparison of observed transplant rates in the two groups.

	Higher proportion transplanted in Very Unlikely group	Same proportion get to transplant	Lower proportion transplanted in Very Unlikely group
Very Likely = better survival	Suggests matched URDs are better than alternative donors	Suggests matched URDs are better than alternative donors	Uninterpretable, biologic assignment did not work
Very Unlikely = better survival	Suggests alternative donors are better than matched URDs, possibly due to faster time to transplant	Suggests alternative donors are better than matched URDs, possibly due to better outcomes with an alternative donor	Suggests alternative donors are better than matched URDs, possibly due to better outcomes with an alternative donor
Very Likely – Very Unlikely	Suggests either searching for a matched URD or going rapidly to transplant with an alternative donor is acceptable, possibly because an improvement in time to transplant is balanced by lower survival after transplant. This could be either due to donor source or transplantation of less fit or higher disease risk patients.	Suggests that matched URDs and alternative donors have the same survival after transplant	Suggests biologic assignment did not work and there was a higher mortality with transplant than without
Comments	Most likely since haploidentical and cord blood grafts are more quickly available than URDs even among patients in the Very Likely group; suggests faster time to identify a donor is contributing to higher transplant rates	Possible, and would suggest that finding a donor is not the limiting factor in getting people to transplant	Unlikely, and would suggest bias in proceeding to transplant based on donor type (biologic assignment did not work)

13. How much guidance about clinical management is provided by the study?

One of the inclusion criteria for the study is the intent to follow a donor search algorithm based on the donor search prognosis. Centers will have already determined that the approach is appropriate for participants. Many centers already follow this algorithm where they search for a matched unrelated donor for patients likely to find one but rapidly shift to other alternative donors for patients unlikely to find a matched donor. As part of the study, the likelihood of finding a matched unrelated donor and summary of the preliminary search will be provided for all participants with the presumption that centers will seek a matched unrelated donor for the Very Likely patients and end up with another alternative donor for the Very Unlikely patients.

Other transplant practices are largely left up to center practices. We extensively discussed clinical management of donor-specific antibodies (DSA) since proceeding to transplant in the face of high antibody levels has been associated with inferior outcomes. Because of concern that some centers may be less experienced with DSA,

we will have a Study Procedure and Reference Manual that will strongly encourage DSA measurement for mismatched donors, give guidance about DSA interpretation, and provide example algorithms for managing DSA. The Study Procedure and Reference Manual will also provide guidance on the number of donors to have in workup.

14. Are you worried that centers will not follow the protocol?

Two of the eligibility criteria are: (a) intent to follow the recommended search strategy based on likelihood of finding a matched unrelated donor, and (b) intent to transplant the patient within 6 months if a suitable donor is found. While we cannot enforce these requirements, we make it clear that centers should only deviate from the protocol guidance if necessary for patient care or patient preference. We will be monitoring the compliance of centers via a donor search tracking case report form that gathers data on how the search proceeds from the time of enrollment and whether patients end up going to transplant with the preferred donor type. From a study level, we will also be monitoring whether the assumptions built into this study about likelihood of finding donors and the proportion who undergo transplant are corroborated by actual trial data. If not, then the study design or sample size may need to be adjusted.

15. What is the purpose of the QOL Substudy?

Given the interest in comparing recipients of matched unrelated donors and haploidentical donors, this study includes a separate Substudy restricted to a homogeneous group of first remission patients with AML/ALL and early stage MDS who receive standard conditioning and GVHD prophylaxis. Collection of CIBMTR CRF forms, patient-reported outcomes and, if separate funding is secured, banked research samples will allow a detailed comparison. Inclusion of all enrolled patients will be too expensive and yield difficult-to-interpret data if there is too much heterogeneity.

The protocol and consent form include descriptions of patient research blood samples, clearly stating that blood draws will only take place if additional funding is secured. Pre-consenting patients to research sampling is necessary to ensure that if funding is obtained, blood draws could be implemented quickly.

16. Accrual estimates – See separate Accrual Plan for estimates.

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



BMT CTN Core and Affiliate transplant 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 Department of Patient Health and Professional Services and made available to centers on the Web.

Monthly accrual reports will be provided to the NIH. Additionally, recruitment reports based on the CIBMTR database will be provided every six months.

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

Both study-specific supplemental forms and transplant outcomes data will be collected on CIBMTR forms via the CIBMTR web-based platform FormsNet3. FormsNet3 is CIBMTR's 21 CFR Part 11 compliant, globally available application for collecting outcomes data electronically. It is a secure Web-based application that is available wherever Web browser functionality is supported. FormsNet3 supports data collection, auditing, and event reporting; web services; and messaging. It offers 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. FormsNet3 is updated regularly, with monthly maintenance releases and quarterly revision and enhancement releases. Centers already provide most clinical data through CIBMTR's well-developed system of HCT and cellular therapy data collection forms through FormsNet3.

Queries will be developed in Oracle Business Intelligence Enterprise Edition (OBIEE) to check for missing and inconsistent data in FormsNet3. Queries will update every 30 minutes and will be distributed to the centers at least monthly.

Patient reported data are collected by the patient 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.

A Study Procedure and Reference Manual will be developed for reference and training of clinical research associates (CRAs).

19. 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.

Transplant outcome data will be collected on standard CIBMTR forms. Whether or not a patient participates in BMT CTN 1702, 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 in the QOL Substudy.

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

Only adverse events related to the study consent process, collection of the optional research blood samples, or completing QOL surveys will be reported via study-specific supplemental forms in FormsNet3 and will be reported according to BMT CTN guidelines. The protocol officer will review all unexpected serious adverse experiences.

We will monitor the Very Unlikely prognosis group for day 100 mortality to ensure that we are not observing a higher rate than historical controls. We will also review the study design assumptions, particularly the ratio of patients who are Very Likely to



find a matched unrelated donor vs. patients who are Very Unlikely to find a matched unrelated donor and percentage proceeding to transplant, on a periodic basis, and may adjust the sample size if needed to maintain power in the event that our assumptions are incorrect.

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

CRA's will be certified for data submission by the DCC after participating in a training session conference call with the protocol coordinator.