BMT CTN 2402 HOPE Resource

Hematopoietic Cell Transplant and Gene Therapy for Non-Malignant Blood Disorders Biobank Resource

FREQUENTLY ASKED QUESTIONS (FAQs)
Version 0.4 dated 2025

1. What are the goals of BMT CTN protocol 2402?

- To establish a resource for research relevant to patients with non-malignant blood diseases receiving potentially curative therapy with hematopoietic cell transplant (HCT) or gene therapy (GT).
- The resource will consist of a variety of biospecimens linked to high quality clinical data, creating a unique repository that will enable investigators to address important questions on the pathophysiology of the underlying diseases and the complications of curative therapies.

2. Why create a multi-center biorepository of pre- and post-HCT and GT research samples?

The use of curative therapy for non-malignant blood disorders (NMBD) has increased across transplant centers due to improvement in conditioning techniques, expansion of donor pools, and growth of GT programs with FDA approval of some products and ongoing clinical trials for promising new agents. Given the growing role of pediatric and adult transplant centers in managing patients with NMBD, it is critical that the HCT community devotes increasing effort to better understand the unique challenges in curative therapy and to develop solutions to improve outcomes. Most studies of curative therapy for NMBD are hampered by small numbers of patients, non-uniform sample collection, and treatment bias secondary to collection from a single or limited number of centers. The HOPE resource addresses these deficiencies through collection of the appropriate types and larger numbers of biospecimens together with detailed clinical data via a multi-center initiative.

3. Why are we only focusing on NMBD and specifically aplastic anemia and hemoglobinopathies?

Although patients with malignant and non-malignant disease share several similar challenges during HCT, non-relapse events such as graft failure, declining donor chimerism, clonal hematopoiesis, immune mediated cytopenias, and hemophagocytic syndrome are more common and a more important cause of treatment failure in patients receiving HCT for NMBD. Additionally, GT is a treatment approach unique to non-malignant diseases that is only beginning to be studied longitudinally. Additionally, the BMT CTN has already assembled a large repository of biospecimens with annotated clinical data from patients receiving HCT for malignancy through BMT CTN 1801 (Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation, Mi-Immune). The focus of the protocol on aplastic anemia and hemoglobinopathies reflects that fact that these are the NMBDs most commonly treated with curative therapies and where analyses of pathophysiology and outcomes can be done with greater statistical power.

Several examples are given in the protocol. However, the resource will include data and specimens from patients with other, more rare, NMBDs which will be available to investigators.

4. How feasible is it to accrue 375 patients over the 5-year timeline of the study?

The expected 375 patient biorepository in non-malignant HCT and GT will represent the largest collection by far of samples and data for HCT and GT for NMBD to date. Per our analysis of CIBMTR HCT data, approximately 800 patients receive HCT for hemoglobinopathies and aplastic anemia annually at BMT CTN Core and PTCTC Consortium centers (n=83). 36 centers perform an average of 5 or more HCT each year (range 5-20 HCT/yr), with 12 of these performing 10 or more HCT per year. Data on GT use is not currently available in CIBMTR, but we anticipate use of GT continuing to rise over the new few years with recent FDA approval of several GT products. Based on prior BMT CTN experience in BMT CTN 1202 and 1801, we assume approximately 25-30% of patients approached will agree to participate. Among the BMT CTN and PTCTC centers, we can estimate that sites will enroll an average of 1-7 patients each year, reaching our goal of 100 patients enrolled on the study annually.

5. What are the incentives for institutions to enroll patients on BMT CTN 2402?

In addition to contributing to group science in a field that requires multi-institutional contributions and supporting the efforts of the BMT CTN, institutions and site primary investigators will also receive direct benefit from patient enrollment including:

- Double accrual credit toward BMT CTN accrual requirements;
- Early access to HOPE Biorepository samples and data at no cost prior to transfer of samples to the NIH/NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC);
- Potential opportunities for authorship inclusion on publications developed from biosamples and data from BMT CTN 2402
- Collaboration with other BMT CTN 2402 institutions in scientific investigations.

Although biorepositories cannot offer the same incentive as clinical trials that may directly benefit the patient, the diversity and depth of samples in the HOPE biorepository are expected to lead to many scientific studies and publications that will offer collaborative opportunities for enrolling sites.

6. Is there a specific outcome for BMT CTN 2402?

No, there are no traditional “primary outcomes” for the protocol. The Hope Resource will be an opportunity for future research, open to investigators to use for research into non-malignant diseases. The target goal of 375 patients was selected based on feasibility and to ensure power to address common complications post-therapy in **the most common NMBDs diseases treated with HCT or GT.**

7. What are some examples of scientific investigations that could be conducted with the HOPE Biorepository?

Through uniform, high quality biosamples from donors and recipients, the biorepository will facilitate investigator-initiated studies to address important questions in the field. Examples of critical investigations that could be addressed with the HOPE Biorepository include:

- Mechanistic insights into graft tolerance
- Biomarker prediction of primary and secondary graft failure
- Prevalence and understanding of clonal hematopoiesis and impact on long-term morbidity
- Comparison between different HCT and GT techniques
- Detailed studies on immune reconstitution

- Late effects of curative therapy in NMBD

These important clinical and scientific questions cannot be addressed with appropriate vigor without the availability of a large and detailed biosample and date repository.

8. Why are germline samples being collected?

Germline samples **will enhance our understanding of HCT and GT for NMBD in multiple ways:**

- Uniformly identify the prevalence of known and yet undescribed genetic drivers of aplastic anemia and inherited bone marrow failure syndromes.
- Provide better understanding of clonal hematopoiesis (as donor or recipient driven) as well as late effects post-transplant (e.g. presence of other germline cancer risk variants not usually tested for that influence post-therapy cancer risk)
- Identification of other recipient or donor genetic influences on transplant outcomes such as genetic polymorphisms involved with drug metabolism, predisposition genetic factors for the development of clonal hematopoiesis or cancer, and non-HLA histocompatibility genetic factors that impact immune tolerance.

The HOPE resource will be unique as no other biorepository offers germline samples for patients with NMBD.

9. What germline samples are being collected and what is the ideal germline sample?

Germline samples can be collected through nail or hair clippings, or through fibroblast culturing following a skin biopsy. Germline samples will be requested for all patients and for related donors. For donors, the options of nail and/or hair clipping are offered to the donor and the collecting center. For the recipient, nail and/or hair clippings and/or a skin biopsy are requested. Ideally, all three types of specimens will be collected, to allow comparisons of utility that are currently lacking. However, priority is placed on the skin biopsy specimen which will be sent to a central processing site (University of Minnesota) to produce cultured fibroblasts. Although this requires an extra procedure, cultured fibroblasts are considered the ideal specimen to procure germline DNA. The also have other unique uses such as development of induced pluripotent stem cells. Although obtaining a skin biopsy may not be an option for each patient and/or center, as most patients will require sedated procedures such as central line placement or bone marrow biopsies prior to HCT, we suggest using these opportunities to perform the procedure for consented patients to minimize discomfort to the recipient.

10. What is the rationale for stool collection?

Over the past decade, the impact of the microbiome on the health of all individuals, including its effects on post-transplant outcomes, has received increasing attention. There are limited microbiome data in patients with aplastic anemia and hemoglobinopathies, but recent research supports the association between the microbiome and SCD disease severity and progression of aplastic anemia in the non-HCT/non-GT setting. Thus, providing stool samples for research into the associations between microbiome disease and curative outcomes is another important use of the HOPE resource that may have patient benefits, such as discovery of undescribed biomarkers or interventions such as microbiome manipulations to reduce inflammation or alter metabolism.

Stool collection was found to be feasible in prior BMT-CTN studies, with >75% success in securing stool samples during the first 30 days post-HCT and 50% thereafter. Most of specimens required by this protocol (4 of 7) are due during expected times of inpatient admission, facilitating collection. Using our experience in 1801, we can also provide kits to patients for at home collections to facilitate compliance.

11. How will investigators access specimens and data collected in this protocol?

At the completion of accrual and follow up, data and specimens will be transferred to the NIH/NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). BioLINCC has a well-established procedure for investigators to access both data and specimens. But as an incentive for participating, investigators and centers enrolling on this protocol will have the opportunity to submit proposals to receive specimens free of charge before the transfer to BioLINCC. The procedure will include submission of a scientific proposal and request for biological samples and data to be reviewed and approved by the BMT CTN Biomarker Committee. The exact time that specimens will be made available is not yet determined pending discussions with NHLBI but, at a minimum, patients must have had their 1-year post-HCT or GT visit and with a reviewed data set locked for investigator use. A detailed plan for releasing data will be developed and reviewed by the DSMB before implementation.