Priorities for Improving Outcomes for Non-Malignant Blood Diseases: A Report from the Blood and Marrow Transplant Clinical Trials Network

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Abstract

Non-malignant blood diseases such as bone marrow failure disorders, immune dysregulation disorders, and hemoglobinopathies often lead to shortened lifespans and poor quality of life. Many of these diseases can be cured with allogeneic hematopoietic cell transplantation, but patients are often not offered the procedure because of perceived insufficient efficacy and/or excess toxicity. In 2018 the Blood and Marrow Transplant Clinical Trials Network convened a task force to identify the most urgently needed yet feasible clinical trials with potential to improve the outcomes for patients with non-malignant diseases. This report summarizes the task force discussions and specifies the network plans for clinical trial development for non-malignant blood diseases.

Introduction:

Non-malignant blood diseases such as bone marrow failure disorders, immune dysregulation disorders, and hemoglobinopathies often lead to shortened lifespans and poor quality of life. Many of these diseases can be cured with allogeneic hematopoietic cell transplantation (HCT), but patients are often not offered the procedure because of perceived insufficient

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efficacy and/or excess toxicity. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), which is funded by the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), is uniquely positioned to strategically prioritize and address these concerns. The BMT CTN includes 20 core centers and consortia that collectively transplant nearly 10000 patients per year. The resulting size and scope of the network is sufficient to conduct clinical HCT trials even in the rarest of diseases. In 2018 the BMT CTN formed a task force to identify the most urgently needed yet feasible clinical trials with potential to improve the outcomes for patients with non-malignant diseases. The task force followed the previously successful format used in State of the Science Symposia that set the scientific priorities of the BMT CTN twice in the past. A task force of eight members and a chair was formed from the 20 BMT CTN core and consortia centers with the final composition intended to maximize diversity of viewpoints and expertise. Proposals were solicited from all members and each proposal was reviewed and critiqued by two task force members prior to discussion during weekly webinars. Proposals were broadly divided into two categories. The first category included proposals to improve outcomes for specific types of non-malignant blood diseases such as bone marrow failure disorders. Studies for sickle cell disease (NCT02766465, NCT03263559) and aplastic anemia (NCT02918292) were not included due to currently open BMT CTN trials in these diseases. The second category included proposals to decrease the toxicity of HCT such as chronic graft-versus-host-disease (GVHD) of the lung. The task force ranked the proposals according to importance of the unmet health need, likelihood of success, and feasibility. The most highly ranked proposals were presented to the BMT CTN Steering Committee for endorsement in February 2019. Afterwards the task force re-convened, modified, and re-prioritized the study concepts. This article summarizes the final report of the BMT CTN non-malignant disorders task force.

Trials to Improve Outcomes for Non-Malignant Blood Disorders

Bone Marrow Failure

Background: Bone marrow failure disorders, either acquired or inherited, are primarily characterized by inadequate production of neutrophils, red blood cells, and/or platelets, although other organs may be involved. Allogeneic HCT is effective treatment for these conditions and for many is the only known cure. Historically, patients with certain inherited bone marrow failure diseases have had poor outcomes following HCT using conventional myeloablative approaches (MAC) such as busulfan combined with cyclophosphamide or TBI-based regimens. While these regimens result in high rates of engraftment, they also come with increased risk for transplant related morbidity and mortality from complications such as sinusoidal obstructive syndrome (SOS). As a result, less intense regimens have been investigated. These less intense regimens, however, carry an increased risk for graft rejection, particularly in patients with competent immune systems and/or normocellular marrows who may require higher intensity conditioning to overcome these barriers to engraftment. Prospective studies are needed to develop less toxic conditioning regimens that are effective at establishing long-term multi-lineage engraftment.
Treosulfan is a pro-drug of an alkylating agent structurally related to busulfan, but with a different mode of alkylation\textsuperscript{8}. Treosulfan has both cytotoxic and immunosuppressive properties and has been increasingly used as the backbone of HCT conditioning regimens in both pediatric and adult patients with hematologic malignancies and nonmalignant diseases, primarily in the European Union\textsuperscript{9–12}. Treosulfan has characteristics that make it particularly appealing for use in HCT. One particularly encouraging characteristic is that it is water soluble and bypasses hepatic enzyme activation and as a result has been associated with a low incidence in SOS\textsuperscript{9,13–15}. A phase II prospective study of treosulfan combined with fludarabine ± rabbit anti-thymocyte globulin (ATG) in 23 patients with bone marrow failure disorders resulted in two-year overall and event-free survival of 96% with a low incidence of acute grades II-IV (39%) and grades III-IV (4%) and NIH chronic (9%) GVHD. The one-year GVHD-free, event-free survival (EFS) was 87% (FIGURE 1). There were no graft rejections. A follow-up report of this regimen in a subset of 14 patients with bone marrow failure disorders revealed highly similar outcomes\textsuperscript{13,16}.

**Hypothesis:** The combination of treosulfan, fludarabine, and rabbit ATG conditioning will be effective in establishing multi-lineage donor engraftment with low incidences of severe acute or NIH chronic GVHD in patients with bone marrow failure disorders.

**Trial Design:** The primary endpoint will be the 1-year GVHD-free, EFS in patients with bone marrow failure disorders undergoing HCT. An event will be defined as death due to any cause, disease recurrence, graft rejection/failure, second HCT, or the occurrence of grade III-IV acute or chronic GVHD.

The trial will enroll patients less than 50 years of age with a bone marrow failure disorder treatable by HCT including but not limited to Diamond Blackfan anemia (DBA), Shwachman Diamond Syndrome (SDS), paroxysmal nocturnal hemoglobinuria (PNH), GATA 2 mutation with associated marrow failure, and congenital amegakaryocytic thrombocytopenia. Patients with idiopathic aplastic anemia will be excluded as this group of patients does not require myeloablative conditioning. Patients with Fanconi anemia would also be excluded due to limited data using treosulfan in this group. Eligible donors include related or unrelated bone marrow or peripheral blood stem cell donors who are matched by high resolution typing for HLA-A, B, C, DRB1, and DQB1 or at most a single class 1 allele mismatch or DQB1 antigen/allele mismatch.

**Feasibility/Logistics:** A sample size of 40 patients is sufficient to determine the one-year GVHD-free, EFS with reasonable confidence. The majority of eligible patients will be children. In the recent past, the pediatric community embraced the BMT CTN’s study for hemophagocytic syndromes, which completed accrual ahead of schedule. Given the number of patients with bone marrow failure disorders transplanted in the US annually, and the strong commitment from pediatric centers, it should be possible to complete accrual within four years. Treosulfan is under an IND in the U.S. but is approved for HCT conditioning in the European Union since June 2019.
Transfusion dependent thalassemia

**Background**—β-thalassemia major is a severe anemia caused by mutations in the β-globin gene. Patients with thalassemia require lifelong blood transfusions, which predisposes them to iron overload and associated organ specific dysfunction. Allogeneic HCT is currently the only established curative therapy for transfusion-dependent thalassemia leading to transfusion independence, resolution of iron burden, and long-term disease-free survival ranging from 78% to 81%.\(^\text{17,18}\) Transplant-related mortality (TRM), often tied to chronic iron overload, is a barrier to increased utilization of allogeneic HCT as a curative therapy. The best reported outcomes are with HLA-matched sibling donors. However, only 30% of children in need of a BMT have a HLA-identical family member and well matched alternative donors are often not available.\(^\text{19}\)

There have been several recent attempts to improve outcomes after allogeneic HCT using alternative donors. The use of bone marrow or cord blood stem cells from unrelated donors following a reduced intensity conditioning (RIC) regimen in 33 patients was accompanied by significant rates of acute and extensive chronic GVHD. Moreover, six patients died of transplant-related toxicity or viral reactivation.\(^\text{20}\) Myeloablative conditioning using related or unrelated donors and augmented GVHD prophylaxis with abatacept or maraviroc in 13 patients resulted in low mortality but chronic GVHD and viral reactivation rates remained high.\(^\text{21}\) Thus, efforts to extend the curative potential of allogeneic HCT through the use of alternative donors has been associated with both significant GVHD and treatment failure rates of 20–30%. Use of haploidentical donors after MAC has produced mixed results. Depletion of αβ T-cell receptor cells and CD19 cells from stem cell grafts was still associated with graft failure, extensive chronic GVHD, post-HCT lymphoproliferative disease, and delayed immune reconstitution.\(^\text{22}\) By contrast, use of haploidentical donors, pre-HCT immune suppression with fludarabine/dexamethasone, full intensity conditioning and post-HCT cyclophosphamide (PT/Cy) for GVHD prophylaxis resulted in 100% engraftment and 94% overall survival in 31 patients.\(^\text{23}\) While this regimen showed promise, it required extensive pre-HCT immune suppression and exposes young patients to the long-term sequelae of myeloablative conditioning. New strategies to achieve long-term disease-free survival without unacceptable GVHD rates or exposure to myeloablative chemotherapy are still needed.

Recently, a multicenter collaboration used an augmented RIC conditioning regimen (ATG/fludarabine/cyclophosphamide and either TBI 400 cGy or thiotepa 10 mg/kg) and GVHD prophylaxis with PT/Cy, MMF, and sirolimus for 23 patients with transfusion dependent thalassemia. Engraftment at day 30 was high at 96% (22/23) and transfusion free survival was 91% (21/23). There were two treatment related deaths – one each of idiopathic pneumonia syndrome and macrophage activation syndrome in the subset of patients receiving thiotepa. Severe acute GVHD grade III/IV was infrequent (4%, 1/23) as was limited chronic GVHD (13%, 3/23).

**Hypothesis:** An augmented RIC HCT platform (ATG/fludarabine/cyclophosphamide and either TBI 400 cGy or thiotepa 10 mg/kg) using the best available donor and PT/Cy will lead to high rates of sustained donor engraftment with minimal toxicities, low rates of GVHD,
and high OS and EFS in pediatric and young adult patients with transfusion dependent thalassemia.

**Trial Design:** The primary endpoint will be the 1-year GVHD-free, EFS. An event will be defined as death due to any cause, disease recurrence, graft rejection/failure, second HCT, or the occurrence of grade III-IV acute or extensive chronic GVHD. The trial will enroll patients age 3 to 40 years with β-thalassemia or other non-sickle cell-related, transfusion dependent thalassemia. Eligible bone marrow donors include: HLA-matched related or unrelated donors, HLA-mismatched unrelated donors or HLA-haploidentical, related (first or secondary degree relative) donor.

**Feasibility/Logistics:** A sample size of 40 patients is sufficient to determine the one-year EFS with reasonable confidence. Although the number of transplants for TDT annually in the US is small, existing collaborations and interest among centers in the U.S, UK and Canada, will be sufficient to achieve accrual within four years. While the use of gene therapy may hold promise in the future (see below), this RIC platform offers an available, curative, HCT option for nearly all patients with limited GVHD and TRM.

**Hemophagocytic Lymphohistiocytosis**

**Background:** Hemophagocytic lymphohistiocytosis (HLH) is an inherited or acquired syndrome characterized by immune dysregulation and pathologic inflammation. The hallmark of this disorder is overproduction of interferon gamma (IFNγ) from dysfunctional T cells. HLH is most often diagnosed in children but can also occur in adulthood.

Allogeneic HCT is curative when the underlying cause is due to intrinsic defects in immune function, although in some cases no genetic mutation is identified. Familial HLH is typically associated with pathogenic variants in genes such as PRF1, UNC13D, STX11, and STXBP2 that regulate NK and T cell cytotoxicity. Immune dysregulation from primary immune deficiencies and inflammasome disorders may also drive the clinical manifestations.

HLH is a challenging condition to transplant due to the high incidence of infection, organ dysfunction, and active inflammation/immune dysregulation pre-HCT. As a result, HCT recipients are at high risk for both TRM and graft rejection. Three-year overall survival with myeloablative conditioning (MAC) was only 43%. A novel reduced intensity conditioning (RIC) regimen combined alemtuzumab on day −14 to −12 to immunoablate the host and decrease graft rejection with moderate dose fludarabine and melphalan to decrease TRM. In a single center pediatric review of 26 patients receiving RIC and 14 patients receiving MAC, three year survival was improved to 92%, but 65% of patients developed mixed chimerism and required immunologic maneuvers including additional re-transplant. The BMT CTN tested this RIC regimen in 46 patients (HLH, n=34; other primary immunodeficiency disorders n=12) in a multicenter study. Overall survival at one year was 80% but only 39% of patients experienced sustained engraftment without donor leukocyte infusion or second HCT. New strategies to improve long term engraftment are needed.

The inflammation in HLH is driven by excess IFNγ produced by dysfunctional T-cells. Emapalumab, an FDA-approved monoclonal antibody against IFNγ, is a safe and effective treatment for relapsed and refractory HLH. Inhibition of IFNγ may be useful in HCT as
IFNγ inhibits hematopoietic stem cell survival and differentiation \(^{31}\) and high IFNγ levels correlate with engraftment syndrome, graft loss, and GVHD \(^{32}\).

**Hypothesis:** Durable engraftment and overall survival for patients with HLH and related conditions undergoing HCT can be improved by the addition of the anti-IFNγ antibody, emapalumab, to a RIC regimen consisting of fludarabine, melphalan, and alemtuzumab followed by allogeneic HCT.

**Trial Design:** The primary endpoint will be survival with durable engraftment at one year. Key secondary endpoints include the incidence of acute and chronic GVHD, TRM, and immune reconstitution kinetics. Emapalumab will be given throughout conditioning. In order to maintain inhibition of IFNγ, CXCL9 levels, which reflect total IFNγ levels, will be checked weekly through day 100 and additional emapalumab dosing will be given if CXCL9 increases above baseline.

The trial will enroll patients 4 months through 45 years with HLH or similar diagnoses such as T-cell severe chronic active EBV, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome and Hyper-IgM syndrome type 1.

**Feasibility/Logistics:** A sample size of 42 patients provides 80% power to detect a 30% improvement in durable engraftment at one year from 39% to 69%. Prior experience in the BMT CTN demonstrated that this number of HLH patients can be accrued within 25 months \(^{28}\).

**Gene Therapy for β-Hemoglobinopathies**

**Background**—β-Thalassemia and sickle cell disease (SCD) are the world’s most widely disseminated hereditary hemoglobinopathies \(^{33}\). Despite better medical therapies such as effective chelation for iron overload \(^{34}\), prediction of stroke risk \(^{34}\), and hydroxyurea to decrease vaso-occlusive crises (VOC) in SCD \(^{35}\), individuals with severe disease require numerous blood transfusions, are frequently hospitalized and suffer early mortality \(^{36}\). Allogeneic HCT offers the potential for cure, but as noted above current rates of toxicity and lack of suitable donors limits its applicability \(^{19}\). A strategy to improve upon current allogeneic HCT results for transfusion dependent thalassemia is a high priority proposal from this task force. Gene therapy for these monogenic disorders is another approach. Recently lentiviral vectors have been used to introduce a modified fetal hemoglobin gene into autologous hematopoietic stem cells which have restored fetal hemoglobin production in the first gene therapy trials for β-thalassemia and sickle cell disease. Pre-clinical and early phase clinical studies have shown preliminary efficacy and safety \(^{37–39}\). Transplantation of autologous CD34+ cells transduced with the lentiviral vector reduced or eliminated the need for long-term red-cell transfusions in 22 patients with severe β-thalassemia without any serious adverse events related to the drug product \(^{38}\). A second trial showed persistent engraftment of vector-marked cells in hematopoietic progenitors without clonal dominance. Transfusion requirements were reduced in both adults and children. In fact, 75% of treated children were able to discontinue all transfusions after gene therapy \(^{39}\). An advantage of gene therapy over HCT is that pre- or post-HCT immunosuppression are not required to improve
engraftment or prevent GVHD. Single agent alkylator conditioning provides sufficient myeloablation to promote homeostatic proliferation of gene modified autologous stem cells following infusion. A case of myelodysplastic syndrome, apparently due to busulfan conditioning, that developed approximately three years after conditioning is a cautionary reminder of the potential risks from this approach.\(^4\)

**Hypothesis:** Autologous hematopoietic stem cells transduced with a gamma globin lentiviral vector will reduce the frequency of blood transfusions in patients with severe \(\beta\)-hemoglobinopathies.

**Trial Design:** The primary endpoint is the number of blood transfusions during the first year after HCT compared to the average number of annual transfusions over the previous three years. Key secondary endpoints include the contribution of gene modified hemoglobin/total hemoglobin, survival, TRM, and for patients with SCD, the frequency of severe VOC. Patients will first undergo plerixafor induced stem cell collection, cytokine growth factors will be avoided to minimize risk of splenomegaly. Autologous hematopoietic stem cells will be transduced with lentiviral vectors to induce modified fetal hemoglobin production. Patients with successful transduction procedures will be infused with gene modified autologous stem cells following single agent alkylator conditioning.

The trial will enroll patients <40 years with severe \(\beta\)-hemoglobinopathies – transfusion dependent \(\beta\)-thalassemia or SCD with severe clinical symptoms (frequent VOC, stroke, or recurrent acute chest syndrome).

**Feasibility/Logistics:** A modest sample size of 20–40 patients would be sufficient to determine if blood transfusion requirements are reduced following gene therapy. Current estimates suggest that there are over 1000 patients in the US with transfusion dependent \(\beta\)-thalassemia. Sickle cell disease is considerably more prevalent in the US due to a 100-fold higher incidence.\(^4\) However, a corporate partner, not yet identified, will be necessary to manufacture the vector and patient-specific cell products, and to co-sponsor a gene therapy trial.

**Trials to Decrease the Toxicity of HCT**

**Lung GVHD**

**Background:** Bronchiolitis obliterans syndrome (BOS) is a chronic obstructive airway disease that occurs in 5–12% of allogeneic hematopoietic cell transplants (HCT).\(^4\) The disorder is characterized by progressive fibro-obliteration of terminal bronchioles, with resultant air trapping, progressive dyspnea, recurrent pulmonary infections and an overall decrease in quality of life. Inhaled steroids, such as fluticasone, may stabilize symptoms but survival following the development of BOS is only 20–40%.\(^4\) The criteria used to define BOS are strict and limit the diagnosis to patients who already have developed severe airflow obstruction, when irreversible fibro-oblitative changes in the lungs have likely already occurred.\(^4\) Earlier intervention is needed to improve outcomes.
BOS 0p is a spirometric parameter defined by a >10% decline in forced expiratory volume in 1 second (FEV1, or >25% decline in FEF25–75) on consecutive pulmonary function tests. BOS 0p has high sensitivity in predicting BOS development in lung transplant recipients and was recently shown to be an independent predictor of BOS in allogeneic HCT recipients (HR 3.22, p<0.001)\textsuperscript{46}. The presence of more than one risk factor for BOS increases the likelihood of a poor outcome. Forty percent of patients with two risk factors, chronic GVHD in any organ other than the lung and BOS 0p, progressed to BOS within one year. The cumulative incidence of BOS 0p is 16% with a median time to onset of 273 days post-HCT.

Treatment options for BOS are unsatisfactory with few trials showing any improvement in lung function, likely due to irreversible changes at the time of diagnosis\textsuperscript{47,48}. Pre-emptive therapy guided by the presence of BOS 0p offers an opportunity to intervene when treatments may have a better chance of efficacy. Therapeutic options include targeting the IL-17 pathway, administration of novel tyrosine kinase inhibitors that impact fibrogenesis, or alpha-1 anti-trypsin (AAT) infusions. AAT, a protease inhibitor that inactivates neutrophil and macrophage serum proteases, protects tissues (primarily the lung and liver) from proteolytic degradation. Congenital deficiency of AAT leads to emphysematous changes in the adult lung. Furthermore, murine lung allograft models have shown that infusions of AAT significantly decreases pulmonary inflammation\textsuperscript{49}. AAT is an attractive option because of a very low toxicity profile and preliminary efficacy in two phase I/II trials for the treatment of steroid-refractory GVHD\textsuperscript{50,51}.

**Hypothesis:** Early identification and pre-emptive treatment of patients at high risk for progression to BOS will prevent its development.

**Trial Design:** The primary endpoint is the incidence of BOS at 12 months. Secondary endpoints include chronic GVHD severity, systemic steroid exposure, and overall survival. Exploratory endpoints include examinations of novel imaging biomarkers, serologic markers (inflammatory, extra-cellular matrix proteins, endothelial injury markers), and sputum microbiome studies.

The trial will enroll subjects older than 8 years of age (the minimum age at which reliable spirometric values can be obtained) with chronic GVHD in at least one organ and spirometric values that fulfill the diagnostic criteria for BOS 0p. The lower age limit of 8 years is needed to ensure accurate spirometry testing. Subjects will be randomized 1:1 to fluticasone plus six months of AAT infusions or placebo infusions.

**Feasibility / Logistics:** A sample size of 94 patients (47 per arm) is sufficient to detect a reduction in the rate of progression to BOS at one year from 40% to 20%. We estimate that approximately 10% of all allogeneic HCT recipients will develop both risk factors (chronic GVHD and BOS 0p) within the first year post-HCT. Currently the majority of eligible patients would not be identified due to infrequent screening by spirometry. However, routine screening four times in the first year (every 3 months between months 3 to 12) would be adequate to identify the number of patients required for this trial. Transplant centers would need to commit to increased spirometry screening to meet enrollment goals.
Cardiovascular Disease in HCT Survivors

**Background:** Advances in hematopoietic cell transplantation (HCT) have led to a 10% improvement in survival each decade since the 1980’s, resulting in an estimated 200,000 HCT survivors alive in the U.S today. Despite these improvements, HCT survivors continue to have substantially higher mortality rates compared with the general population. In particular, the risk of cardiovascular-related mortality is more than twice that of the general population, and the magnitude of risk increases with time from HCT. However, examining cardiovascular-related mortality alone underestimates the true burden of cardiovascular morbidity. HCT survivors have a 4-fold higher risk of developing cardiovascular disease (CVD) compared to the general population, adding to the already high burden of chronic health-related conditions in these survivors.

It has been increasingly recognized that aggressive monitoring and management of CVD risk factors can result in clinically significant reduction in future cardiovascular events. For example, in patients with hypertension, a management strategy with a goal SBP of <140mmHg may not be as effective as trying to achieve lowest feasible/tolerable SBP to reduce future CVD risks. At present, there are no established evidence-based targeted interventions to reduce CVD risk after HCT, due to the paucity of information on appropriate risk-stratification after HCT. Armenian and colleagues recently developed a risk-prediction model for CVD after HCT, incorporating demographic, cancer treatment, and modifiable risk factors at one year post-HCT. Patients were stratified into statistically distinct low-, intermediate-, and high-risk groups, corresponding to 10-year cumulative incidences of CVD of 3.7%, 9.9%, and 26.2%, respectively. This model’s one-year post-HCT starting time point capitalizes on the so-called “teachable moment” effect, where survivors, having survived one life-threatening disease, may be more motivated to try an approach to prevent additional illness. Studies in long-term HCT survivors further indicate that patients’ engagement in risk-based survivorship care declines with time from HCT, a trend that coincides with the highest risk of new-onset cardiovascular events. It is in this context that new paradigms in health management should be explored, tackling existing barriers to survivorship care in a geographically diverse and growing population of long-term survivors.

The proliferation of high-speed wireless internet connectivity provides an opportunity for creative solutions to healthcare problems. Real-time home and mobile health monitoring can be accomplished using Bluetooth-enabled devices (blood pressure monitor, pulse oximeter, weight scale, glucometer) that transmit data via the internet to healthcare providers. In turn, health care providers can proactively manage health conditions by frequent direct feedback and interaction with patients. Pilot studies testing one of these systems (mTelehealth™) are ongoing at City of Hope and Fred Hutchinson Cancer Research Center.

**Hypothesis:** Intensive monitoring and management strategies using mTelehealth will reduce cardiovascular risk factors in HCT survivors.

**Trial Design:** The primary endpoint will be to increase the prevalence of patients with adequate control of modifiable CV risk factors (hypertension, diabetes, physical inactivity)
one year after intervention by 30%. Secondary endpoints include adherence to intervention, CVD-related biomarkers (6-minute walk test, blood biomarkers), health-related quality of life cumulative incidence of CVD at 5 years, and overall survival. Patients with high CVD risk will be randomized to intensive monitoring and management vs. standard post-HCT care. Patients assigned to intensive monitoring and management will be equipped with internet connected home health monitoring devices and data will be reviewed in real time centrally. Abnormal patient data will trigger the implementation of established algorithms by an advanced care practitioner. Triggered actions can range from confirmation of abnormal value reading (e.g. text, phone call), patient-directed intervention (e.g. recheck blood pressure in 30 minutes, take blood pressure medication if not already done), alert primary care provider on record, or escalation to emergency care if appropriate responses have not been met.

Eligible patients will include one-year HCT survivors, have intermediate/high CVD risk, and do not have documented CVD.

**Feasibility/Logistics:** The patient population clearly exists within the BMT CTN network. A barrier to this study is the necessary advanced care provider and patient education and training in the use of remote health monitoring equipment, but this can be accomplished through partnership with health care support companies interested in developing these approaches.

**Conclusions:** The task force agreed that while all proposals addressed important unmet needs for patients that could potentially benefit from HCT, feasibility issues preclude pursuing trials for gene therapy for hemoglobinopathies, lung GVHD, or cardiac toxicity at this time. In particular, trials of gene therapy for hemoglobinopathies are already underway under the auspices of the pharmaceutical industry. However, the BMT CTN remains interested in testing gene therapy for hemoglobinopathies as new approaches become ready to transition from the laboratory to the clinic. There was strong support for novel conditioning with treosulfan for bone marrow failure, alternative donor HCT for transfusion dependent thalassemia, and augmented conditioning for HLH. The task force recommended that both the bone marrow failure and the thalassemia proposals be high priorities for the BMT CTN. These studies have potential to change the management of patients with rare, non-malignant blood disorders and require the support of organizations like the BMT CTN to be successfully conducted. The HLH trial was considered to also be meritorious but requires central CXCL9 testing which is not yet available. The BMT CTN Steering Committee endorsed the recommendations in June 2019, and subsequently prioritized the development of a protocol for treosulfan conditioning for bone marrow failure diseases. BMT CTN expects to launch this trial in 2020.

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Highlights:

- Non-malignant blood diseases are curable by allogeneic BMT
- Too few patients are offered BMT due to perceived risks
- The BMT CTN has prioritized diseases for clinical trial development
- Bone marrow failure is the top priority followed by thalassemia
Figure 1:
Overall survival, event free survival and GVHD-free event free survival in 23 patients with bone marrow failure disorders who underwent HCT using treosulfan-based conditioning