CureAA: Clinical Trial of Upfront Haploidentical or Unrelated Donor BMT to Restore Normal Hematopoiesis in Aplastic Anemia

A Phase II Trial of Non-Myeloablative Conditioning and Transplantation of Haploidentical Related, Partially HLA-Mismatched, or Matched Unrelated Bone Marrow for Newly Diagnosed Patients with Severe Aplastic Anemia
Version 2.0

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PROTOCOL SYNOPSIS
Clinical Trial of Upfront Haploidentical or Unrelated Donor BMT to Restore Normal Hematopoiesis in Aplastic Anemia (CureAA)

Co-Principal Investigators: Amy DeZern and Sally Arai

Study Design: This study is a prospective, multicenter Phase II study with participants receiving haploidentical transplantation or unrelated donor transplantation for previously untreated severe aplastic anemia (SAA).

Primary Objective: The primary objective is to estimate graft versus host disease (GVHD)-free failure-free survival (GFFS) (a composite endpoint of survival without Grade III-IV acute GVHD (aGVHD), chronic GVHD (cGVHD) requiring immunosuppression, or primary or secondary graft failure requiring second definitive therapy) at 1 year after initiation of conditioning. GFFS will be evaluated separately for each transplant cohort.

Secondary Objectives: Secondary objectives are the following:

1. Estimate overall survival (OS) at 1 year after initiation of conditioning.
2. Estimate FFS (a composite end point of survival without initiation of treatment with a second definitive therapy for curative intent) at 1 year after initiation of conditioning.
3. Estimate the probability of being engrafted (i.e., without primary or secondary graft failure) and alive at 1 year after initiation of conditioning.
4. Estimate the cumulative incidences of neutrophil recovery at Day +28 and Day +56 post-hematopoietic stem cell transplantation (HSCT), platelet recovery at Day +100 post-HSCT, and red blood cell recovery at Day +100, Day +180, and Day +365 post-HSCT.
5. Estimate the cumulative incidences of primary, secondary, and any graft failure at 1 year post-HSCT.
6. Estimate the hematologic response classification according to the NIH criteria at Day +100, Day +180, and Day +365 post-HSCT.
7. Estimate the cumulative incidences of Grade II-IV and Grade III-IV aGVHD at Day +100 post-HSCT.
8. Estimate the cumulative incidences of all cGVHD and cGVHD requiring immunosuppression at 1 year post-HSCT.

Exploratory Objectives: Exploratory objectives are the following:

1. Describe the pace and quality of immune reconstitution by measuring CD4, CD19, and CD56 counts pre-HSCT and at Day +100, Day +180, and Day +365 post-HSCT.
2. Describe the rates of specific infectious complications (CMV viremia and disease, EBV viremia, and PTLD) within the first year after HSCT.

3. Quantify how many available donors each patient has, including 8/10, 9/10, and 10/10 unrelated donors and all haploidentical donors.
4. Describe the time to enrollment after HLA typing of the recipient.
5. Describe the time from diagnosis of SAA until 1) start of conditioning and 2) until HSCT.
6. Describe total and CD34+ cell doses for haploidentical and unrelated donors.
7. Describe times to donor activation, donor selection, start of conditioning, and transplant from enrollment.
8. Describe the quality of life for SAA participants treated on this protocol.

Eligibility Criteria: Diagnosis of SAA, without a fully matched related sibling donor available, but with a haploidentical or unrelated marrow donor available. Exclusions include inherited bone marrow failure syndrome, previous treatment for SAA including high-dose immunosuppressive therapy or hematopoietic stem cell transplantation (HSCT), history of solid organ transplant, uncontrolled infection, inadequate organ function, pregnancy, and performance score < 60.

Treatment Description: Participants will be treated with a preparative regimen of fludarabine (150 mg/m^2), cyclophosphamide (29 mg/kg), low dose total body irradiation (TBI, 400 cGy), and Thymoglobulin® (4.5 mg/kg). GVHD prophylaxis will be with post-HSCT cyclophosphamide (100 mg/kg), tacrolimus, and mycophenolate mofetil (MMF).

Accrual Objective: The goal is 60 participants in total who initiate the protocol-specified conditioning regimen, 30 in each of the haploidentical and unrelated donor transplant cohorts. Additional participants may be screened, consented, and registered in order to reach accrual goals.

Accrual Period: The estimated accrual period is 3 years.

Study Duration: Participants will be followed for 1 year post-HSCT.

Correlative Studies: Samples will be banked pre- and post-HSCT for future submitted protocols for use of specimens.

Stopping Guidelines: Key safety endpoints for the study are graft failure, early mortality, and Grade III-IV acute GVHD. The rates of graft failure by Day 56 post-HSCT, Grade III-IV acute GVHD by Day 100 post-HSCT, and mortality by Day 115 post-ATG preparation will be monitored on a daily basis using truncated sequential probability ratio tests (SPRT) for binary data. The SPRTs will test the null hypotheses that the graft failure rate does not exceed 10%, that the Grade III-IV acute GVHD rate does not exceed 15%, and that the early mortality rate does not exceed 10%.

TREATMENT SCHEMA

Days -9 **Thymoglobulin®** 0.5 mg/kg intravenous (IV) with pre-meds

↓

Days -8,-7 **Thymoglobulin®** 2 mg/kg IV daily with pre-meds

↓

Days -6, -5 **Fludarabine** 30 mg/m^2 IV daily (adjusted for renal function)
Cyclophosphamide (CTX) 14.5 mg/kg IV daily
Start steroid taper per institutional practice from Thymoglobulin®

↓

Days –4→ -2 **Fludarabine** 30 mg/m^2 IV daily (adjusted for renal function)
Day –1 **Total body irradiation (TBI)** 400 cGy delivered in a single fraction

↓

Day 0 Infuse bone marrow per institutional standards

↓

Days 3, 4 **Cyclophosphamide** (PTCy) 50 mg/kg IV daily
Mesna per institutional practice
(First dose of PTCy must be administered 60-72 hrs after START of infusion of marrow)

↓

Day 5 Begin **Tacrolimus**
Begin mycophenolate mofetil (**MMF)** 15 mg/kg (PO) 3 times a day (TID) (maximum daily dose 3 g/day)
Begin G-CSF at 5 mcg/kg/day until absolute neutrophil count (ANC) is > 1500 for 3 days

(At least 24 hours after the last dose of PTCy)

↓

Day 28 Assess Chimerism in peripheral blood, assess graft versus host disease (GVHD)

↓

Day 35 Discontinue MMF

↓

Day 56 Assess Chimerism in peripheral blood and bone marrow (with biopsy)
Assess GVHD

↓

Day 180 Discontinue tacrolimus if no GVHD and full chimera
Evaluate disease
Assess Chimerism in peripheral blood, assess GVHD

↓

Day 365
Evaluate disease

Assess Chimerism in peripheral blood and bone marrow

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CHAPTER 1

1 BACKGROUND

1.1 Bone Marrow Transplantation (HSCT) and Immunosuppressive Therapy for SAA

Acquired severe aplastic anemia (SAA) is a rare, life-threatening hematopoietic stem cell disorder that manifests with pancytopenia.[1, 2] Bone marrow failure results from autoimmune destruction of hematopoietic stem cells.[1] Without definitive treatment, mortality from SAA approaches 70% at 2 years. Fungal infections are the leading cause of death; however, hemorrhage, evolution to clonal disease (myelodysplastic syndromes [MDS], leukemia, and paroxysmal nocturnal hemoglobinuria [PNH]), and transfusional iron overload are other causes of severe morbidity and mortality.

Immunosuppressive therapy (IST) has been the standard front-line treatment for SAA for decades, except for patients aged < 40 years with a suitable human leukocyte antigen (HLA)-matched sibling donor (MSD) where bone marrow transplantation (hematopoietic stem cell transplantation [HSCT]) is standard first-line therapy.[3, 4] The standard IST regimen (ATG and cyclosporine) has undergone modest improvements to decrease the time to hematologic response, [4, 5] but longer-term durability remains relatively unchanged even with the addition of eltrombopag. The hematopoietic response after IST is ~ 70% - 80% even with recent augmentation of IST by eltrombopag.[3, 4, 6] Failure-free survival, defined as patients alive and in remission without clonal disease more than 10 years after IST, remains < 40% in most series.[1, 3, 7-10] In the Phase 3 RACE trial (A prospective Randomized multicenter study comparing horse antithymocyte globulin (hATG) + Cyclosporine A (CsA) with or without eltrombopag as front-line therapy for SAA), event-free survival (defined as time from start of treatment to either relapse, death, treatment failure or clonal evolution [whichever occurs first]) for the ATG, cyclosporine, eltrombopag regimen was only 56% at 1 year and 46% at 2 years.[5] When IST fails, patients often require HSCT.

Unfortunately, complications following IST may negatively affect HSCT utilization, donor options, and post-HSCT outcomes. Among patients receiving IST, clonal evolution to MDS or acute myeloid leukemia (AML) occurs in about 13%.[11] The most common MDS-associated clonal cytogenetic abnormality after IST for SAA is monosomy 7, which has notoriously poor outcomes with HSCT.[12] IST failure can also lead to higher rates of donor specific antibodies and therefore, limit the availability of suitable mismatched donor (related or unrelated) options. Long-term immunosuppressive use with cyclosporine can also limit quality of life post-IST with orthopedic complications such as avascular necrosis, organ complications including renal failure, or pulmonary fungal infections.[13] All of these issues could preclude HSCT as an option for an individual patient with SAA. Although 90 out of 197 patients enrolled in the RACE Trial were non-responders after IST, only 23 patients proceeded to HSCT.[5] In contrast, successful allogeneic bone marrow transplantation (alloBMT) in SAA not only overcomes the complications of the disease, but also eliminates the risk of relapse and secondary clonal disease. Innovations in recent decades have steadily reduced the morbidity and mortality of adult patients undergoing transplantation from donors other than MSDs (alternative donor HSCT). Standard platforms exist that allow rapid hematopoietic reconstitution-- representing a cure in SAA.[14] Long-term historical survival after HSCT is ~ 90% in patients aged < 20 years, [15, 16] and 75% in older patients.[14, 16] Due to concerns for morbidity and mortality, HSCT with an unrelated or HLA-haploidentical (haplo) related donor is currently reserved following failure of IST in most centers.[17-23] However, whether alternative donor HSCT should be reserved only as salvage therapy following failure of IST or performed upfront is currently unknown. This multicenter clinical trial is intended to bring alternative donor HSCT to the forefront of therapy for all HSCT-eligible SAA patients.

1.2 Regimen for HSCT in SAA

For nearly 40 years, the treatment of choice for young patients with SAA has been MSD HSCT. This medical preference was related to rapid recovery of hematopoiesis, minimal complications, mitigation of clonal evolution rates, and impressive rates of overall survival (OS).[24] Cyclophosphamide (50 mg/kg/day × 4 days) with or without ATG, has traditionally been used as conditioning before these MSD HSCTs. Although this regimen is non-myeloablative, the immunosuppression is sufficient to allow engraftment in most cases. TBI and busulfan are avoided for MSD HSCT to reduce transplant-related complications such as mucositis, GVHD, second malignancies, and infertility. Survival rates following MSD allogeneic HSCT steadily improved since the 1970s largely because of improved supportive care, refined HLA typing, and better GVHD prophylaxis.[25] However, late HSCT-related complications such as chronic GVHD (cGVHD) occur in up to one-third of patients, with many of these patients requiring long-term therapy for their GVHD. In patients under 30 years of age, the event-free survival after HLA-matched sibling HSCT ranges from 70% to 90%. These reduced rates are predominantly due to GVHD (the rates of which steadily increase with age) and late graft failures.[26]

Patients without a MSD must choose an alternative donor – haploidentical relatives (siblings, parents, cousins, aunt, uncles, etc.), or HLA-matched or mismatched unrelated donors. Mixed chimerism or late secondary graft failure and GVHD remain obstacles to longer-term successful outcomes after alternative donor HSCT for SAA. These outcomes are ripe for improvement.

More recent research efforts in SAA HSCT have focused on transplant feasibility using mismatched donors to expand the donor pool. The most promising approach to facilitate engraftment and mitigate the risk of GVHD is the use of post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis. These regimens have also augmented the TBI dosing from 200 cGy to 400 cGy in 2019 to enhance engraftment, as learned from studies in sickle disease and MDS patients. These studies demonstrated success with haploidentical donors with > 90% full donor chimerism and < 10% GVHD.[27, 28] The use of PTCy has also resulted in decreased GVHD in the matched unrelated donor setting, with wide adoption of this GVHD prevention strategy for patients with both hematologic malignancies and non-malignant diseases.[29, 30]

There is prior experience with PTCY. In the BMT CTN 1502 trial, NCT02918292, reported the outcomes of 31 pediatric and adult patients transplanted using reduced-intensity conditioning, related HLA-haploidentical (haplo) donors, and post-transplantation cyclophosphamide-based graft versus host (GVHD) prophylaxis. Because the trial offered an alternative to individuals without fully matched unrelated donors, over 60% of the enrollment was from underrepresented race/ethnicity patients. Twenty-four patients were alive with engraftment at 1 year with an additional patient alive with autologous recovery of hematopoiesis. Patients experienced low rates of graft versus host disease, with no severe chronic GVHD. Key post hoc analysis showed higher cell doses from bone marrow harvests are crucial to the success of this approach. This practice changing study expands the donor pool and access to BMT across all populations. This successful trial led to the obvious next step of this upfront trial. The trial did, however, only use 200 cGY TBI. Given the rarity of SAA, there have been no comparative studies of conditioning or GVHD prophylaxis regimens.

1.3 Supportive Pilot Data

Haploidentical Transplantation

In a single-center study published in 2023, [28] the authors demonstrated an OS rate of 92% at 3 years using HLA-haplo HSCT for pediatric and adult participants with treatment-naïve SAA. The OS for those receiving 400 cGy was 100%. This pilot study opened for enrollment in August 2016 and continued through July 2020. Twenty participants were treated on trial, and thereafter 7 participants were treated identically for further pilot data in the recent publication. Median follow-up for all patients was 40.9 months (95% confidence interval [CI]: 29.4, 55.7 months). The minimum follow-up was 6.0 months, and the maximal follow-up was 73.8 months. Of the

27 transplanted participants, 14 (52%) were male, with 37% of the cohort self-reported as non-white. There were 3 (11%) participants who were Asian/ Pacific Islander, 6 (21%) were Black, and 1 (3%) was mixed or other race with 1 (3%) reporting as Hispanic. The median age at enrollment was 25 (range, 3-63, interquartile range [IQR], 17-52) years. The median age of the haplo donors was 30 years (range, 13-56, IQR, 26-44). Twenty-five participants were alive, of whom 24 had sustained engraftment at 1 year, showing a feasibility of 88.9% (95% CI: 70.8%, 97.7%) of getting to BMT, engrafting and having graft present at 1 year. The OS for the 27 participants was 92% (95% CI: 83%,100%) at 1, 2, and 3 years.

The proportion of participants alive and engrafted at one year (graft failure-free survival) was 89% (95% CI: 77%, 100%). In this trial, the TBI dose was increased from 200 to 400 cGy to reduce graft failure after graft loss in 3 of the first 7 patients. All 20 consecutive participants who received 400 cGy are alive and well with > 95% donor engraftment in whole blood and CD3 compartments.

Two (6%) deaths were reported post-transplant. Two participants died of infection (cytomegalovirus [CMV] in an adult patient with secondary graft failure and Epstein-Barr virus [EBV] in a pediatric participant with primary graft failure). A third participant had secondary graft failure but later became 100% chimeric using the identical conditioning platform and a second HLA-haplo HSCT.

Twenty-six of 27 participants achieved neutrophil recovery by Day 28. The median time to neutrophil recovery was 17 (range 14-88) days. The Day 28 cumulative incidence of neutrophil recovery was 96% (95% CI: 87%-100%). The median time to platelet recovery was 25.5 days with 90% transfusion independence by Day 100. The Day 100 incidence of platelet recovery was 88% (95% CI: 74%-100%). The median time to red cell recovery was 25.5 days with 90% transfusion independence by Day 60.

Eighteen (67%) individual participants experienced infections post-transplant. Of a total of 39 infection events, 37 were Grade 2 and 2 were Grade 5 by Common Terminology Criteria for Adverse Events (CTCAE) grading. Both of the documented Grade 5 infections occurred in the 2 participants who lost grafts and died of viral infection in that setting. The majority of documented infections were viral reactivation documented by polymerase chain reaction (PCR), followed by bacterial infections. Four (4) participants had documented fungal infections and 2 were in participants with graft failure. These participants did not pursue a 2nd transplant. Eleven (11) participants experienced CMV reactivation with 6 (55%) requiring therapy. One (1) participant had documented EBV-associated post-transplant lymphoproliferative disease (PTLD) that developed following secondary graft failure.

Rates of acute GVHD (aGVHD) and cGVHD were both less than 10%, and no participant developed Grade 3-4 acute nor moderate/severe cGVHD. The cumulative incidence of Grade II-IV aGVHD at Day 100 was 7% (95% CI: not applicable [NA], 17%) and cGVHD at 2 years was 4% (95% CI: NA, 11%).

Unrelated Donor Transplantation

The identical regimen published in the haplo setting [28] as above has also been used in the unrelated donor setting. Also in the single-center setting, 11 adult participants (median age: 25 years; range: 24 to 38 years) with treatment-naïve or refractory SAA were transplanted with matched donor marrow grafts (related and unrelated) with the Baltimore regimen as previously published.[31, 32]

The median follow-up of this 11-participant cohort was 53.8 (range: 6-99) months. The OS for 11 participants is 100% at 1 and 2 years, and 90% (95% CI: 73%, 100%) at 3 years. The median time to neutrophil recovery was 17 (range: 14-41) days. The Day 28 cumulative incidence of neutrophil recovery was 91% (95% CI: 69%-100%). The median time to platelet recovery was 26 days with 91% transfusion independence by Day 100. The median time to red cell recovery was 31 days with 91% transfusion independence by Day 100. This is quite consistent with published timelines from other donor sources.[31] Ten (10) of the 11 participants had sustained

> 95% donor chimerism in both whole blood and CD3 compartments through one year. Nine (81%) participants experienced infections post-transplant. Of a total of 14 infection events, 11 were Grade 2 and 3 were Grade 3, again by CTCAE grading. Two (2) of the documented Grade 3 infections occurred in a participant with secondary graft failure from adenovirus. Two (2) participants experienced CMV reactivation evidenced by viremia treated to undetectable by Day 100, and no patients had EBV. The cumulative incidence of Grade II-IV aGVHD at Day 100 was 9% (95% CI: NA, 27%), while the cumulative incidence of cGVHD at 2 years was 19% (95% CI: NA, 45%); no case of GVHD was beyond Grade 2 skin and mouth, and all lacked any other organ involvement.[31] Additionally, the standard of care for GVHD prophylaxis in patients receiving matched unrelated donor and mismatched donor HSCT has also recently shifted with a rapid rise in the use of PTCy.[33] This shift is due in part to the work of the BMT- CTN and others with studies showing superior outcomes with lower rates of GVHD utilizing PTCy-based GVHD prophylaxis.[34-37]

Other groups have reported comparably low GVHD rates when PTCy is used for GVHD prophylaxis in the setting of mismatched unrelated donors.[38, 39] An NMDP study reported on 80 patients that received mismatched unrelated donor bone marrow transplantation for hematologic malignancies (7/8 HLA match in 61%, 6/8 HLA-matched in 24%, remaining 4-5/8 HLA-matched). Overall survival at 1-year was 76% (90%CI 67.3-83.3) and did not differ by HLA match grade (7/8 vs 6/8 or less). Survival outcomes were compared to contemporary haploidentical controls reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) and found to be similar. The results of this study prompted a larger phase II clinical trial that is ongoing (NCT 04904588) utilizing peripheral blood stem cell grafts.

1.4 Summary

In conclusion, a major challenge in treating acquired SAA is the management of patients who desire a path to a cure but do not have a MSD. Although IST produces hematologic recovery in a substantial proportion of patients, in many of those patients, recovery is not complete, and all remain at risk for subsequent hematologic disorders such as MDS or AML. Many patients have historically been deemed ineligible for HSCT simply because they lack a suitable donor. Here, we seek to increase options for these patients, allowing HSCT to be considered as a potential treatment by using a novel GVHD prophylaxis strategy with PTCy that allows expansion of the donor pool to include haplo donors and unrelated donors (URDs). We have chosen age 3 years to start this protocol as this was the youngest patient in the pilot. We hypothesize that this approach will improve survival without transplant-associated morbidity by demonstrating low toxicity, reducing rates of GVHD and showing rapid hematologic recovery without graft failure making HSCT a viable option for upfront treatment of all patients. Additionally, we will evaluate key secondary endpoints traditionally used to evaluate success of upfront IST such as overall survival (OS), failure-free survival (FFS) and hematologic response according to the National Institutes of Health (NIH) criteria.[40] Clinical comparison of these endpoint measures with current results achieved with upfront IST will help in determining if a future randomized trial comparing IST with this approach to HSCT is warranted.

CHAPTER 2

2 STUDY DESIGN

2.1 Study Overview

This study is a prospective Phase II trial to assess if it is effective for previously untreated SAA participants to be transplanted using non-myeloablative conditioning and PTCy. This is a parallel cohort study comprised of two cohorts: haplo transplant and URD transplant. The accrual goal is 30 participants enrolled and starting protocol-specified conditioning in each cohort, yielding 60 participants in total.

2.2 Hypotheses and Objectives

2.2.1 Hypotheses

Primary Hypothesis:

Using the regimen described below, the point estimate of GVHD-free, failure-free survival (GFFS) at 1 year after initiation of conditioning will be greater than or equal to 75% in participants who receive a bone marrow transplant from a haplo donor or URD for first-line therapy in SAA.

2.2.2 Objectives

Primary Objective:

Estimate GVHD-free failure-free survival (GFFS) (a composite end point of survival without Grade III-IV aGVHD, cGVHD requiring immunosuppression, or primary or secondary graft failure requiring second definitive therapy) at 1 year after initiation of conditioning. GFFS will be evaluated separately for each transplant cohort.

Secondary Objectives:

1. Estimate OS at 1 year after initiation of conditioning.
2. Estimate FFS (a composite end point of survival without initiation of treatment with a second definitive therapy for curative intent) at 1 year after initiation of conditioning.
3. Estimate the probability of being engrafted (i.e., without primary or secondary graft failure) and alive at 1 year after initiation of conditioning.
4. Estimate the cumulative incidences of neutrophil recovery at Day +28 and Day +56 post-HSCT, platelet recovery at Day +100 post-HSCT, and red blood cell recovery at Day +100, Day +180, and Day +365 post-HSCT.
5. Estimate the cumulative incidences of primary, secondary, and any graft failure at 1 year post-HSCT.
6. Estimate the hematologic response classification according to the NIH criteria at Day +100, Day +180, and Day +365 post-HSCT.
7. Estimate the cumulative incidences of Grade II-IV and Grade III-IV aGVHD at Day +100 post-HSCT.
8. Estimate the cumulative incidences of all cGVHD and cGVHD requiring immunosuppression at 1 year post-HSCT.

Exploratory Objectives:

1. Describe the pace and quality of immune reconstitution by measuring CD4, CD19, and CD56 counts pre-HSCT and at Day +100, Day +180, and Day +365 post-HSCT.
2. Describe the rates of specific infectious complications (CMV viremia and disease, EBV viremia, and PTLD) within the first year after HSCT.
3. Quantify how many available donors each patient has, including 8/10, 9/10, and 10/10 unrelated donors and all haploidentical donors.
4. Describe the time to enrollment after HLA typing of the recipient.
5. Describe the time from diagnosis of SAA until 1) start of conditioning and 2) until HSCT.
6. Describe total and CD34+ cell doses for haploidentical and unrelated donors.
7. Describe times to donor activation, donor selection, start of conditioning, and transplant from enrollment.
8. Describe the quality of life for SAA participants treated on this protocol.

2.3 Participant Eligibility Criteria for Enrollment

2.3.1 Participant Inclusion Criteria

1. Age 3 years to 75 years (see Section 2.5).
2. Confirmed diagnosis of acquired SAA defined as:[41]
    a. Bone marrow cellularity < 25% **or** variable marrow cellularity but with < 30% residual hematopoietic cells deemed HYPOcellular for age AND
    b. Two (2) out of 3 of the following (in peripheral blood).
        i. Neutrophils < 0.5 $x10^9$/L
        ii. Platelets < 20 $x10^9$/L
        iii. Reticulocyte count < 20 $x10^9$/L (< 60 x 10^9/L using an automated analysis)
3. No suitable fully matched related donor as per Investigator's discretion (6/6 match for HLA-A and B at intermediate or high-resolution and DRB1 at high-resolution using deoxyribonucleic acid [DNA]-based typing) available.
4. Available donor per Section 2.4.
5. Participant and/or legal guardian must sign informed consent.
6. Adequate organ function defined by institutional transplant standards or defined as below:
    a. Cardiac: Left ventricular ejection fraction (LVEF) at rest > 40% with no clinical signs of cardiac failure. For participants aged < 13 years, shortening fraction (SF) ≥ 26% by echocardiogram or multigated acquisition (MUGA) may be substituted for LVEF.
    b. Hepatic: Total bilirubin < 2.0 mg/dL unless Gilbert's disease is present
    c. Renal:
        i. For participants ≥ 13.0 years of age at the time of enrollment: estimated creatinine clearance (CrCl) > 60 mL/minute (per institutional standard). Please refer to Body Weight calculations in Appendix C.

ii. For participants < 13.0 years of age at enrollment: glomerular filtration rate (GFR) estimated by the updated Schwartz formula[1] ≥ 90 mL/min/1.73 m^2. If the estimated GFR is < 90 mL/min/1.73 m^2, then renal function must be measured by 24-hour creatinine clearance or nuclear GFR, and must be > 50 mL/min/1.73 m^2.

d. Pulmonary:

i. For participants ≥ 13.0 years of age:

- Diffusing capacity of the lung for carbon monoxide (DLCO, corrected/adjusted for hemoglobin [Hb]) > 50%, **or**
- Spirometry with forced expiratory volume 1 (FEV1) > 50% predicted (without administration of bronchodilator) **and** forced vital capacity (FVC) > 50% predicted.

ii. For participants < 13.0 years of age unable to perform pulmonary function tests (PFTs) due to age or developmental ability: (1) no evidence of dyspnea at rest **and** (2) no need for supplemental oxygen **and** (3) O_2 saturation > 92% on room air at sea level (with lower levels allowed at higher elevations per established center standard of care [e.g., Utah, 4,200 feet above sea level, does not give supplemental oxygen unless below 90%]).

7. Karnofsky or Lansky performance status ≥ 60%.
8. Females and males of childbearing potential must agree to practice 2 effective methods of contraception at the same time or agree to abstinence.

2.3.2 Participant Exclusion Criteria

1. Inherited bone marrow failure syndromes such as Fanconi anemia and short telomere syndromes must be ruled out according to center standards. It is recommended that functional testing for Fanconi Anemia (di-epoxybutane [DEB] chromosomal breakage analysis) and telomere length assessment be performed. If available, genetic panels for inherited bone marrow failure syndromes can be considered as an alternative to functional testing.
2. Clonal cytogenetic abnormalities consistent with pre-MDS or MDS on marrow examination (e.g., monosomy 7 and other MDS-defining changes per recent pathology guidelines).[42, 43]
3. Formal diagnosis of MDS by World Health Organization (WHO) 2022 or International Consensus Classification (ICC).[42, 43]
4. Recipient positive for HLA antibodies against a mismatched HLA in the selected donor determined by the presence of donor specific HLA antibodies (DSA) to any mismatched HLA allele/antigen at any of the following loci (HLA-A, -B, -C, –DRB1, DRB3, DRB4, DRB5, -DQA1, -DQB1, -DPA1, -DPB1) with median fluorescence intensity (MFI) >3000 by microarray-based single antigen bead testing. In patients receiving red blood cell or platelet transfusions, DSA evaluation must be performed or repeated post-transfusion and

[1] Schwartz formula: CrCl (mL/min/1.73m^2) = [length (cm) x k] / serum creatinine

k = 0.45 for infants 1 to 52 weeks old
k = 0.55 for children 1 to 13 years old
k = 0.55 for adolescent females 13-18 years old
k = 0.7 for adolescent males 13-18 years old

immediately prior to initiation of recipient preparative regimen to ensure there is confirmation of no DSA to the selected donor when conditioning starts.

5. Prior desensitization attempt for HLA antibodies to chosen donor. Any intervention with the sole intent to reduce the level of HLA DSA, (e.g., plasmapheresis, intravenous immunoglobulin [IVIG], MMF, etc.) would constitute a desensitization attempt.
6. Prior treatment for SAA (e.g., immunosuppressive therapy using ATG, calcineurin inhibitors [CNIs], thrombopoietin receptor agonists or androgens). Short courses of steroids or IVIG that were not explicitly administered for SAA therapy will be allowed.
7. Prior allogeneic stem cell transplant.
8. Prior solid organ transplant.
9. Known life-threatening reaction (i.e., anaphylaxis) to Thymoglobulin® (Sanofi) that would prohibit use for the participant as this study requires use of the Thymoglobulin® (Sanofi) preparation of ATG.
10. Uncontrolled bacterial, viral, or fungal infection at the time of enrollment. Uncontrolled is defined as currently taking medication and with progression or no clinical improvement on adequate medical treatment.
11. Female participants who are pregnant, as detected using a pregnancy test as per institutional practice, or breast-feeding.
12. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent > 5 years previously will be allowed. Cancer treated with curative intent ≤ 5 years previously will not be allowed unless approved by the Protocol Chairs and/or Protocol Officer.

Of note, participants with seropositivity for the human immunodeficiency virus (HIV) may be considered if viral load is undetectable. Similarly, carriers of hepatitis B (HepB) or hepatitis C (HepC) may not have a detectable viral load of HepB virus or HepC virus.

Participants with HIV that is well-controlled on combination antiretroviral therapy and no AIDS-related complications within the past 12 months are eligible.

Infections other than HIV:

- Prior infections must be controlled
- HepB participants are eligible if on effective suppressive therapy and otherwise meet inclusion/exclusion criteria
- HepC participants are eligible if otherwise meet inclusion/exclusion criteria

2.4 Donor Selection Criteria

1. Donor selection is based on HLA typing and relationship to recipient (Table 2.4.1).
2. When more than one donor is available, the donor with the lowest number of HLA allele mismatches will be chosen unless there is HLA incompatibility due to HLA antibodies or a medical reason. In cases where there is more than one donor with the least degree of mismatch, donors will be selected based on the most favorable combination of HLA compatibility and ABO compatibility. Prioritization is given to the lowest number of mismatches in the Host Versus Graft (HVG) direction to minimize the risk of graft failure.[44]

3. All Donors must be typed at high-resolution for a minimum of HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 and recommend -DQA1 and DPA1 for cases with possible participant –DQA1 or DPA1 anti-HLA antibodies.
    a. For URDs, must be unrelated to the participant and high-resolution HLA-matched at 8/10, 9/10, or 10/10 (HLA-A, -B, -C, -DRB1, -DQB1) with up to one mismatch allowed at HLA-A, -B, -C, or -DRB1.
    b. For Haplo Donors, available relative of the patient who is a haploidentical match, including biological parents, siblings or half siblings, children, uncles/aunts, first cousins, etc. Eligible haploidentical donors will have 2-4 mismatches if HLA-A, -B, -C, and -DRB1 typing is used; 2-5 mismatches if HLA-A, -B, -C, -DRB1, and -DQB1 typing is used; and 2-6 mismatches if HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 typing is used. A unidirectional mismatch in either the graft versus host or host versus graft direction is considered a mismatch. The donor and recipient must demonstrate that they are a full haplotype match by being identical at a minimum of one allele (at high-resolution DNA based typing) at the following genetic loci: HLA-A, -B, -C, and DRB1 if 8 allele typing is used; HLA-A, -B, -C, -DRB1, and -DQB1 if 10 allele typing is used; and HLA-A, -B, - C, -DRB1-, DQB1, and -DPB1 is 12 allele typing is used by the local center.
4. Age $\geq$ 18 years at the time of signing informed consent.
5. Meet the medical suitability requirements of donor registries' (unrelated) or individual sites' (haploidentical) for bone marrow (BM) donation.
6. Must undergo eligibility screening according to current Food and Drug Administration (FDA) requirements. Donors who do not meet one or more of the donor screening requirements may donate under urgent medical need.
7. Must agree to donate BM.
8. Additional considerations for donor selection should be given to:
    a. Prioritize donors under 35 years of age but depends on clinical situation, e.g., BM and size of donor
    b. Avoid donors where the estimated cell dose (total nucleated cells [TNC]) will be $<2.5x10^8$/kg recipient weight. Cell dose can be estimated using the following NMDP formula:[45] Estimated maximum donor volume[2] x 0.183e8/mL = Estimated total nucleated cells
    c. ABO compatibility
    d. CMV matching
    e. B-Leader genotype for HLA-B mismatched donors
    f. Male over female for larger donor weight or donor weight if known
    g. Domestic donors over international donors for speed of acquisition

[2]Estimated maximum donor volume (mL) = Donor weight (in kg) x 20 mL/kg

Table 2.4.1: Donor Selection

Suggested Haplo Donor Selection Algorithm
NOTE: Any donor chosen must be medically and psychologically fit and consent to donation. The list below are considerations and are not a hierarchy. Direct questions may be addressed to the protocol chairs.
• No anti-donor specific HLA antibody as described in Section 2.3.2, criterion 4
• Younger donor over older donor -- Degree of HLA match or degree of kinship are not prioritized
• ABO compatible over minor incompatible over major incompatible
• CMV-compatible (seronegative into seronegative or seropositive into seropositive) over CMV-incompatible
Suggested Unrelated Donor Selection Algorithm[46]
• High-resolution matches for Antigen Recognition Domain matching level (ARD), for 7 matched alleles if applicable • Select HLA-C*03.03 vs C*03:04 mismatch, if present • No other preference for mismatched loci (HLA-A/B/C/DRB1) or other allele combinations
• Younger donor over older donor
• Select matched/permissive DPB1 mismatch based on the algorithm developed by Crivello et al [47, 48] (https://www.ebi.ac.uk/ipd/imgt/hla/matching/dpb_v2/)
• Minimize mismatches at HLA-DRB3/4/5 and HLA-DQB1
• Select donor with single allele mismatched at patient's homozygous locus (HLA-A/B/C/DRB1), if applicable
• Avoid mismatches of allotypes targeted by DSAs, including DQA1 and DPA1 as described in Section 2.3.2, criterion 4
• Avoid donors where estimated cell dose will be <2.5x10^8/kg. Cell dose can be estimated using the following NMDP formula: [45] Estimated maximum donor volume[1] x 0.183e8/mL = Estimated total nucleated cells
• Prioritize domestic donors over international donors
Transplant center practice may differ in additional considerations to use in the selection among multiple donors equivalent for the characteristics above.
Abbreviations: ARD: Antigen Recognition Domain; CMV: cytomegalovirus; DSA: donor specific HLA antibodies; HLA: human leukocyte antigen; URD: unrelated donor [1]Estimated maximum donor volume (mL) = Donor weight (in kg) x 20 mL/kg

2.5 Site Eligibility

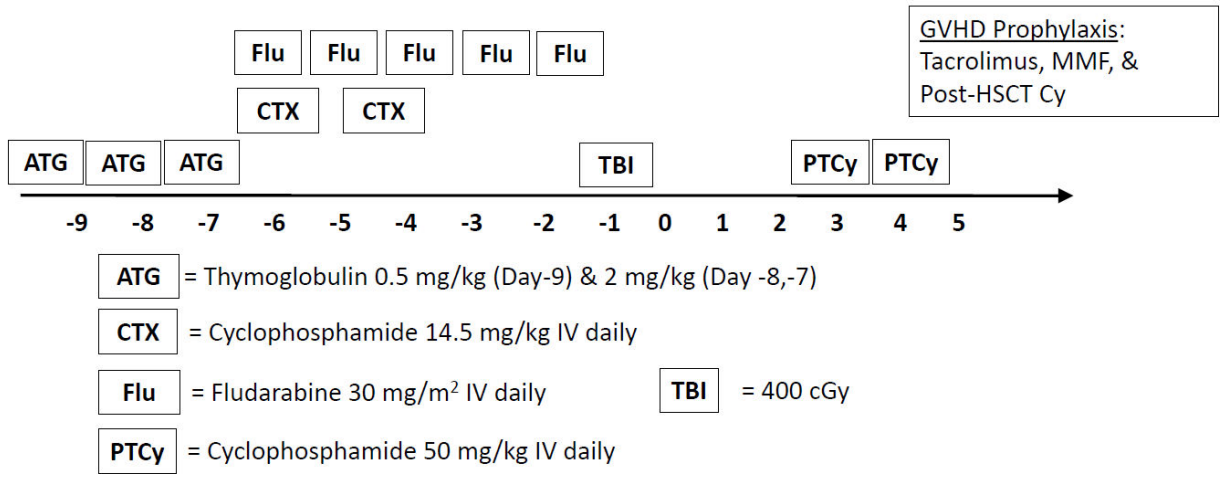
1. PTCTC sites who currently have the TransIT Trial open (or planned to open) and are Pediatric-only sites will not open this trial until TransIT completes enrollment.
2. PTCTC TransIT sites that have an adult HSCT program may activate this trial for participants older than 25 years.

2.6 Treatment Plan

2.6.1 Conditioning and GVHD Prophylaxis

The conditioning and GVHD prophylaxis schematic is provided in Figure 2.6.1. Refer to Appendix C for weight-based dosing adjustments as outlined in this section by medication.

Figure 2.6.1: Conditioning and GVHD Prophylaxis Schematic



2.6.1.1 Conditioning for Bone Marrow Recipients

2.6.1.1.1 Fludarabine

The fludarabine dose will be 30 mg/m^2 intravenously (IV) daily for 5 days from Day -6 to Day -2 (total dose received 150 mg/m^2). Fludarabine will be dosed on body surface area based upon the recipient's actual body weight if the participant is < 125% of ideal body weight (IBW). For participants ≥ 125% of IBW, fludarabine will be dosed based upon the recipient's adjusted ideal body weight (AIBW) as per Appendix C. For participants who have an estimated or measured creatinine clearance < 70 mL/min/1.73 m^2, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the participant's creatinine changes.

2.6.1.1.2 Pre-HSCT Cyclophosphamide

The cyclophosphamide dose will be 14.5 mg/kg IV daily for 2 days from Day -6 to Day -5 and administered as a 1-2 hr infusion (total dose received 29 mg/kg). Cyclophosphamide dosing should be based on recipient's actual body weight in all participants < 125% of IBW. For participants ≥ 125% of IBW, cyclophosphamide will be dosed based upon the recipient's adjusted ideal body weight (AIBW) as per Appendix C. Hydration, as well as doses and schedule for uroprotective agents (i.e., mesna), may be administered per institutional practice. Mesna has generally been utilized for the Day +3 and Day +4 post-HSCT cyclophosphamide doses but not for the lower pre-HSCT doses.

2.6.1.1.3 Total Body Irradiation

TBI is to be delivered in a **single fraction** of 400 cGy on Day -1. TBI may be delivered from either linear accelerator or Cobalt sources (per institutional practice).

2.6.1.1.4 Thymoglobulin®

The Thymoglobulin® (Sanofi) preparation of rabbit ATG will be dosed upon actual body weight. The dose will be 0.5 mg/kg IV on Day -9 over 6 hrs and 2 mg/kg IV on Days -8 and -7 over 4 hrs. Premedication should be administered per institutional protocol. **Note: Thymoglobulin® (Sanofi) is the required preparation of ATG for this study and will be provided by Sanofi. Other supplies of ATG may not be used.**

2.6.1.2 Marrow Product Handling & Infusion

Participants will receive unprocessed marrow unless there is a major ABO incompatibility, in which case red blood cells will be depleted from the donor marrow using institutional practices. Institutional practices will determine if there will be processing for minor ABO incompatibilities. Donor BM will be harvested with a target yield of 4 x 10^8 nucleated cells per kilogram of recipient IBW, and a recommended minimum yield of 2.5 x 10^8 nucleated cells per kilogram of recipient IBW. It is recommended that no more than 10 mL per aspirate be taken. In addition to calculating the TNC dose per kilogram, a sample of the product to be infused will be sent for flow cytometry to determine the content of CD34+ cells. The use of cryopreserved marrow is not permitted. Please refer to Appendix F for additional BM harvesting guidelines.

The infusion will be done per institutional standards.

Note: The participant is not to receive steroids as an antiemetic or any other immunosuppressive agent from Day 0 until at least 24 hours after completion of Day +4 cyclophosphamide dose unless used for adrenal support or during a medical emergency (e.g., treatment of anaphylaxis). Guidelines for management of suspected cytokine release syndrome (CRS) are provided in Appendix K. In the event that a participant requires steroids, please notify the Emmes Protocol Coordinator.

2.6.1.3 GVHD Prophylaxis

2.6.1.3.1 Post-HSCT Cyclophosphamide

Cyclophosphamide 50 mg/kg IV daily will be given for 2 days on Days +3 and +4 (total dose received 100 mg/kg) after transplantation. The first dose of cyclophosphamide must be administered 60-72 hours after the start of the marrow infusion. Cyclophosphamide and mesna will be given post-transplant and dosed based on IBW or actual body weight, whichever is less. For participants ≥ 125% of IBW, cyclophosphamide will be dosed based upon the recipient's adjusted ideal body weight (AIBW), as per Appendix C. Hydration, as well as doses and schedule for uroprotective agents (i.e., mesna), should follow local institutional practice. Mesna has generally been utilized for the Day +3 and Day +4 post-HSCT cyclophosphamide doses but not for the lower pre-HSCT cyclophosphamide doses.

2.6.1.3.2 Tacrolimus

Tacrolimus IV or by mouth (per os, PO) should be started on Day +5 (24 hours after the end of the infusion of post-HSCT cyclophosphamide) and administered per institutional standards to maintain a trough level of 10-15 ng/mL. The recommended IV starting dose is 0.03 mg/kg/day either as a continuous infusion or divided into q12 hour IV bolus dosing based on actual body weight. PO equivalent dosing is acceptable at a suggested starting dose of 0.05-0.1 mg/kg/dose PO BID. If the participant converts from IV to PO once therapeutic levels are achieved, a suggested IV to PO conversion of 1:3 can be used or per institutional standards. Tacrolimus will be continued at therapeutic doses until at minimum Day +180 or longer per institutional preference. If there is no evidence of GVHD, then taper as per institutional standard. Please see Section 2.6.4.2.5 on Tacrolimus for further information.

2.6.1.3.3 Mycophenolate Mofetil

The MMF dose will be 15 mg/kg PO TID up to 1 g TID (or IV equivalent) starting on Day +5 (24 hours after the end of the infusion of post-HSCT cyclophosphamide; max dose 3000 mg/day) and will be discontinued after the last dose on Day +35 or may continue if active GVHD is present.

2.6.1.3.4 Growth Factor

Granulocyte colony stimulating factor (G-CSF) will be given IV or subcutaneously (SQ) starting on Day +5 (24 hours after the end of the infusion of post-HSCT cyclophosphamide) at 5 mcg/kg/day (rounded to nearest vial size) until absolute neutrophil count (ANC) is > 1500 for 3 days. Pegfilgrastim (Neulasta®) and granulocyte macrophage colony stimulating factor (GM-CSF) are not permitted.

2.6.2 GVHD Treatment

In the event of the development of either aGVHD or cGVHD, therapy will be at the discretion of treating centers. For participants with aGVHD or cGVHD refractory to standard of care treatments, investigational agents may be considered. Discussion with the protocol chair or protocol officer is encouraged.

2.6.3 Supportive Care

2.6.3.1 Infectious Disease Prophylaxis

Antifungal prophylaxis will be administered according to institutional practices. It is important to follow levels of cyclosporine and tacrolimus for participants receiving one of the azole antifungal medications. Please see Section 2.6.4.2.5.

Pneumocystis jiroveci pneumonia (PJP) prophylaxis will be administered according to institutional practices. Recommendations include starting approximately 1-month post-HSCT (or later if white blood cells [WBCs] not recovering) and continuing until the participant has been off of all immunosuppressive medications for at least 3 months.

Viral prophylaxis for herpes simplex virus (HSV) and varicella zoster virus (VZV) will be administered according to institutional practices. Recommendations include continuation for at least 1 year post-HSCT and while on immunosuppressive medications.

Prophylaxis for CMV with letermovir or institutional standards for participants at risk of CMV reactivation, defined as either CMV immunoglobulin G (IgG) positive pre-transplant, or CMV negative but receiving a CMV positive stem cell product as well as continuation of CMV monitoring through weaning of all immunosuppression is strongly recommended. Viral prophylaxis for EBV (including use of rituximab) may be administered according to institutional practices.

Prophylactic and empiric antibiotics as well as IVIG will be administered according to institutional practices. Re-immunization may be performed according to institutional practices.

2.6.3.2 Infectious Disease Monitoring

CMV viremia as tested by DNA PCR will be monitored at minimum weekly after transplant until Day +100. Participants who are viremic or show evidence of end organ CMV disease may be treated according to institutional practices. For participants at risk of CMV reactivation, defined as either CMV immunoglobulin G (IgG) positive pre transplant, or CMV negative but receiving a CMV positive stem cell product, prophylaxis with letermovir or institutional standards as well as continuation of CMV monitoring though weaning of all immunosuppression is strongly recommended.

EBV viremia as tested by DNA PCR will be monitored at minimum weekly after transplant until Day +100. If the participant becomes viremic, as determined by the treating provider, the recommendation is to use rituximab (375 mg/m^2 IV x 1) or treat according to institutional practice. If the participant develops persistent EBV viremia or signs/symptoms of EBV-related PTLD despite rituximab administration, treatment is recommended according to institutional practice.

Adenovirus viremia as tested by DNA PCR will be monitored at minimum weekly after transplant until Day +100. Participants who are viremic or show evidence of adenovirus disease may be treated according to institutional practices.

Screening for additional infections, including HHV-6, may be done per institutional practice but is not mandated by protocol. In addition, all Grade 2 and 3 infections, according to the BMT CTN Technical Guideline (see Appendix H for infection grading), will be reported on the infection data capture form up to 1 year post HSCT.

2.6.3.3 Management of Graft Failure

Participants experiencing primary or secondary graft failure or poor graft function are managed according to institutional practices.

For this protocol, lineage-specific, myeloid, and T cell chimerism measurements are required. Myeloid engraftment might not proceed at the same rate as T cell engraftment. In the presence of neutrophil recovery, a participant who achieved a myeloid chimerism greater than or equal to 5% donor with < 5% donor chimerism in the T cell compartment is not considered a primary graft failure as recovery of the myeloid compartment has priority in aplastic anemia.

In the event that Day 100 chimerism results in less than 50% donor in either myeloid or T cell compartment, additional lineage-specific chimerism testing should be performed every 4 weeks or as clinically indicated until the chimerism is greater than or equal to 50% donor and/or remains at a constant range for 3 consecutive tests.

Patients not meeting graft failure but having sustained cytopenia of 2 or 3 lineages for over 2 weeks and meeting the following criteria may be treated as having poor graft function (based on the combined European Society for Blood and Marrow Transplantation [EBMT] and American Society for Transplantation and Cellular Therapy [ASTCT] definitions):[49, 50]

- frequent dependence on blood/platelet/growth factor support, and
- with full donor chimerism of > 95%, and
- hypoplastic-aplastic BM, if performed, and
- absence of other explanations, such as drugs or infections.

Management of graft failure and poor graft function is per institutional standards. Mixed chimerism not fitting the definition of graft failure should be managed per Appendix G.

2.6.3.4 Management of ATG Intolerance

Participants who experience a new, severe, or life-threatening reaction to ATG and are therefore unable or unwilling to receive the full planned cumulative dose will continue to be evaluated for the study, but their conditioning regimen may then be altered per local Investigator discretion with documentation of the deviation in the data system.

2.6.4 Risks and Toxicities

2.6.4.1 General

The agents being used in the study are used extensively in the HSCT setting and have well-defined toxicity profiles. In addition, there are many expected toxicities of allogeneic HSCT. The following are examples of toxicities that are serious but not unexpected: Grade 4 cytopenias; neutropenic fever and sepsis; bacterial, fungal, and viral (including CMV, Polyomavirus [BK virus]) infection; severe mucositis; severe GVHD; hepatic veno-occlusive disease; pulmonary toxicities; hemorrhagic cystitis; transplant-associated thrombotic microangiopathy (TA-TMA), renal insufficiency; bleeding without hemodynamic compromise.

2.6.4.2 Drug Information

2.6.4.2.1 Fludarabine

Fludarabine is a purine analog antimetabolite. Side effects of fludarabine include:

- Cardiac: edema
- Gastrointestinal: vomiting, anorexia, nausea, mucositis
- General: fatigue, fever, chills
- Hematologic: anemia, thrombocytopenia, neutropenia
- Hepatic: increased liver function tests
- Neurologic: paresthesia, confusion, seizure, agitation, visual disturbances, pain, coma
- Pulmonary: cough, shortness of breath
- Renal: renal impairment, hematuria
- Miscellaneous: infection, general organ damage, hearing loss, rash, allergic reaction

Dose adjustments: Dose adjustments of fludarabine are required for renal insufficiency, prior brain radiation, prior intrathecal chemotherapy, and weight (see Section 2.6.1.1.1).

2.6.4.2.2 Cyclophosphamide & Mesna

Cyclophosphamide is an alkylating agent whose metabolites form cross-links with DNA resulting in cell cycle-nonspecific inhibition of DNA synthesis and function. Cyclophosphamide side effects include:

- Cardiac and vascular: heart failure (which can result in edema, effusion, dyspnea)
- Cutaneous: alopecia, rash, hyperpigmentation of skin and nails
- Gastrointestinal: nausea, vomiting, diarrhea, anorexia, abdominal pain, mucositis, stomatitis
- General: lethargy
- Hematologic: leukopenia, thrombocytopenia, anemia
- Pulmonary: pulmonary fibrosis
- Renal: renal impairment
- Endocrine: amenorrhea, gonadal function impairment, sterility, syndrome of inappropriate antidiuretic hormone secretion (SIADH) - with associated cerebral edema
- Genitourinary: hemorrhagic cystitis
- Miscellaneous: infection, allergic reaction, secondary malignancy

Dose adjustments: Dose adjustments for cyclophosphamide will be made for weight (see Section 2.6.1.3.1).

Mesna (sodium-2-mercapto ethane sulphonate) is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxasophosphorines (cyclophosphamide and ifosfamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxasophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxasophosphorines.

The total daily dose of mesna is determined per institutional practice.

At the doses used for uroprotection, mesna is virtually non-toxic. However, potential adverse effects include nausea, vomiting, diarrhea, abdominal pain, altered taste, rash, itching, headache, joint or limb pain, hypotension, and fatigue.

2.6.4.2.3 Thymoglobulin®

Thymoglobulin® (Sanofi) is a rabbit preparation of ATG. Thymoglobulin side effects include:

- Cardiovascular: tachycardia, hypertension, hypotension
- Cutaneous: rash, itching
- Endocrine: hyperkalemia, hyperphosphatemia, hypokalemia, acidosis
- Gastrointestinal: nausea, vomiting, abdominal pain, diarrhea, constipation
- Hematologic: anemia, thrombocytopenia, leukopenia, febrile neutropenia
- Hepatobiliary: transaminases increased
- Musculoskeletal: myalgia, arthralgia, weakness
- Neurologic: headache, insomnia, anxiety, pain
- Respiratory: dyspnea
- Miscellaneous: infection, fever, infusion reaction, allergic reaction including anaphylaxis and anaphylactic shock, CRS (please see Appendix K for guidelines on grading and management of suspected CRS), sweating, chills, edema, serum sickness, malignancy (lymphoma or lymphoproliferative disorders)

Dose adjustments: Dose adjustments for Thymoglobulin will not be made.

2.6.4.2.4 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an ester prodrug of the active immunosuppressant mycophenolic acid (MPA). Side effects of MMF include:

- Cardiac and vascular: hypertension, hypotension, tachycardia, edema
- Cutaneous: rash
- Endocrine and metabolic: hypocalcemia, hypokalemia, hyperuricemia, hyperkalemia, hypomagnesemia
- Gastrointestinal: nausea, vomiting, dyspepsia, abdominal pain, diarrhea
- Genitourinary: teratogenicity, miscarriage, limited effectiveness of birth control
- Hematologic: leukopenia, thrombocytopenia, anemia
- Neurologic: headache, tremors, insomnia, dizziness, progressive multifocal leukoencephalopathy (PML)
- Pulmonary: dyspnea, cough, interstitial lung disease
- Miscellaneous: change in vision, infection, secondary malignancy, arthralgia, myalgia

Drug interactions: MMF activity is decreased with oral antacids and cholestyramine. There are no pharmacokinetic (PK) interactions with cotrimoxazole, oral contraceptives, or cyclosporine. Acyclovir or ganciclovir blood levels may increase due to competition for tubular secretion. High doses of salicylates or other highly protein-bound drugs may increase the free fraction of MPA and exaggerate the potential for myelosuppression.

Dose adjustments: No dose adjustments are required for liver dysfunction. For renal insufficiency, MMF dosing should not be modified unless dialysis is needed, in which case MMF can be reduced to 25-50% of the starting dose. If toxicity is suspected, a trough MPA level should be checked. If the level is greater than 2 mcg/mL, it will require a dose reduction.

2.6.4.2.5 Tacrolimus

Tacrolimus is a macrolide immunosuppressant that inhibits lymphocytes through calcineurin inhibition.

Tacrolimus side effects include:

- Cardiovascular: pericardial effusion, hypertension (which may cause arrhythmia, angina, myocardial infarction)
- Cutaneous: itching, rash
- Endocrine and metabolic: hyperglycemia, hypomagnesemia, hypokalemia, hyperkalemia, hypophosphatemia, hyperlipidemia
- Gastrointestinal: constipation, diarrhea, nausea, vomiting, anorexia, bowel perforation, dyspepsia
- General: fever, fatigue
- Hematologic: anemia, thrombocytopenia, leukopenia, thrombotic microangiopathy
- Hepatic: liver dysfunction
- Neurologic: paresthesia, headache, tremor, posterior reversible encephalopathy syndrome (PRES), dizziness, insomnia, confusion, altered mental status, seizure, blindness
- Pulmonary: pleural effusion, dyspnea
- Renal: renal impairment which may require dialysis, peripheral edema
- Miscellaneous: infection, post-transplant lymphoproliferative disorders, allergic reaction, secondary malignancy

Drug interactions: Tacrolimus is well-absorbed orally. Tacrolimus is extensively metabolized by the cytochrome P-450 (CYP3A4) system and metabolized products are excreted in the urine. Drugs that may increase tacrolimus levels include tri-azole drugs (especially voriconazole, isavuconazonium sulfate, and posaconazole), nephrotoxic drugs, calcium channel blockers, cimetidine and omeprazole, metoclopramide, macrolide antibiotics, quinupristin/dalfopristin, danazol, ethinyl estradiol, methylprednisolone, and HIV protease inhibitors. Drugs that may decrease tacrolimus levels include some anticonvulsants (phenobarbital, phenytoin, carbamazepine), caspofungin, rifamycins, and St. John's wort.

Dose adjustments: The tacrolimus dose is adjusted to maintain a serum trough level of 5-15 ng/mL, with a target of 10-15 ng/mL. Participants with hepatic or renal insufficiency should receive doses at the lower end of concentrations (5-10 ng/mL). No dose adjustments are required in participants undergoing hemodialysis.

Due to extreme interactions with voriconazole and posaconazole, the tacrolimus dose should be empirically lowered when these azoles are initiated at steady state levels of tacrolimus. Guidelines are provided in Table 2.6.1 below. Dose adjustments for therapy with other azoles may be indicated. However, the initial tacrolimus dose (on Day 5) remains fixed to ensure participants become therapeutic initially.

Dosing considerations with concurrent azole therapy: Triazole antifungal medications are expected to increase serum CNI levels; therefore, dosages of CNIs should be adjusted accordingly. Guidelines are provided in Table 2.6.1 below. Of note, reversal of azole-mediated inhibition of CYP3A4 (and others) and P-glycoprotein is gradual when azoles are stopped. Therefore, immediate significant dose increases in tacrolimus are not advised when azoles are stopped. Rather, tacrolimus dose increases should be cautious and based on more frequent monitoring of levels as appropriate.

Table 2.6.1: Suggested Preemptive Dose Reduction of Tacrolimus when Azoles are Initiated at Steady State Levels of Tacrolimus

Antifungal	Tacrolimus	
	Dose ↓	Comment
Voriconazole	67%	At least 50% reduction strongly advised
Posaconazole	67%	At least 50% reduction strongly advised
Itraconazole	50%	At least 50% reduction strongly advised
Fluconazole	25%	No reduction suggested/Consider mold-active azole as above

2.6.4.2.6 Filgrastim (G-CSF)

Filgrastim side effects include:

- Cardiovascular: chest pain, hypertension
- Dermatologic: rash, erythema, alopecia, irritation at injection site
- Endocrine and metabolic: increased lactate dehydrogenase
- Gastrointestinal: diarrhea, nausea
- Genitourinary: urinary tract infection
- Hematologic: anemia, thrombocytopenia, leukocytosis, vasculitis
- Hepatic: increased liver enzymes
- Musculoskeletal: myalgia, arthralgia, muscle spasms
- Neurologic: headache, dizziness, fatigue, generalized pain, hypoesthesia
- Renal: glomerulonephritis

- Respiratory: cough, dyspnea, upper respiratory tract infections, acute respiratory distress syndrome
- Miscellaneous: bone pain, fever, allergic reaction, splenomegaly, splenic rupture, capillary leak syndrome

Dosing considerations: Dose reduction or interruption of therapy should be considered if glomerulonephritis due to filgrastim occurs.

2.6.4.2.7 Total Body Irradiation

TBI side effects include:

- Cutaneous: erythema, hyperpigmentation, alopecia
- Gastrointestinal: nausea, vomiting, diarrhea, parotitis, mucositis, abdominal cramping
- General: fever, fatigue
- Genitourinary: gonadal impairment
- Hepatic: hepatic sinusoidal obstruction syndrome
- Hematologic: myelosuppression, anemia, thrombocytopenia
- Pulmonary: interstitial pneumonitis
- Renal: nephropathy
- Miscellaneous: infection, short stature, vertebral deformities, cataracts, secondary malignancy, hormonal impairment

2.6.4.3 Toxicity Grading

Toxicities are graded using the National Cancer Institute (NCI) CTCAE Version 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

2.7 Study Conduct

This study will be conducted in accordance with the protocol, the BMT CTN Administrative Manual of Procedures (MOP, located on the BMT CTN Website), and the following: a) Consensus ethical principles derived from international guidelines including the Declaration of Helsinki; b) Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines and c) Applicable laws and regulations. The NMDP single Institutional Review Board (IRB) of Record will oversee this study and conduct the study-specific reviews as required by federal regulations and per the NMDP IRB SOPs. Site personnel will enter data in the electronic data capture system as described in the BMT CTN 2207 forms guide.

Source documentation should be made available for monitoring visits, audits, and regulatory inspections as described in the BMT CTN Administrative MOP. Participating Principal Investigators (PIs) bear ultimate responsibility for training of site staff as well as the scientific, technical, and administrative aspects of conduct of the protocol, even when certain tasks have been delegated to coinvestigators, sub-investigators, or staff. The PIs have a responsibility to protect the rights and welfare of participants and comply with all requirements regarding the clinical obligations and all other pertinent requirements in 21 Code of Federal Regulations (CFR) part 312. In addition to following applicable federal, state, and local regulations, Investigators are expected to follow ethical principles and standards and receive training in GCP every 3 years and human subjects training within the past 3 years and thereafter as per institutional requirements.

CHAPTER 3

3 STUDY ENDPOINTS AND DEFINITIONS

3.1 Primary Endpoint: GVHD-free, Failure-Free Survival (GFFS)

The primary endpoint is GFFS at 1 year after initiation of conditioning. Events for GFFS include Grade III-IV aGVHD, cGVHD requiring immunosuppression, primary or secondary graft failure requiring second definitive therapy, failure to receive an HSCT infusion, and death. GFFS is defined as the time interval from start of conditioning until the first of these events occurs. For failure to receive an HSCT infusion, the date will be at the time the decision not to proceed to HSCT is made.

3.2 Secondary Endpoints

3.2.1 Overall Survival (OS)

Events for OS include death from any cause. OS is defined as the time interval from initiation of conditioning until death. The OS probability will be assessed at 1 year after initiation of conditioning.

3.2.2 Failure-Free Survival (FFS)

Events for FFS include treatment failure or death. Treatment failure is defined as the initiation of treatment with a second definitive therapy. FFS is defined as the time interval from start of conditioning until the start date of a second definitive therapy or death, whichever occurs first. The FFS probability will be assessed at 1 year after initiation of conditioning.

3.2.3 Being Alive and Engrafted

The proportion of patients who are alive with donor cells present at 1 year after initiation of conditioning will be described, where the presence of donor cells is defined as achieving at least 5% myeloid donor chimerism (whole blood or marrow) in the most recent measurement through 1 year.

3.2.4 Neutrophil Recovery

Neutrophil recovery is achieving an ANC ≥ 0.5 $x10^9$/L for 3 consecutive measurements on different days, with the first of the 3 days being defined as the day of neutrophil recovery. The cumulative incidences of neutrophil recovery at Day +28 and Day +56 post-HSCT will be estimated.

3.2.5 Red Blood Cell Recovery

Red blood cell (RBC) recovery is defined as Hb level ≥ 7 g/dL with no red cell transfusion in the preceding 7 days. The first day of the 7 days will be defined as the day of RBC recovery. The cumulative incidences of RBC recovery at Day +100, Day +180, and Day +365 post-HSCT will be estimated.

3.2.6 Platelet Recovery

Platelet recovery is defined by achieving a platelet count ≥ 20 x 10^9/L with no platelet transfusions in the preceding 7 days. The first 7 days of the sustained platelet count will be defined as the day of platelet recovery. The cumulative incidence of platelet recovery at Day +100 post-HSCT will be estimated.

3.2.7 Primary Graft Failure

Primary graft failure is defined as the occurrence of any of the following:

1. Lack of neutrophil recovery by Day +56 post-HSCT.
2. Failure to achieve at least 5% myeloid donor chimerism (whole blood or marrow) on any measurement up to and including Day +56 post-HSCT.
3. Administration of a second definitive therapy, which is defined as a second transplant (following conditioning regimen) or a course of ATG. A CD34+ boost or use of growth factors will NOT be considered as a second definitive therapy.

The proportion of patients with primary graft failure through Day +56 post-HSCT will be estimated.

3.2.8 Secondary Graft Failure

Secondary graft failure is defined as the occurrence of any of the following:

1. Initial neutrophil recovery (ANC greater than or equal to 0.5 x10^9/L measured for 3 consecutive measurements on different days) with whole blood or marrow donor chimerism greater than or equal to 5%, followed by sustained subsequent decline in ANC to less than 0.5 x 10^9/L with whole blood or marrow donor chimerism declining to less than 5%.
2. Administration of a second definitive therapy, which is defined as a second transplant (following conditioning regimen) or a course of ATG. A CD34+ boost or use of growth factors will NOT be considered as a second definitive therapy.

The cumulative incidence of secondary graft failure at 1 year post-HSCT will be estimated.

3.2.9 Hematologic Response

Hematologic response will be assessed according to the modified NIH criteria [40] determined at Day +100, Day +180, and Day +365 post-HSCT. Complete response (CR) is defined as meeting all 3 peripheral blood count criteria: 1) ANC > 1x 10^9/L; 2) Hb > 10g/dL; and 3) platelet count > 100 x 10^9/L. Partial response (PR) is defined as blood counts no longer satisfying criteria for SAA and having transfusion independence (defined as no need for packed red blood cell [PRBC] or platelet transfusions) but insufficient for a CR.

3.2.10 GVHD

Acute and chronic GVHD are graded according to the BMT CTN Technical Guideline. See Appendix I for guidance in grading, with detailed grading direction in the Technical Guideline document.

The cumulative incidences of Grade II-IV and Grade III-IV aGVHD at Day +100 post-HSCT and the cumulative incidences of all cGVHD and of cGVHD requiring immunosuppression will be estimated at 1 year post-HSCT.

3.3 Exploratory Endpoints

3.3.1 Time to Enrollment

The median time to enrollment in days after HLA typing of the recipient will be estimated.

3.3.2 Time from Diagnosis of SAA to Conditioning and to Transplant

The median time from SAA diagnosis to conditioning start and to HSCT will be estimated.

3.3.3 Time to Donor Activation, Donor Selection, Start of Conditioning, and Transplant

The median times in days from enrollment to the day of donor activation, day of donor selection, day conditioning is initiated, and day of transplant will be estimated.

3.3.4 Donor Availability

The number and types (haploidentical and 8/10, 9/10, and 10/10 URDs) of available donors for participants will be described.

3.3.5 HSCT Cell Dose

The total nucleated cell dose and CD34+ cell doses received by transplanted participants will be described.

3.3.6 Immune Reconstitution

Quantitative assessments of peripheral blood CD4, CD19, and CD56 positive lymphocytes will be done through flow cytometric analysis at baseline, Day +100, Day +180, and Day +365 post-HSCT.

3.3.7 Infection

All Grade 2 and 3 infections will be reported according to the BMT CTN Technical Guideline. See Appendix H for guidance in infection grading. CMV viremia and disease, EBV viremia, and PTLD will be collected as per Section 2.6.3.2.

3.3.8 Health Related Quality of Life (HR-QoL)

HR-QoL will be measured at Baseline and then at Day +100, Day +180, and Day +365 post-HSCT using the following instruments/questionnaires: Patient-Reported Outcomes Measurement Information System (PROMIS; anxiety, depression, anger, fatigue, physical function, cognitive function, ability to participate in social roles & activities subscales), Comprehensive Score of Financial Toxicity (COST), occupational function items, and sociodemographic/social determinants of health items. The scales will be scored according to the recommendations of the developers. See Section 4.3.8.3 for detailed descriptions of the instruments. HR-QoL will be described for each treatment arm over time. Participants aged 8+, and parents/guardians of participants aged 5-7, who are able to read and speak in English or Spanish are eligible to participate in the HR-QoL component of this trial.

CHAPTER 4

4 PARTICIPANT ENROLLMENT AND EVALUATION

4.1 Cohort Selection

1. Each participating institution declares a preferred donor source (URD or haplo) to the Data Coordinating Center (DCC)/Emmes at the time of site activation.
2. If the preferred donor source is not available for a given participant, the center may use the other donor source and document it in the data capture system.

4.2 Enrollment Procedures

Participants will be registered using the Advantage eClinical Electronic Data Capture System. The following procedures should be followed:

1. Prior to initiation of the conditioning regimen, an authorized user at the transplant center completes the Demographics Form and Enrollment Form in Advantage eClinical, at which point a study number will be generated. After the participant is enrolled in the screening segment, the authorized user should complete the HLA Forms to verify an eligible HLA match score. This eligibility screening includes a question confirming that the participant (or legally authorized representative) signed informed consent. The eligibility screening also includes a question confirming that the donor (or legal guardian) signed informed consent, agrees to provide marrow, and weighs at least 20 kg.
2. After filling out the HLA Forms, the authorized user will be able to enroll the participant in the transplant segment. **The participant is not officially enrolled on study and may not begin study treatment until they are enrolled in the transplant segment.**

4.3 Study Monitoring

4.3.1 Follow-up Schedule

The follow-up schedule for study visits is outlined in Table 4.3.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the BMT CTN 2207 forms guide.

Table 4.3.1: Follow-Up Schedule

Study Visit	Target Day Post-Transplant
week 1	7 ± 3 days
week 2	14 ± 3 days
week 3	21 ± 3 days
week 4	28 ± 3 days
week 5	35 ± 3 days
week 6	42 ± 3 days
week 7	49 ± 3 days
week 8	56 ± 3 days
week 9	63 ± 3 days
week 10	70 ± 3 days
week 11	77 ± 3 days
week 12	84 ± 3 days
Day 100	100 ± 7 days
6 months	180 ± 28 days
12 months	365 ± 45 days

4.3.2 Data Capture Forms

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the study forms guide. Forms that are not entered into the data capture system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the data capture system and integrated into the DCC's master database, or until an exception is granted.

Reporting Participant Deaths: Recipient death information must be entered into the data capture system within 24 business hours of knowledge of the participant's death. If the cause of death is unknown at that time, it does not need to be recorded at that time. However, once the cause of death is determined, the Death Form must be updated in the data capture system.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive HSCTs done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all United States [US] allotransplant recipients.) Enrollment on BMT CTN #2207 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post-transplant Report Forms must also be submitted for all participants enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

Weekly GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Technical Guideline. Participants should be assessed weekly until Day +100 post-transplant for GVHD. After Day +100, participants will be assessed at each follow-up visit through 12 months for the presence of GVHD. For scheduling, a target day range has been provided in Table 4.3.1.

4.3.3 Adverse Event Reporting

4.3.3.1 Definitions

Adverse Event: An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Serious Adverse Event: A serious adverse event (SAE), as defined by per 21 CFR 312.32, is any AE that results in one of the following outcomes, regardless of causality and expectedness:

- **Results in death**.
- **Is life-threatening**. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect**; or
- **Is an important medical event** when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias and convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered an SAE). Any event is considered an SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Anticipation:

- **Anticipated AEs** are those that are listed in the protocol, the informed consent document, package inserts, or have been previously identified as resulting from the underlying disease or the transplant process. In non-Investigational New Drug (IND) trials such as this one, anticipated is often referred to as expected.
- **Unanticipated AEs** would include those that have not been listed in the protocol, the informed consent document, package inserts, or have not been previously identified as resulting from the underlying disease or the transplant process. Unanticipated events also include events that would normally be anticipated, but vary in nature, intensity, or frequency, as determined by the investigator. In non-IND trials such as this one, unanticipated is often referred to as unexpected.

4.3.4 Classification of Adverse Events by Severity

The severity refers to the intensity of the reported event. The Investigator must categorize the severity of each reportable SAE according to the NCI CTCAE Version 5.0. CTCAE guidelines can be referenced at the following website: http://ctep.cancer.gov/reporting/ctc.html. For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of 1 through 5 using the following CTCAE guidelines:

- **Grade 1**: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE

4.3.5 Classification of Adverse Events by Relationship to Study Intervention

The relationship of each reported event to the study treatment will be assessed by the Investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the SAE, temporal relationship to any study treatment interventions and de-challenge or re-challenge according to the following guidelines:

- **Possibly, Probably, or Definitely Related:** there is a reasonable possibility that the study treatment caused the event. A relationship of possibly, probably, or definitely related to the investigational product is considered related for the purposes of regulatory authority reporting.
- **Unlikely, or Not Related:** There is no reasonable possibility that the investigational product caused the event. An unlikely or not related relationship to the investigational product is not considered related for the purposes of regulatory authority reporting

4.3.6 Required Adverse Event Reporting

Adverse event reporting will be consistent with BMT CTN procedures (BMT CTN Administrative MOP, Chapter 6). It is BMT CTN policy that events meeting reporting requirements must be reported even if the Investigator is unsure whether a relationship exists between the adverse event and the use of study treatment.

Unanticipated SAEs will be reported through an expedited AE reporting system via the Advantage eClinical data capture system. Unanticipated life-threatening and fatal SAEs must be reported within 24 hours of knowledge of the event. All other unanticipated SAEs must be reported within 3 business days of knowledge of the event. Events entered in the data capture system will be reported using NCI's CTCAE Version 5.0.

Anticipated AEs will be reported using NCI's CTCAE Version 5.0 at regular intervals as defined on the Form Submission Schedule, including calendar-driven case report forms (e.g., Toxicity and GVHD forms) and event-driven case report forms (e.g., Relapse/Progression, Infection, and Death forms). Any anticipated life-threatening SAE not collected on another study form must be reported through the expedited AE reporting system via the data capture system within 24 hours of knowledge of the event.

This trial will also have 3 adverse events of special interest (AESIs): pregnancy, medication error related to Thymoglobulin® and overdose of Thymoglobulin®. If any of these AESIs occur, this event should be reported on the AE data capture forms as an expedited event within 24 hours of knowledge of the event, whether it is considered a non-serious event or an SAE, and regardless of anticipation assessment.

The National Heart, Lung, and Blood Institute (NHLBI)/Data and Safety Monitoring Board (DSMB) will receive unanticipated SAEs within 7 days of Medical Monitor assessment that it meets reporting guidelines. The DSMB will also review summary reports of all unanticipated SAEs on an annual basis.

4.3.7 Procedure in Case of Pregnancy

If a female participant becomes pregnant during the study intervention period or within 30 days from the study intervention, the Investigator should report the information through an expedited AE reporting system via the data capture system. If a partner of a male participant becomes pregnant during the study intervention period or within 90 days from the last study intervention, the Investigator should report the information through an expedited AE reporting system via the data capture system. In the event of a pregnancy, the pregnant study participant or pregnant partner of a male participant will be approached by the Investigator to obtain the study-specific pregnancy consent. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data, and other related information will be requested.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) are mentioned below.

- “Spontaneous abortion” includes miscarriage, abortion, and missed abortion.
- Death of an infant within 30 days after birth should be reported as an SAE regardless of its relationship with the study intervention.
- If an infant dies more than 30 days after birth, it should be reported if a relationship between the death and intrauterine exposure to the study intervention is judged as “possible” by the Investigator.
- In the case of a delivery of a living newborn, the “normality” of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

Information will be collected at the time of delivery/birth and 180 and 360 days after birth.

4.3.8 Participant Evaluations

Table 4.3.5 summarizes participant clinical assessments over the course of the study. Table 4.3.1 outlines the timing windows of assessments.

4.3.8.1 Pre-transplant Evaluations

The following observations must be performed within 30 days prior to enrollment (unless noted otherwise):

1. History, physical examination, height, and weight.
2. Karnofsky or Lansky performance status (Karnofsky for patients age 16 and older; Lansky for patients age ≤15.99 at the time of enrollment)
3. Hematopoietic cell transplantation-comorbidity index (HCT-CI).

4. Complete blood count (CBC) with differential, reticulocyte count and chemistries (creatinine, bilirubin, alkaline phosphatase, AST, ALT, ferritin, magnesium).
5. Calculation of estimated CrCl, and GFR by radionucleotide scan or urine collection, if indicated.
6. Chest x-ray or chest computerized tomography (CT) scan (contrast not required for CT chest).
7. HLA typing by high-resolution methodology at HLA -A, -B, -C, DPB1, and DRB1 loci, ABO and Rh typing. Confirmatory donor typing must be completed < 100 days prior to enrollment.
8. Presence of anti-donor HLA antibodies (positive anti-donor HLA antibody is defined as the presence of donor specific HLA antibodies [DSA] to any mismatched HLA allele/antigen at any of the following loci [HLA-A, -B, -C, –DRB1, DRB3, DRB4, DRB5, -DQA1, -DQB1, -DPA1, -DPB1] with MFI >3000 by microarray-based single antigen bead testing).
9. CMV antibody test, hepatitis panel (hepatitis A [HepA] antibody [Ab], HepB surface Ab [sAb], HepB surface antigen [sAg], HepB Core Ab [IgG or total with IgG], HepC Ab), HSV, syphilis, HIV and human T-lymphotropic virus type 1 (HTLV1) I/II Ab, VZV Ab, and EBV serostatus.
10. LVEF or, for participants aged < 13.0 years, shortening fraction measurement by echocardiogram or MUGA.
11. Pulmonary function testing: FEV1, FVC, and DLCO (corrected for Hb). For participants aged < 13.0 years and participants unable to perform PFTs due to age or developmental ability, pulse oximetry is an acceptable alternative.
12. Baseline electrocardiogram (EKG).
13. BM aspirate/biopsy with cytogenetics or fluorescence in situ hybridization (FISH, if failed cytogenetics) within 60 days prior to enrollment.
14. Testing for telomere biology studies per institution standards to rule out short telomere disorders. Genetic panels for inherited bone marrow failure syndromes can be considered as an alternative to telomere length testing.
15. Recommend diepoxybutane (DEB) testing on peripheral blood to rule out Fanconi Anemia (at any time prior to enrollment). Genetic panels for inherited bone marrow failure syndromes (IBMFS) can be considered as an alternative to functional testing. If patients have clinical characteristics suspicious for Shwachman-Diamond syndrome, this disorder should be excluded by pancreatic isoamylase testing or gene mutation analysis. Other testing per center may be performed to exclude IBMFS.
16. Pregnancy test for females of childbearing potential (testing per institutional practice).
17. Optional blood samples as described in Appendix B:
    a. Future research (all participants who consent): 38 mL whole blood prior to conditioning.
18. Optional donor sample as described in Appendix B.
    a. Future research: 20 mL whole blood prior to collection.
19. Absolute lymphocyte numbers by flow cytometry for lymphocyte subpopulations to include CD4, CD19, and CD56.
20. Serum quantification of IgG, immunoglobulin M (IgM), and immunoglobulin A (IgA).

21. Baseline peripheral blood samples for chimerism analysis by molecular methods (participant and donor).
22. HR-QoL: Patient-Reported Outcome (PRO) assessments for participants able to complete surveys in English or Spanish (see Section 3.3.8).

4.3.8.2 Post-transplant Evaluations

1. History, physical exam, and weight weekly until Day +28, then at Day +100, Day +180, and Day +365.
2. History and physical exam to assess GVHD and other morbidities weekly until Day +100, then at Day +180, and Day +365. GVHD evaluation and grading per BMT CTN Technical Guideline. Chronic GVHD Provider Survey to be completed by a clinician at the time of participant assessment. For scheduling purposes, a target day range has been provided in Table 4.3.1.
3. Karnofsky or Lansky performance status at Day +365 (Karnofsky for patients age 16 and older; Lansky for patients age $\leq$15.99 at the time of enrollment).
4. CBC with differential at least 2 times a week from Day 0 until ANC > 0.5 x 10^9/L for 3 consecutive measurements over 3 or more days. CBC performed at least twice per week until Day +28, then weekly until Day +100, then at Day +180 and Day +365.
5. Reticulocyte count for assessment of hematologic response on Day +100, Day +180, and Day +365.
6. Chemistries (creatinine, bilirubin, alkaline phosphatase, AST, ALT) twice a week until Day +28 and then weekly until Day +100, then at Day +180 and Day +365. Cyclosporine or tacrolimus levels will be measured at least once weekly until Day +100, and then at each follow-up visit until the drug is tapered off.
7. Toxicity assessments at Day +28, Day +56, Day +100, Day +180, and Day +365.
8. Absolute lymphocyte numbers by flow cytometry for lymphocyte subpopulations to include at minimum CD4, CD19, and CD56 at Day +100, Day +180, and Day +365.
9. Serum quantification of IgG, IgM, and IgA at Day +365.
10. Quantification of peripheral blood (whole blood and CD3) or marrow chimerism (including lineage-specific, myeloid, and T cell chimerisms per institutional standards) at Day +28, Day +56, Day +100, Day +180, and Day +365. In the event that Day +100 chimerism results at less than 50% donor in either myeloid or T cell compartment, additional chimerism testing of the same compartment should be performed every 4 weeks or as clinically indicated until the chimerism is greater than or equal to 50% donor and/or stabilizes. Bone marrow testing is optional per institutional standards.
11. EBV DNA quantitative PCR testing, CMV DNA quantitative PCR testing, and adenovirus DNA quantitative PCR testing on peripheral blood at least weekly until Day +100 and then per institutional practice. It is recommended to continue weekly or every other week until the participant is off of all immunosuppression.
12. HR-QoL: PRO assessments at Day +100, Day +180, and Day +365 post-transplant for participants able to complete surveys in English or Spanish.
13. Organ function testing post-HSCT per institutional standards – PFT, echocardiogram, renal function testing at Day +365 are recommended.

14. Screening for TA-TMA is recommended as this complication can lead to anemia and thrombocytopenia post-HSCT. Screening may include monitoring LDH, urinalysis for proteinuria, urine quantification of protein/creatinine ratio, or other institutional guidelines [51].
15. BM aspirate/biopsy with cytogenetics or fluorescence in situ hybridization (FISH, if failed cytogenetics) Day +100. If the institutional standard is not to perform a Day +100 BM aspirate/biopsy, then collection is optional.
16. Optional blood samples as described in Appendix B:
    a. Future research (all participants who consent): 38 mL whole blood at Day +28, Day +56, Day +100, Day +180 and Day +365.

4.3.8.3 Patient-Reported Outcome (PRO) Surveys

The CIBMTR Survey Research Group (SRG) centrally coordinates all PRO survey assessments. At the time a participant is enrolled in the study, the SRG receives an email notification and adds that participant to CIBMTR's electronic Patient-Reported Outcomes (ePRO) system for data collection tracking. Transplant Centers provide participant contact information securely to the SRG.

Age-appropriate PROs will be collected using PROMIS® domains, COST, occupational functioning items, and sociodemographic/social determinants of health items (See Appendix J for sample questions).

Participants and/or their parent/guardian will complete PRO measures at baseline (before the start of conditioning) and at Day +100, Day +180 and Day +365 post-transplant.

Respondents may choose to complete PRO surveys on paper or electronically, and in English or Spanish. The same survey items will be used in paper and electronic versions of the surveys. If participants or parent/guardians are unable to complete the PRO surveys in these modes and languages, they are still eligible for study enrollment and will complete all other study assessments and tests.

Baseline PRO surveys will be collected by the center electronically or on paper forms after consent and before randomization. Centers will be provided with paper PDFs of the baseline survey and a set of unique electronic survey links in both English and Spanish for each age group. Surveys may also be administered verbally if needed. Centers will record participant responses on a paper copy of the survey contemporaneously while reading survey questions and response choices to the participant. Electronically collected PRO surveys are directly entered in the ePRO system via the unique links.

The SRG will centrally collect all post-treatment PRO surveys starting at Day +100. Centers will securely provide participant contact information to the SRG upon enrollment. At Day +100, the SRG will attempt to contact the participant by phone to confirm contact information, remind them of survey assessment time points and confirm how they want to complete PRO surveys (paper or electronic). After speaking by phone with the participant, or if they are unreachable by phone, the SRG will send the Day +100 survey assessment by email and/or mail. The SRG will continue to contact the participant via email, phone and/or mail to collect survey assessments at Day +180 and Day +365. The SRG will follow-up by phone and email with non-responders up to approximately six contact attempts or until the visit window closes, to minimize missing surveys. The SRG may also administer surveys verbally by phone if needed. The SRG will record participant responses in the electronic version of the survey contemporaneously while reading questions and response choices to the patient. If the SRG is unable to get response from enrolled participants, they may request that local study coordinators remind participants or administer the PRO surveys at clinical visits.

The participant or their parent/guardian will be asked to complete the PRO surveys, depending on the age of the participant at the time of each PRO survey time point.

- Under age 5 – PRO surveys not completed.
- Age 5-7 – Pediatric versions of PRO surveys completed by the parent/guardian (see Table 4.3.2)
- Age 8-17 – Pediatric versions of PRO surveys completed by the participant, with occupational function, sociodemographic and social determinants of health items completed by the parent/guardian (see Table 4.3.3).
- Age 18 and older – Adult versions of PRO surveys completed by the participant (see Table 4.3.4).

4.3.8.4 Patient-Reported Outcomes Measurement Information System (PROMIS) Domains

Seven PROMIS domains will be used to measure detailed functioning and symptom burden for participants. PROMIS measures utilize T-score metrics, with higher scores indicating more of the concept (i.e., physical function or depression). Scores are normalized to 50 with a standard deviation of 10, and scores greater than 0.5 times standard deviation (i.e., < 45 or > 55, compared to the general population) are considered clinically meaningful.

The PROMIS domains for adult patients are Anxiety, Depression, Anger, Fatigue, Physical Function, Cognition, Ability to Participate in Social Roles & Activities. The PROMIS domains for pediatric participants are Anxiety, Depressive Symptoms, Anger, Fatigue, Mobility, Cognition, Peer relationships.

4.3.8.5 Financial Impact Scales

The COST, and items about return to work/school, income, insurance, and household burden measure the impacts of treatment on finances and economic status of the patient households.

4.3.8.6 PRO Compensation

To compensate participants for their effort and time and ensure high compliance on PRO surveys, participants will receive $20 for each completed PRO survey timepoint. The SRG will track all completed surveys and coordinate remuneration.

Table 4.3.2: Pediatric (Age 5-7) PRO Assessments

Assessment	# items	Estimated completion time	Respondent	Baseline	Day 100	Day 180	Day 365
PROMIS® domains							
Anxiety	8	1-2 minutes	Parent/Guardian	X	X	X	X
Depressive Symptoms	8	1-2 minutes	Parent/Guardian	X	X	X	X
Anger	5	1-2 minutes	Parent/Guardian	X	X	X	X
Fatigue	10	1-2 minutes	Parent/Guardian	X	X	X	X
Mobility	8	1-2 minutes	Parent/Guardian	X	X	X	X
Cognition	7	1-2 minutes	Parent/Guardian	X	X	X	X
Peer relationships	8	1-2 minutes	Parent/Guardian	X	X	X	X
Occupational function items	4	1 minute	Parent/Guardian	X		X	X
Sociodemographics/ social determinants of health	9	1-2 minutes	Parent/Guardian	X			
Total length	67			9-17 min	7-14 min	8-15 min	8-15 min

Table 4.3.3: Pediatric (Age 8-17) PRO Assessments

Assessment	# items	Estimated completion time	Respondent	Baseline	Day 100	Day 180	Day 365
PROMIS® domains							
Anxiety	8	1-2 minutes	Participant	X	X	X	X
Depressive Symptoms	6	1-2 minutes	Participant	X	X	X	X
Anger	5	1-2 minutes	Participant	X	X	X	X
Fatigue	10	1-2 minutes	Participant	X	X	X	X
Mobility	8	1-2 minutes	Participant	X	X	X	X
Cognition	7	1-2 minutes	Participant	X	X	X	X
Peer relationships	7	1-2 minutes	Participant	X	X	X	X
Occupational function items	4	1 minute	Parent/Guardian	X		X	X
Sociodemographics/ social determinants of health	9	1-2 minutes	Parent/Guardian	X			
Total length	64			9-17 min	7-14 min	8-15 min	8-15 min

Table 4.3.4: Adult (Age 18+) PRO Assessments

Assessment	# items	Estimated completion time	Respondent	Baseline	Day 100	Day 180	Day 365
PROMIS® domains							
Anxiety	8	1-2 minutes	Participant	X	X	X	X
Depression	8	1-2 minutes	Participant	X	X	X	X
Anger	7	1-2 minutes	Participant	X	X	X	X
Fatigue	8	1-2 minutes	Participant	X	X	X	X
Physical Function	8	1-2 minutes	Participant	X	X	X	X
Cognition	8	1-2 minutes	Participant	X	X	X	X
Ability to Participate in Social Roles & Activities	8	1-2 minutes	Participant	X	X	X	X
Comprehensive Score of Financial Toxicity (COST)	12	2-3 minutes	Participant	X		X	X
Occupational function items	8	1 minute	Participant	X		X	X
Sociodemographics/ social determinants of health	16	2 minutes	Participant	X			
Total length	91			12-20 min	7-14 min	10-18 min	10-18 min

Table 4.3.5: Summary of Assessments

Study Assessments / Testing	Baseline (Pre-conditioning)	During conditi-oning[14]	0	7	14	21	28	35	42	49	56	63	70	77	84	100	180	365
History, Physical Exam, Weight, and Height[16]	X		X	X	X	X	X									X	X	X
Karnofsky/Lansky Performance Status[15]	X																	X
HCT-CI	X																	
CBC[1], Differential, and Blood Chemistries[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reticulocyte Count	X															X	X	X
CrCl and GFR Assessment[3]	X																	
HLA Typing & Anti-Donor Antibody Testing	X																	
Infectious Disease Titers[4]	X																	
LVEF or Shortening Fraction for < 13 years	X																	
Electrocardiogram	X																	
Chest X-ray or Chest CT Scan[5]	X																	
Pulmonary Function Tests[6]	X																	
BM Aspirate for Pathology and Cytogenetics[7]	X															X		
Testing for Fanconi Anemia/telomere disorders[8]	X																	
Pregnancy Test (females of childbearing potential only)	X																	
CD4, CD19, and CD56 Counts	X															X	X	X
Serum Quantification of IgG, IgM, and IgA	X																	X
Chimerism[9]	X						X				X					X	X	X
CMV, EBV, and Adenovirus DNA Quantitative PCR Testing[10]				X	X	X	X	X	X	X	X	X	X	X	X	X		
Toxicity Assessments							X				X					X	X	X
Acute GVHD				X	X	X	X	X	X	X	X	X	X	X	X	X		
Chronic GVHD (including Provider surveys)[11]																X	X	X
Comprehensive CIBMTR Forms	X															X	X	X
HR-QoL	X															X	X	X
Optional Research Blood Draw for Biorepository[12]	X						X				X					X	X	X
Organ Function Testing post-HSCT (per Institutional Standards)																		X[13]

[1] CBC performed 2 times weekly from Day 0 until ANC > 0.5 x 10^9/L for 3 consecutive measurements on different days. CBC performed twice per week until Day +28, then weekly until Day +100, then at Day +180 and Day +365.

[2] Blood chemistries include: creatinine, bilirubin, alkaline phosphatase, AST, ALT, ferritin (baseline only), magnesium (baseline only), and cyclosporine or tacrolimus level. Cyclosporine or tacrolimus levels will be measured at least once weekly until Day +100 and then at each follow-up visit until tapered off. Blood chemistries performed twice weekly until Day +28 and then weekly until Day +100, then at Day +180 and Day +365.[3] Calculation of estimated CrCl, and GFR by radionucleotide scan or urine collection, if indicated.

[4] Infectious disease titers include: hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab [IgG or total with IgG], HepC Ab), CMV Ab, HIV, HSV, syphilis, HTLV1 I/II Ab, VZV Ab, and EBV serostatus.
[5] Contrast not required for chest CT scan.
[6] DLCO (corrected for Hb), FEV1, and FVC or pulse oximetry for participants aged < 13.0 years if unable to perform standard PFT.
[7] BM aspirate and biopsy (cytogenetics is required, local MDS panel recommended) within 60 days prior to enrollment. Day +100 marrow is optional per institutional standards.
[8] Results of DEB testing on peripheral blood or comparable testing on marrow to rule out Fanconi anemia at any time prior to enrollment. Testing for telomere biology studies per institution standards to rule out short telomere disorders. Genetic panels for inherited bone marrow failure syndromes (IBMFS) can be considered as an alternative to functional testing. If patients have clinical characteristics suspicious for Shwachman-Diamond syndrome, this disorder should be excluded by pancreatic isoamylase testing or gene mutation analysis.
[9] Chimerism to be measured by standard molecular testing of a peripheral blood (whole blood and CD3) sample or marrow chimerism (including lineage-specific, myeloid, and T cell chimerisms). Peripheral blood samples for chimerism assessment at baseline should be collected from the participant and the donor. In the event that Day +100 chimerism results at less than 50% donor in either myeloid or T cell compartment, additional chimerism testing of the same compartment should be performed every 4 weeks or as clinically indicated until the chimerism is greater than or equal to 50% donor and/or stabilizes.
[10] EBV, CMV, and adenovirus monitoring is required weekly until Day +100, and then per institutional practices. It is recommended to continue monitoring weekly or every other week until off all immunosuppression.
[11] Chronic GVHD Provider Survey to be completed by a clinician at the time of participant assessment.
[12] Optional research blood draws as outlined in Appendix B.
[13] Recommended: PFT, echocardiogram, renal function testing
[14] Window of assessments: see Table 4.3.1.
[15] Karnofsky for patients age 16 and older; Lansky for patients age 12-15.99 at the time of enrollment
[16] Height only required at baseline

CHAPTER 5

5 STATISTICAL CONSIDERATIONS

5.1 Study Overview

This study is a multicenter, Phase II, parallel cohort trial to assess the safety and efficacy of HSCT using haploidentical or URD BM with Thymoglobulin® (Sanofi)(ATG)-containing preparative regimens in participants with previously untreated SAA. The two cohorts are: (1) haplo transplant and (2) URD transplant. The accrual goal for each cohort is 30 participants who have enrolled and initiated protocol-specified conditioning in each cohort, yielding 60 participants in total.

5.1.1 Accrual Duration

It is estimated that 36 months of accrual will be necessary to enroll the targeted sample size.

5.1.2 Primary Objective and Endpoint

The primary endpoint is GFFS. Events contributing to this endpoint are defined in Section 3.1. The primary objective is to assess the GFFS probability at 1 year after initiation of conditioning for each cohort.

5.1.3 Randomization and Blinding

This is a parallel cohort trial in which each participant's transplant cohort is determined by the donor type that they receive (haplo or URD) or, for those not proceeding to transplant, by the selected donor type at start of conditioning. The donor type is expected to match the center's donor preference in most cases. Outcomes will not be compared between the two transplant cohorts. Therefore, no randomization or blinding will be performed.

5.2 Sample Size and Power Considerations

The sample size of 30 participants per cohort was determined to provide estimates of GFFS probabilities at 1 year after initiation of conditioning for each cohort with CIs that are sufficiently narrow. A 1-year GFFS rate of 75% or higher is particularly desirable. Table 5.2.1 displays possible 90% CIs for GFFS, under an assumption of complete follow-up on all participants and using exact Clopper-Pearson binomial CIs. If a cohort has an observed 1-year GFFS rate of 76.7% or higher, the CI will be no wider than 27.9% and will rule out GFFS rates less than 60%. There is expected to be minimal, if any, withdrawal or loss to follow-up before 1 year; in the event that some participant(s) withdraw or are lost to follow-up before 1 year, their GFFS time will be censored, and the Kaplan-Meier estimator will be used for estimation.

Table 5.2.1: Possible Confidence Intervals for GFFS Probability at 1 Year After Initiation of Conditioning in a 30-Participant Cohort

Observed Rate (%)	90% CI* for True Rate	Width of 90% CI
96.7% (29/30)	85.1% - 99.8%	14.7%
90.0% (27/30)	76.1% - 97.2%	21.1%
83.3% (25/30)	68.1% - 93.2%	25.1%
76.7% (23/30)	60.6% - 88.5%	27.9%
70.0% (21/30)	53.5% - 83.4%	29.9%
63.3% (19.30)	46.7% - 77.9%	31.2%
56.7% (17/30)	40.2% - 72.1%	32.0%
50.0% (15/30)	33.9% - 66.1%	32.2%

* Clopper-Pearson CI

5.3 Interim Analysis and Stopping Guidelines

Interim analyses will be performed for safety only, not for efficacy or futility. Participants will be monitored for key safety endpoints on a daily basis for evidence of excess risk. If rates significantly exceed pre-set thresholds (see Sections 5.3.1, 5.3.2, and 5.3.3), the NHLBI will be notified in order that the DSMB can be advised. The policies and composition of the DSMB are described in the BMT CTN MOP. The monitoring guidelines serve as a trigger for consultation with the DSMB and are not formal stopping rules that mandate automatic closure of study enrollment.

Safety outcomes to be monitored include graft failure, Grade 3-4 aGVHD, and early mortality. Graft failure events to be considered include both primary and secondary graft failures occurring through Day +56 post-HSCT in all transplanted participants. Grade 3-4 aGVHD events to be monitored are those occurring through Day +100 post-HSCT in all transplanted participants. Mortality will be monitored up to 115 days from the first day of preparative regimen (Day -9) in all participants receiving the first dose of ATG. The rationale for monitoring mortality from the first day of ATG preparation in all participants receiving the first dose of ATG is to guard against excessive early mortality including death due to the intervention in participants who never proceed to transplant, although this event is expected to be extremely uncommon. The monitoring period for mortality is set to 115 days from the first day of ATG preparation to ensure that this time point aligns with the Day +100 post-HSCT evaluation for participants receiving a transplant.

A truncated sequential probability ratio test (SPRT) for binary data [52] will be used to monitor each safety endpoint. This sequential testing procedure preserves the type I error rate at a prespecified level across all of the daily examinations. The binary SPRT can be represented graphically, with the rejection boundary of the SPRT defined by a straight line. At each examination, the number of evaluable participants is plotted against the cumulative number of events; if the number of events meets or exceeds the boundary, the SPRT rejects the null hypothesis, concluding there is evidence of excessive risk. Otherwise, the SPRT continues until the targeted enrollment goal is reached. Each safety outcome will be monitored separately by transplant cohort to guard against excess risk for a specific transplant type.

5.3.1 Graft Failure by Day 56 Post-HSCT

Graft failure will be monitored through Day +56 post-HSCT among participants who proceed to transplant. Events for this safety endpoint include both primary and secondary graft failure. A graft failure rate of up to 10% is anticipated based on prior experience with HSCT using haploidentical and URDs. A safety monitoring boundary was derived using a binary SPRT that compares a null graft failure rate of 10% to a targeted excessive rate of 30%. The type I error rate for this procedure is 3.7%, corresponding to a critical value of 14.354 for the probability ratio and a rejection boundary with intercept 1.973 and slope 0.159 for the number of events versus participants. The 2 transplant cohorts will be monitored separately using this stopping guideline.

Table 5.3.1 displays the SPRT in a tabular form, showing the rejection boundary values for the number of Day +56 graft failures corresponding to the number of evaluable participants. At least 3 events must be observed in order to trigger review.

Additionally, if 2 Day +56 graft failures occur among the first 5 participants in a cohort, accrual to the cohort will be halted and will resume only when all other transplanted participants pending evaluation reach the Day +56 time point without flagging the stopping guideline.

Table 5.3.1: Stopping Guideline for Graft Failure through Day +56 Post-HSCT in a 30-Participant Cohort

Number of Evaluable Participants*	Rejection Boundary for # Events
3 - 5	3
6 - 10	4
11 - 16	5
17 - 21	6
22 - 26	7
27 - 30	8

* Evaluable participants are those who underwent HSCT.

Table 5.3.2 shows the operating characteristics of this test over a range of true graft failure rates. Uniform accrual of 30 participants to the cohort over a 3-year period is assumed. The operating characteristics were computed exactly using procedures described in Jennison & Turnbull 1999, Chapter 12.[53] This procedure rejects the null hypothesis 3.6% of the time when the true Day 56 graft failure rate is 10% and 80.1% of the time when the rate is 30%. If the true rate is 30%, the DSMB will be consulted at approximately 22 months after opening on average, when 5 events have been observed in 18 enrolled participants.

Table 5.3.2: Operating Characteristics of Sequential Monitoring Procedure for Graft Failure through Day +56 Post-HSCT in a 30-Participant Cohort

True Graft Failure Rate	10%	15%	20%	25%	30%
Probability of Early Stopping	0.036	0.155	0.368	0.608	0.801
Mean Month Stopped	37.4	35.2	31.5	26.8	22.0
Mean # Events	3.0	4.2	5.0	5.3	5.2
Mean # Participants Enrolled	29.4	27.9	25.0	21.4	17.8

5.3.2 Grade 3-4 Acute GVHD through Day +100 Post-HSCT

The occurrence of Grade 3-4 aGVHD onset will be monitored through Day +100 post-HSCT among participants who proceed to transplant. The Grade 3-4 aGVHD rate is expected not to exceed 15% based on prior experience with HSCT in this population. A safety stopping rule was constructed using a binary SPRT contrasting a null rate of 15% to a targeted excessive rate of

35%. The type I error rate for this procedure is 6.6%, corresponding to a critical value of 8.811 for the probability ratio and a rejection boundary with intercept 1.951 and slope 0.224 for the number of events versus participants. The 2 transplant cohorts will be monitored separately using this procedure.

The stopping rule is tabulated in Table 5.3.3, showing the rejection boundary values for the number of Day +100 Grade 3-4 aGVHD events corresponding to the number of evaluable participants. At least 3 events must be observed in order to trigger review.

Additionally, if 2 Day +100 Grade 3-4 aGVHD events occur among the first 4 participants in a cohort, accrual to the cohort will be halted and will resume only when all other transplanted participants pending evaluation reach the Day +100 time point without flagging the stopping guideline.

Table 5.3.3: Stopping Guideline for Grade 3-4 Acute GVHD through Day +100 Post-HSCT in a 30-Participant Cohort

Number of Evaluable Participants*	Rejection Boundary for # aGVHD Events
3 - 4	3
5 - 8	4
9 - 12	5
13 - 16	6
17 - 20	7
21 - 25	8
26 - 29	9
30	10

* Evaluable participants are those who underwent HSCT.

Table 5.3.4 shows the operating characteristics of this test over a range of true Grade 3-4 aGVHD rates. Uniform accrual of 30 participants to the cohort over a 3-year period is assumed. The operating characteristics were computed exactly using procedures described in Jennison & Turnbull 1999, Chapter 12.[53] This procedure rejects the null hypothesis 6.5% of the time when the true Day +100 aGVHD rate is 15% and 80.2% of the time when the rate is 35%. If the true rate is 35%, the DSMB will be consulted at approximately 23 months after opening on average, when 6 events have been observed in 19 enrolled participants.

Table 5.3.4: Operating Characteristics of Sequential Monitoring Procedure for Grade 3-4 Acute GVHD through Day +100 Post-HSCT in a 30-Participant Cohort

True Acute GVHD Rate	15%	20%	25%	30%	35%
Probability of Early Stopping	0.065	0.195	0.398	0.620	0.802
Mean Month Stopped	38.3	35.9	32.3	27.8	23.3
Mean # Events	4.4	5.5	6.1	6.2	6.0
Mean # Participants Enrolled	29.1	27.5	25.0	21.8	18.6

5.3.3 Mortality by Day 115 After Initiation of Conditioning

Mortality will be monitored through 115 days from the first day of conditioning (approximately 100 days post-HSCT for participants receiving a transplant) among participants who initiate the conditioning regimen. The mortality rate is not expected to exceed 10% in either cohort. A safety monitoring boundary for mortality was developed using an SPRT that contrasts a 10% null rate to a 30% targeted excessive rate. The type I error rate for this procedure is 3.7%, corresponding to

a critical value of 14.354 for the probability ratio and a rejection boundary with intercept 1.973 and slope 0.159 for the number of events versus participants. The 2 transplant cohorts will be monitored separately using this stopping guideline.

Table 5.3.5 displays the stopping guideline for mortality, showing the rejection boundary values for the number of deaths through Day +115 after initiation of conditioning by the number of evaluable participants. At least 3 events must be observed in order to trigger review.

Additionally, if 2 Day +115 deaths occur among the first five participants in a cohort, accrual to the cohort will be halted and will resume only when all other participants pending evaluation reach the Day +115 time point without flagging the stopping guideline.

Table 5.3.5: Stopping Guideline for Mortality through Day +115 After Initiation of Conditioning in a 30-Participant Cohort

Number of Evaluable Participants*	Rejection Boundary for # Deaths
3 - 5	3
6 - 10	4
11 - 16	5
17 - 21	6
22 - 26	7
27 - 30	8

* Evaluable participants are those who initiated conditioning.

Table 5.3.6 shows the operating characteristics of this test over a range of true mortality rates. Uniform accrual of 30 participants to the cohort over a 3-year period is assumed. The operating characteristics were computed exactly using procedures described in Jennison & Turnbull 1999, Chapter 12.[53] This procedure rejects the null hypothesis 3.6% of the time when the true Day 115 mortality rate is 10% and 80.1% of the time when the rate is 30%. If the true rate is 30%, the DSMB will be consulted at approximately 24 months after opening on average, when 5 events have been observed in 19 enrolled participants.

Table 5.3.6: Operating Characteristics of Sequential Monitoring Procedure for Mortality through Day +115 After Initiation of Conditioning in a 30-Participant Cohort

True Mortality Rate	10%	15%	20%	25%	30%
Probability of Early Stopping	0.036	0.155	0.368	0.608	0.801
Mean Month Stopped	39.1	36.9	33.2	28.4	23.7
Mean # Events	3.0	4.2	5.0	5.3	5.2
Mean # Participants Enrolled	29.5	28.1	25.6	22.4	19.1

5.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be described for all participants. Characteristics to be examined are age, gender, race/ethnicity, performance status, serum bilirubin level, serum creatinine level, graft type, HLA match, donor age, donor gender, donor race and ethnicity, donor and recipient blood types, and cell dose infused (TNC per kg recipient body weight and if available CD34 count per kg recipient body weight).

5.5 Statistical Analysis Plan

5.5.1 Analysis Populations

5.5.1.1 Primary Analysis Population

The primary analysis population will consist of all participants who initiate the protocol-specified conditioning regimen. Participants will be classified in the transplant cohort (haplo or URD) corresponding to the type of donor selected at the time conditioning is started, even if the infusion is not given.

5.5.1.2 Transplanted Population

The transplanted population will consist of all participants who received a transplant, classified in the transplant cohort (haplo or URD) corresponding to the type of transplant received.

5.5.1.3 Safety Population

The safety population will consist of all participants who initiate the preparative regimen and receive at least one dose of ATG.

5.5.2 Analysis of the Primary Endpoint

5.5.2.1 Analysis Methods

The primary endpoint analysis will focus upon estimating the GFFS probabilities at 1 year after initiation of conditioning for each of the two transplant cohorts. Events for GFFS include Grade III-IV aGVHD, cGVHD requiring immunosuppression, primary or secondary graft failure requiring second definitive therapy, and death. GFFS is defined as the time interval from start of conditioning until the first of these events occurs. Participants who are event-free and withdraw, are lost to follow-up, or complete study follow-up without experiencing an event will be censored at their last contact date. Kaplan-Meier curves will be used to display GFFS from start of conditioning to Day +365 after start of conditioning for each cohort. If no censoring occurs, sample proportions and 90% Clopper-Pearson CIs will be used to estimate 1-year GFFS probabilities. In the presence of censoring, the Kaplan-Meier estimator will give point estimates of GFFS and the beta product confidence procedure [54] will provide 90% exact CIs; the latter reduces to Clopper-Pearson CIs when censoring is absent. GFFS will be analyzed using the primary analysis population.

It is suspected that upfront HSCT using the protocol regimen will produce similar GFFS outcomes for both haplo and URD transplants. If true, data from both cohorts can be combined to obtain more precise estimates of GFFS. A test-then-pool procedure [55] will be employed to allow the possibility of pooling cohort data if their outcomes are similar. The procedure proceeds as follows:

1. Estimate 1-year GFFS probabilities separately for the two cohorts.
2. Compute the difference in GFFS estimates from Step 1.
3. If the magnitude of the difference does not exceed a threshold value of 0.05, a 5% absolute difference in GFFS, combine cohort data and report GFFS point and interval estimates computed from pooled data analysis. Otherwise, only report GFFS estimates from separate analyses of the two cohorts.

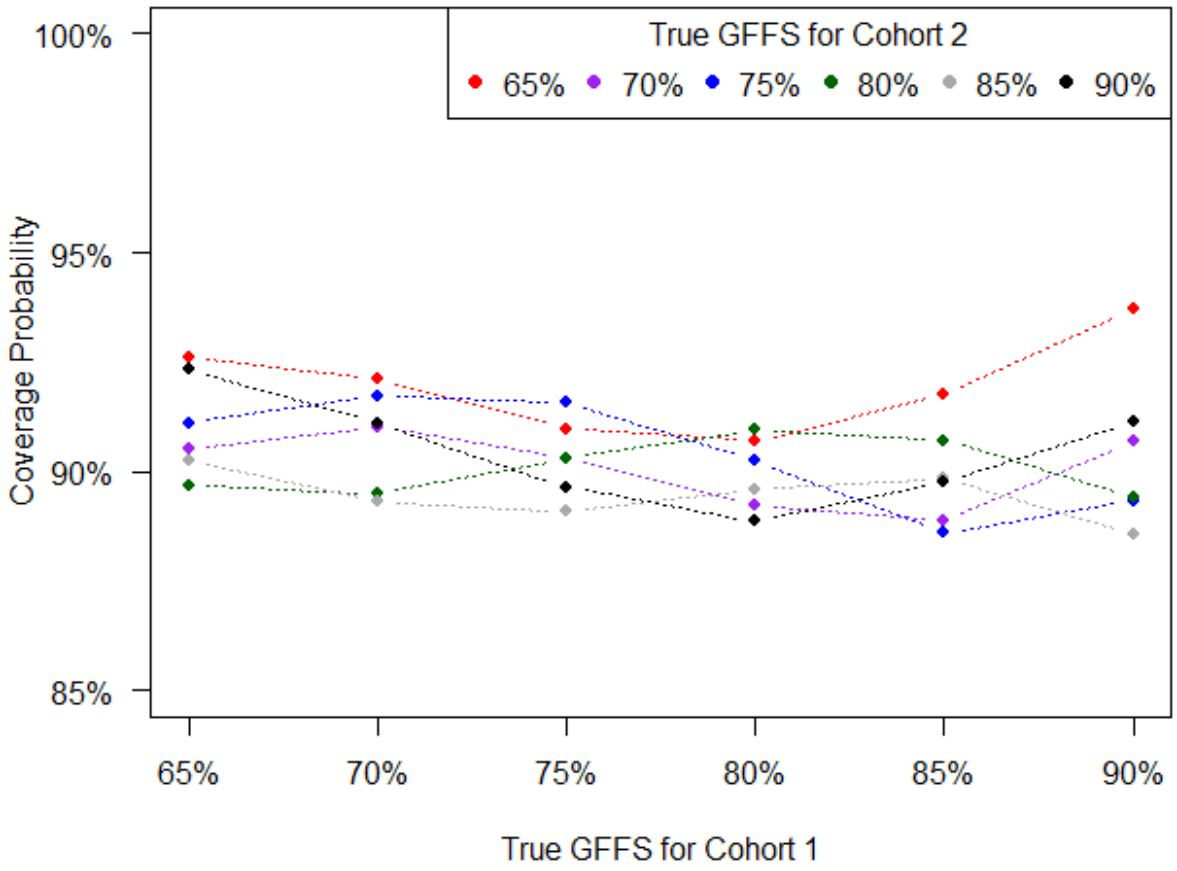
The estimates from separate analyses of the transplant cohorts will be reported, regardless of whether a pooled analysis is performed.

5.5.2.2 Simulation Study of Test-Then-Pool Procedure

A limitation of the test-then-pool procedure is that it can sometimes pool data sources in situations where the true GFFS probabilities are not similar and pooling is undesirable. This could result in biased estimation and CIs that have actual coverage probabilities falling short of their nominal levels. A simulation study was conducted to investigate this possibility under the proposed analysis method. The accuracy of estimates for cohort 1, haplo HSCT, is described; however, because each cohort will be analyzed in the same manner, the results apply identically to both cohorts. True 1-year GFFS probabilities of 65%, 70%, 75%, 80%, 85%, and 90% were considered for each cohort and 100000 trials were simulated for each pair of possible rates with no censoring. The test-then-pool procedure was applied for each simulated trial to obtain a point estimate and nominal 90% CI for GFFS in cohort 1. The true coverage probability was estimated using the proportion of simulated trials where the CI contained the true GFFS probability for cohort 1. Bias was similarly estimated by computing the average difference in the point estimates from the true probability in cohort 1.

Figure 5.5.1 displays Monte Carlo estimates of the coverage probabilities for the CI for cohort 1 at each pair of true GFFS rates considered for cohorts 1 and 2. The estimated coverage probabilities are 88% or higher across all configurations, lying close to or exceeding the nominal 90% level. The coverage probabilities tend to meet or exceed 90% in situations where the cohorts' GFFS rates are equal or within 5% of each other; coverage falls below 90% mainly in cases where the rates are not close. For instance, if the cohort 1 GFFS rate is 75%, coverage probabilities exceed 90% when the cohort 2 rate is 65-80% and are approximately 89% when cohort 2's rate is 85-90%. The estimated bias was small across all scenarios, not exceeding 0.2% in magnitude for any configuration. These simulations support the ability of the test-then-pool procedure to provide GFFS estimates with small bias and nominal 90% CIs with accurate coverage rates.

Figure 5.5.1: Coverage Probabilities of Nominal 90% Confidence Intervals from Test-Then-Pool Procedure for Cohort 1 Estimated from 100000 Simulated Trials



5.5.3 Analysis of Secondary Endpoints

5.5.3.1 Failure-free Survival (FFS)

Events for FFS include death and the receipt of a second definitive therapy. FFS is defined as the time interval from initiation of conditioning until the first of these events occurs. Participants who are event-free and withdraw, are lost to follow-up, or complete study follow-up without experiencing an event will be censored at their last contact date. Kaplan-Meier curves will be used to display FFS from start of conditioning to Day +365 after the start of conditioning for each cohort. If no censoring occurs, sample proportions and 90% Clopper-Pearson CIs will be used to estimate 1-year FFS probabilities. In the presence of censoring, the Kaplan-Meier estimator will give point estimates of FFS and the beta product confidence procedure [54] will provide 90% exact CIs. FFS will be analyzed using the primary analysis population.

It is suspected that FFS outcomes may be similar for haplo and URD transplants. If true, data from both cohorts can be combined to obtain more precise estimates of FFS for them. A test-then-pool procedure [55] will be employed to allow the possibility of pooling cohort data if their outcomes are similar. The procedure proceeds as follows:

1. Estimate 1 year FFS probabilities separately for the two cohorts.
2. Compute the difference in FFS estimates from Step 1.

3. If the magnitude of the difference does not exceed a threshold value of 0.05, a 5% absolute difference in FFS, combine cohort data and report FFS point and interval estimates computed from pooled data analysis. Otherwise, only report FFS estimates from separate analyses of the two cohorts.

The estimates from separate analyses of the transplant cohorts will be reported, regardless of whether a pooled analysis is performed.

5.5.3.2 Overall Survival (OS)

OS is defined as the time interval from initiation of conditioning until death. Participants who withdraw, are lost to follow-up, or complete study follow-up alive will be censored at their last contact date. Kaplan-Meier curves will be used to display OS from start of conditioning initiation to Day +365 after the start of conditioning for each cohort. If no censoring occurs, sample proportions and 90% Clopper-Pearson CIs will be used to estimate 1-year OS probabilities. In the presence of censoring, the Kaplan-Meier estimator will give point estimates of OS and the beta product confidence procedure [54] will provide 90% exact CIs. OS will be analyzed using the primary analysis population.

It is suspected that OS may be similar for haplo and URD transplants. If true, data from both cohorts can be combined to obtain more precise estimates of OS for them. A test-then-pool procedure [55] will be employed to allow the possibility of pooling cohort data if their outcomes are similar. The same procedure will be used as is described for the analysis of FFS in Section 5.5.3.1.

5.5.3.3 Neutrophil Recovery

Neutrophil recovery will be analyzed using the transplanted population The time interval from transplant until neutrophil recovery will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to recovery treated as a competing risk. Estimates and 90% CIs of the cumulative incidence of neutrophil recovery will be provided at Day +28 and Day +56 post-HSCT for each cohort.

5.5.3.4 Red Blood Cell Recovery

RBC recovery will be analyzed using the transplanted population. The time interval from transplant until RBC recovery will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to recovery treated as a competing risk. Estimates and 90% CIs of the cumulative incidence of RBC recovery will be provided at Day +100, Day +180, and Day +365 post-HSCT for each cohort.

5.5.3.5 Platelet Recovery

Platelet recovery will be analyzed using the transplanted population The time interval from transplant until platelet recovery will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to recovery treated as a competing risk. Estimates and 90% CIs of the cumulative incidence of platelet recovery will be provided at Day +100 post-HSCT for each cohort.

5.5.3.6 Graft Failure

Graft failure will be analyzed using the transplanted population. The frequencies and proportions of participants with primary graft failure through Day +56 post-HSCT will be described for each transplant cohort. Participants who die before Day +56 without experiencing primary graft failure

will be classified as non-failures for this analysis. Proportions will be estimated using sample proportions and 90% CIs.

The time interval from transplant until secondary graft failure will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to secondary failure treated as a competing risk. Estimates and 90% CIs of the cumulative incidence of secondary graft failure will be provided at Day +365 post-HSCT for each cohort.

The time from transplant until any graft failure (primary or secondary) will be described for each transplant cohort using the Aalen-Johansen estimator, with death treated as a competing risk. Estimates and 90% CIs of the cumulative incidence of any graft failure will be provided at Day +365 post-HSCT for each cohort.

5.5.3.7 Hematologic Response

Hematologic response will be analyzed using the transplanted population. The frequencies and proportions of participants with complete, partial, and no hematologic response will be described at Day +100, Day +180, and Day +365 post-HSCT for each transplant cohort. Proportions will be estimated using sample proportions and 90% CIs.

5.5.3.8 Acute GVHD

Acute GVHD will be analyzed using the transplanted population. The time intervals from transplant until Grade II-IV and Grade III-IV aGVHD onset will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to aGVHD onset treated as a competing risk. Estimates and 90% CIs of the cumulative incidences of Grade II-IV and Grade III-IV aGVHD will be provided at Day +100 post-HSCT for each cohort.

5.5.3.9 Chronic GVHD

Chronic GVHD will be analyzed using the transplanted population. The time intervals from transplant until any cGVHD onset and cGVHD onset requiring immunosuppression will be described for each transplant cohort using the Aalen-Johansen estimator, with death prior to onset treated as a competing risk for each outcome. Estimates and 90% CIs of the cumulative incidences of any cGVHD onset and cGVHD onset requiring immunosuppression will be provided at Day +365 post-HSCT for each cohort. The maximum severity of cGVHD will be tabulated for each cohort.

5.5.3.10 Being Alive and Engrafted

This outcome will be analyzed using the primary analysis population. The frequencies and proportions of participants who are alive and engrafted at 1 year after initiation of conditioning will be described for each transplant cohort. Failures for this endpoint include death, failure to receive an HSCT infusion, and the failure to achieve at least 5% myeloid donor chimerism (whole blood or marrow) in the most recent measurement through 1 year. For failure to receive an HSCT infusion, the event time will be the day that the decision not to proceed to HSCT is made. Proportions will be estimated using sample proportions and 90% CIs.

5.5.4 Analysis of Exploratory Endpoints

5.5.4.1 Time to Enrollment

The time interval from HLA typing to enrollment will be described in the primary analysis population by transplant cohort using the sample median, quartiles, minimum, and maximum.

5.5.4.2 Time from Diagnosis of SAA to Conditioning and to Transplant

The time interval from SAA diagnosis to start of conditioning will be described in the primary analysis population by transplant cohort using the sample median, quartiles, minimum, and maximum. The time interval from SAA diagnosis to HSCT will be described in the transplanted population by transplant cohort using the sample median, quartiles, minimum, and maximum.

5.5.4.3 Times to Donor Activation, Donor Selection, Start of Conditioning, and Transplant

The time intervals from enrollment to donor activation, donor selection, and start of conditioning will be described in the primary analysis population by transplant cohort using the sample median, quartiles, minimum, and maximum. The time interval from enrollment to HSCT will be described in the transplanted population by transplant cohort using the sample median, quartiles, minimum, and maximum.

5.5.4.4 Donor Availability

The number of available donors will be described in the primary analysis population by transplant cohort using the sample median, quartiles, minimum, and maximum. Available donors will be described overall and separately by graft type for haploidentical and for 8/10, 9/10, and 10/10 URDs.

5.5.4.5 HSCT Cell Dose

The TNC and CD34+ cell doses received will be described in the transplanted population by transplant cohort using the sample median, quartiles, minimum, and maximum.

5.5.4.6 Immune Reconstitution

Levels of peripheral blood CD4-, CD19-, and CD56-positive lymphocytes will be measured by flow cytometry analysis at baseline and Day +100, Day +180, and Day +365 post-HSCT. These cell populations will be analyzed in the transplanted population.

The level of each cell population will be summarized for each transplant cohort using descriptive statistics at each assessment time considered. Changes in levels from baseline to each follow-up assessment time will be evaluated within each cohort. Logarithmic and other transformations will be applied to the cell levels to induce normality. If a normalizing transformation is identified, a linear mixed model will be used to assess changes in levels over time, with fixed effects for assessment times (Day +100, Day +180, and Day +365) and random effects to account for correlations of levels within each participant. If no normalizing transformation is found, a nonparametric analysis will be conducted using Wilcoxon signed rank tests to evaluate the changes in cell levels between each pair of assessment times.

5.5.4.7 Infection

The number of Grade 2-3 infections and number of participants infected will be summarized by type, severity, and time period in the transplanted population by transplant cohort. The incidences of CMV viremia and disease, EBV viremia, and PTLD will be described for each cohort.

5.5.4.8 Health Related Quality of Life (HR-QoL)

HR-QOL will be assessed at baseline and at Day +100, Day +180, and Day +365 post-HSCT using the PROMIS domains for anxiety, depression, anger, fatigue, physical function, cognitive function, and ability to participate in social roles & activities. The COST, occupational functioning

items, and sociodemographic/social determinants of health will be assessed at baseline and at Day +180 and Day +365 post-HSCT. These measures will be analyzed using the transplanted population.

The distributions of scores for the PROMIS domains and COST will be described by descriptive statistics at each assessment time point for each transplant cohort. Responses to occupational functioning, and sociodemographic/social determinants of health items will be tabulated by frequency and percentages at each assessment time for each cohort.

Changes in scores from baseline to each follow-up assessment time will be evaluated for the PROMIS domains and COST. A linear mixed model will be used for each score and cohort to assess changes over time, with fixed effects for assessment times and random effects to account for correlations of scores within each participant.

5.5.5 Analysis of Safety Endpoints

The frequency of Grade 3-5 AEs per CTCAE version 5.0 will be tabulated by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary for each transplant cohort. The frequency and proportion of participants having at least one Grade 3-5 AE will be summarized by SOC and PT. Detailed listings of unexpected SAEs, including grade and relationship to treatment, will be presented. Adverse events will be summarized using the safety population.

APPENDIX A

HUMAN SUBJECTS

1. Participant Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Prinicipal Investigator or his/her designee at each transplant center will contact the candidates, provide the participant with information about the purpose of the study, and obtain consent. The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local IRB. The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval to the DCC.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a participant identifier (ID) code. The code relaying the participant's identity with the ID code will be kept separately at the center. The ID code will be generated by and kept on file at the BMT CTN DCC upon enrollment.

3. Participation of Women and Minorities

Women, ethnic minorities, and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of SAA in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

APPENDIX B

LABORATORY PROCEDURES

OPTIONAL RESEARCH SPECIMENS

Participants and donors consenting to the optional future research will have samples collected for future research supporting the protocol. All research sample aliquots will be given unique bar code designations that cannot be linked back to the participant's name or other identifying information. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the protocol. Samples sent to researchers cannot be linked with any remaining samples at the repository.

Patient samples will be collected both prior to the initiation of conditioning and at Day +28, Day +56, Day +100, Day +180 and Day +365 post-treatment as specified in the table on the next page. Donor samples will be collected at a single timepoint prior to marrow collection. All research samples will be collected and shipped same day to the BMT CTN Repository for processing and sample aliquot storage. Sample collection and shipping procedures are detailed in the BMT CTN 2207 Research Sample Information Guide.

Subjects	Sample Type & Volume	Sample Collection Time Points	Sample Collection and Processing Summary	Shipping Specifications
Patients	**Peripheral Blood** (SST Clot Tube) 5 mL	**Pre-Conditioning** Day -9 **Post-Treatment** Day 28, 56, 100, 180, and 365	Collect the blood sample and place into a SST Vacutainer tube containing clot activator. Allow blood samples to clot upright for 30-60 minutes in a tube rack prior to centrifugation.	Centrifuged blood sample tube will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository, processed into five 0.5 mL serum aliquots, and stored at -80ºC.
	Peripheral Blood (EDTA) 3 mL		Collect the blood sample and place into a Vacutainer tube containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix.	Blood sample tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Biorepository, processed into three 1.0 mL whole blood aliquots, and stored and -80ºC.
	Peripheral Blood (NaHep) 30 mL		Collect the blood sample and place 10 mL into each of three Vacutainer tubes containing sodium heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix.	Blood sample tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Biorepository, processed into three 5x10^6 PBMC aliquots and ten 0.5 mL plasma aliquots, and stored in LN2 and -80ºC respectively.
Donors	**Peripheral Blood** (EDTA) 20 mL	**Prior to Marrow Collection**	Collect the blood sample and place into a Vacutainer tube containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix.	Blood sample tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Biorepository, processed into three 1.0 mL whole blood aliquots, and stored and -80ºC.

Windows for Submitting Optional Research Samples	
Day -9	Prior to initiation of conditioning (Day -9 -7 days)
Pre-Collection (Donor)	Prior to marrow collection
Day +28	Day 28 ± 3 days
Day +56	Day 56 ± 3 days
Day +100	Day 100 ± 7 days
Day +180	Day 180 ± 28 days
Day +365	Day 365 ± 45 days

APPENDIX C

WEIGHT CALCULATIONS

Use the following calculations according to medication specific instructions in Section 2.6.1.1:

Adjusted IBW (AIBW) Formula:

AIBW = IBW + [(0.25) x (actual body weight – IBW)]

IBW for Participants ≥ 18 Years of Age (Devine equation):

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

For participants less than 5 feet, subtract 2.3 kg/inch

Note for Centers using the metric system, the following equations can be used:

Males IBW = 50 kg + [(cm ÷ 2.54 – 60) x 2.3 kg]

Females IBW = 45.5 kg + [(cm ÷ 2.54 – 60) x 2.3 kg]

For participants less than 152.4 cm feet, subtract 2.3 kg/2.54 cm

IBW for Participants 1 to 17 Years of Age:

Less than 60 inches

IBW = (ht^2 x 1.65)/1000 where ht = cm, IBW = kg

More than 60 inches

Males IBW = 39.0 + [2.27 x (ht - 60)] where ht = inches, IBW = kg

Females IBW = 42.2 + [2.27 x (ht - 60)] where ht = inches, IBW = kg

Examples of calculations:

EXAMPLE CALCULATION 1:

A 62-year-old female TBW 60 kg, height 64 inches

IBW = 54.7 kg

EXAMPLE CALCULATION 2:

A 62-year-old female Weight 86 kg, height 64 inches

IBW 54.7 kg

TBW/IBW = 86/54.7 = 157% IBW

AIBW = IBW + 0.25(TBW – IBW) = 54.7 + 0.25(86 – 54.7) = 62.5 kg

EXAMPLE CALCULATION 3:

A 62-year-old Male Weight 86 kg, height 68 inches

IBW 68.4 kg

TBW/IBW = 86/68.4 = 126% IBW

AIBW = IBW + 0.25(TBW – IBW) = 68.4 + 0.25(86 – 68.4) = 72.8 kg

APPENDIX D

CAMITTA [56] CRITERIA FOR SAA

Peripheral Blood Cytopenias	**Non-severe (Moderate) Aplastic Anemia** (not meeting criteria for severe disease)	**Severe Aplastic Anemia** (any 2 of 3)	**Very-severe Aplastic Anemia** (meets criteria for severe disease and absolute neutrophils < 200)
BM Cellularity	< 25%	< 25%	< 25%
ANC		**<** 500 / mL	**<** 200 / mL
Platelet Count		**<** 20,000 / mL	
Reticulocyte Count		**<** 1.0% corrected **or** **<** 60,000 / mL	

APPENDIX E

ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ADL	Activity of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
aGVHD	Acute Graft Versus Host Disease
AIBW	Adjusted Ideal Body weight
AIHA	Autoimmune hemolytic anemia
alloBMT	Allogenic Bone Marrow Transplantation
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ARD	Antigen Recognition Domain
ASBMT	American Society for Blood and Marrow Transplantation
AST	Aspartate Aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	Antithymocyte globulin
BAL	Bronchoalveolar Lavage
BiPap	Bi-level positive airway pressure
BM	Bone Marrow
BMT	Bone Marrow Transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BOS	Bronchiolitis Obliterans Syndrome
BSA	Body Surface Area
CBC	Complete Blood Count
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
cGVHD	Chronic Graft Versus Host Disease
cGY	Centigray
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central Nervous System
CoNS	Coagulase-Negative Staphylococci
COST	Comprehensive Score of Financial Toxicity
CPAP	Continuous Positive Airway Pressure
CPK	Creatine Phosphokinase
CR	Complete Response
CrCl	Creatinine Clearance
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CSA	Cyclosporin A
CSF	Cerebrospinal Fluid

Abbreviation	Definition
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Effects
CTX	Cyclophosphamide
CXR	Chest X-Ray
CYP3A4	Cytochrome P450 3A4
DCC	Data Coordinating Center
DEB	Diepoxybutane
DIC	Disseminated Intravascular Coagulopathy
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLI	Donor Lymphocyte Infusion
DNA	Deoxyribonucleic Acid
DSA	Donor Specific HLA Antibodies
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
EBMT	European Society for Blood and Marrow Transplantation
Echo	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EKG	Electrocardiogram
ePRO	electronic Patient-Reported Outcomes
FEV1	Forced Expiratory Volume 1
FFP	Fresh Frozen Plasma
FFS	Failure-Free Survival
FISH	Fluorescence In Situ Hybridization
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFFS	Graft Failure-Free Survival
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GVHD	Graft Versus Host Disease
hATG	Horse Antithymocyte Globulin
HCT	Hematopoietic Cell Transplant
HCT-CI	Hematopoietic Cell Transplant Comorbidity Index
HepA	Hepatitis A
HepB	Hepatitis B
HepC	Hepatitis C
Hgb	Hemoglobin
HHV-6	Human Herpesvirus 6
HIV	Human Immunodeficiency Virus
HLA	Human Lymphocyte Antigen
HLH	Haemophagocytic Lymphohistiocytosis
Hr	Hour
HR-QoL	Health Related Quality of Life
HSCT	Hematopoietic Stem Cell Transplantation
HSV	Herpes Simplex Virus
HTLV1	Human T-Lymphotropic Virus type 1
HVG	Host Versus Graft

Abbreviation	Definition
HypoMg/Ca/Phos	Hyopmagnesemia/Hypocalcemia/Hypophosphatemia
IBW	Ideal Body Weight
ICC	International Consensus Classification
ICH	International Council for Harmonization
ICU	Intensive Care Unit
ID	Identifier
IFD	Invasive Fungal Disease
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International Normalized Ratio
I&O	Input and Output
IQR	Interquartile Range
IRB	Institutional Review Board
IST	Immunosuppressive Therapy
ITP	Idiopathic Thrombocytopenic Purpura
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KCS	Keratoconjunctivitis sicca
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LPS	Lansky Performance Status
LSS	Lee chronic GVHD Symptom Scale
LVEF	Left Ventricular Ejection Fraction
MAS	Macrophage Activation Syndrome
Max	Maximum
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
MMF	Mycophenolate Mofetil
MOP	Manual of Procedures
MPA	Mycophenolic Acid
MSD	Matched Sibling Donor
MUGA	Multigated Acquisition
NA	Not Applicable
NAT	Nucleic Acid Testing
NCI	National Cancer Institute
Neuro	Neurological
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NOS	Not Otherwise Specified
OS	Overall Survival
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PFT	Pulmonary Function Test
PI	Principal Investigator

Abbreviation	Definition
PJP (or PCP)	*Pneumocystis Jiroveci* Pneumonia
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PNH	Paroxysmal Nocturnal Hemoglobinuria
PO	Per Os (by mouth)
PR	Partial Response
PRBC	Packet Red Blood Cell
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-Reported Outcome
P-ROM	Photographic Range of Motion
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Termothrombin Time
PTCTC	Pediatric Transplantation and Cellular Therapy Consortium
PTCy	Post-transplant Cyclophosphamide
PTLD	Post-Transplant Lymphoproliferative Disease
PTT	Partial Thromboplastin Time
q	Quaque (*each*)
RACE	A prospective Randomized multicenter study comparing horse Antithymocyte globulin (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia
RBC	Red Blood Cell
ROM	Range of Motion
RSV	Respiratory Syncytial Virus
SAA	Severe Aplastic Anemia
sAb	Surface Antibody
SAE	Serious Adverse Event
sAg	Surface Antigen
SCTOD	Stem Cell Transplant Outcomes Database
SD	Standard Deviation
SF	Shortening Fraction
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
SOC	System Organ Class
SOP	Standard Operating Procedure
SOS	Sinusoidal Obstruction Syndrome/
SPRT	Sequential Probability Ratio Test
SRG	Survey Research Group
SQ	Subcutaneous
STAT	Immediately
TA-TMA	Transplant-Associated Thrombotic Microangiopathy
TBI	Total Body Irradiation
TID	Ter in Die (3 times a day)
TNC	Total Nucleated Cell
US	United States
VOD	Veno-Occlusive Disease
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WHO	World Health Organization

APPENDIX F

BONE MARROW HARVEST GUIDELINES [57]

Bone marrow is usually harvested from the posterior iliac crests while the donor is under regional (spinal or epidural) or general anesthesia. Two individuals, usually a physician and a nurse practitioner or physician's assistant, perform the harvest, one on each posterior iliac crest. The BM cavity is entered through a skin puncture, after sterile prepping and draping. The posterior superior iliac spine is used as a starting anatomic landmark for the procedure. Large bore needles attached to 50 mL syringes rinsed with a heparinized solution are used for aspirating the marrow using a quick, vigorous suctioning technique. No more than 3-5 mL of a blood-BM mixture should be withdrawn from a single aspirate, since aspirating more will dilute the marrow cells with peripheral blood. After 3-5 mL are aspirated, additional aspirates can by withdrawn from the same marrow puncture as long as the needle position is repositioned, i.e., withdrawing the needle 0.5 cm while changing the position of the bevel by 90°. Generally, 10-30 punctures into the marrow are made through a single skin puncture. Limiting any one skin puncture to 10-30 marrow punctures will also limit blood contamination as a result of local area bleeding. Thereafter, 2-3 additional skin punctures are made on each side of the iliac crest, each one several centimeters lateral to the previous, proceeding as far as necessary toward the anterior superior iliac spine to acquire sufficient marrow. The usual marrow harvest target for transplantation is 4×10^8 nucleated marrow cells per kg of the transplant recipient's ideal weight, so that the volume collected (generally between 500 and 1500 mL) will vary on the size of the recipient and the marrow cell concentration (see below). The aspirated marrow is collected into semi-closed or closed system of filters and a bag containing anticoagulant (Fenwall, BioAcess).

The collection iIs based on the target number of cells specified for the recipient. The nucleated cell/mL should be assessed during the procedure with a cell count that is called back to the operating room. Calculation of the total volume needed to achieve the target dose should then be used to clinically determine the final harvest volumes. Erring on the high end is preferred to underestimating doses. Equations used to calculate are as follows:

1. Prior to the procedure, determine the weight of the collection bag or tare the scale. The weight of the product (total weight minus bag or weight above the tared weight) is then divided by 1.058, the specific gravity of marrow. This result (A) is the volume of the marrow.
2. The marrow nucleated cell count (B) is determined by the nucleated cell count from the lab in cells/mL *corrected by subtracting the number of peripheral blood white cells/mL presumed to be contaminating the marrow* and is then multiplied by the volume (A) to calculate the TNC: A x B = TNC. (Example: if marrow count is 27 and peripheral white cell count is 6, then the marrow mononuclear cell count would be 21 = B)
3. TNC should then be divided by IBW to determine TNC/kg achieved (target 4×10^8 nucleated cells/kg recipient IBW).

PRODUCT SAMPLING: BSC:_____Tech:_____ Date:_____ Time: _____

Volume (ml) (gross weight – tare) ÷ 1.058 **(A)**	Nucleated Cell Count (cells/ml) **(B)**	Total Nucleated Cells **(C)** (A) x (B)	Nucleated Cells/kg **(D)** (C) ÷ Body Weight
ml	x 10^6/ml		10^6/kg

(tare weight of Fenwal 2 L bag = 62gm)

(1.058 is the specific gravity that we use to convert weight to volume for BM)

APPENDIX G

GUIDANCE FOR MIXED CHIMERISM

Chimerism measurements should be assessed as per protocol requirements (Table 4.3.5). Primary and secondary graft failure are also defined (Section 3.2.6 and Section 3.2.7). There will be participants who meet criteria for mixed chimerism post-transplant who require special attention.

Any donor chimerism below 95% in the myeloid or the T cell compartment should be considered mixed chimerism.

Less than 50% donor CD3 chimerism in the early post-transplant period has correlated in malignant diseases with increased risk of graft loss or rejection.

In aplastic anemia, a graft is considered functional if it results in correction of the underlying marrow failure with increase in neutrophils and/or transfusion independence from baseline, even in the setting of mixed chimerism.

Low early T cell chimerism could be a harbinger of rejection or may improve spontaneously over time.

Recommendations to reduce the risk of mixed chimerism and to manage mixed chimerism, if it occurs:

1. Optimize cell counts in the donor harvest to achieve at least a goal of 4 x 10^8 nucleated cells/kg recipient weight (minimum 2.5 x 10^8 nucleated cells/kg recipient weight)
2. Ensure optimal compliance with all post-transplant immunosuppression.
    a. Mycophenolate mofetil should be given via IV in participants whom the oral preparation is not well tolerated.
    b. Monitor levels of tacrolimus (as often as daily) to ensure therapeutic troughs.
3. If post-Day 28, Day 56, or Day 100 chimerism is low, increase frequency of monitoring per protocol (Table 4.3.5), with monthly chimerisms until stable or resolved.
4. Do not stop immunosuppression. Consider up-titrating dose of calcineurin inhibitor to ensure trough in the upper end of goal range.
5. In most situations, we do not advise donor lymphocyte infusion (DLI) as a first approach for reduced chimerism due to the risk of GVHD. For participants with poor graft function and established donor chimerism, CD34+ selected cell boosts or growth factors can be considered.
6. Continue close clinical follow-up.
7. Notify protocol chairs or medical monitor with questions or concerns.

APPENDIX H
BMT CTN INFECTION GRADING TABLE AND RECURRENCE INTERVAL DEFINITIONS

From BMT CTN Technical Document Infectious Diseases v2.0, dated September 9, 2024

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacteremia with skin flora [ex. Coag Neg Staph (CoNS, S. epi), Corynebacterium, or Cutibacterium (Proprioniobacterium)] requiring antibiotics for ≤ 14 days of therapy for treatment Bacterial focus NOS requiring antibiotics for ≤ 14 days of therapy for treatment (e.g urinary tract infection) Bacterial focus NOS requiring only topical, ocular, or otic treatments Cellulitis responding to initial therapy within 14 days Any bacterial pneumonia not requiring supplemental oxygen *C difficile* toxin or PCR positive stool with diarrhea < 1L/day without abdominal pain (child < 20 mL/kg/day)	Bacteremia due to other organisms (not skin flora) Bacterial focus (including bacteremia) with persistent signs/symptoms or persistent positive cultures requiring antibiotics for > 14 days of therapy Cellulitis requiring a change in therapy due to progression or systemic treatment for >14 days Localized or diffuse infections requiring incision with or without drain placement but no debridement Any pneumonia documented or presumed to be bacterial requiring low flow oxygen *C difficile* toxin or PCR positive stool with diarrhea ≥ 1L/day (child ≥ 20 mL/kg/day) or with abdominal pain	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis, brain abscess) Severe shock with bacteremia. Endocarditis Brain abscess or meningitis without bacteremia Active Tuberculosis infection Fasciitis or other skin and soft tissue infection requiring surgical debridement Bacterial pneumonia requiring high flow oxygen or positive pressure ventilation *C difficile* toxin or PCR positive stool with ileus, colon dilation, or toxic megacolon, or need for surgical bowel resection (colectomy, ileostomy)

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Fungal infections	Mucocutaneous candidiasis (excluding esophagitis) (e.g., oral thrush, vaginal candidiasis) and dermatophyte infections (tinea)	*Candida* esophagitis diagnosed by endoscopy Fungal sinusitis confirmed radiologically without orbital, brain or bone involvement. Fungal pneumonia or pulmonary nodules (unless requiring high-flow oxygen or positive pressure ventilation) Fungal skin and soft tissue infection without fungemia, involvement of other sites, or need for debridement *Pneumocystis jirovecii* pneumonia (unless requiring high-flow oxygen or positive pressure ventilation)	Fungemia including candidemia Fungal sinusitis confirmed radiologically with orbital, brain, or bone involvement Fungal pneumonia or pulmonary nodules presumed to be fungal requiring high-flow oxygen or positive pressure ventilation Disseminated infections (defined as multifocal pneumonia with 1 or more additional site of involvement, cutaneous spread, CNS involvement) with any fungus (yeast or mold) *Pneumocystis jirovecii* pneumonia requiring high-flow oxygen or positive pressure ventilation

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Viral infections	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring oral antiviral therapy or observation Dermatomal zoster (shingles) affecting ≤ 2 dermatomes Asymptomatic CMV viremia not requiring treatment EBV viremia not requiring treatment Adenoviral infection not requiring treatment HHV-6 viremia not requiring treatment BK viremia or viruria with cystitis not requiring intervention except anti-spasmodics or pain medication Symptomatic upper and lower tract respiratory virus (excludes adenovirus, SARS-CoV-2 [COVID]) not requiring oxygen Viremia (virus not otherwise specified) not requiring therapy	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring IV nutrition or IV antiviral therapy VZV infection involving 3 or more dermatomes CMV viremia requiring therapy or CMV viremia requiring a change in therapy due to resistance or with persistent viremia beyond 4 weeks while on treatment EBV viremia requiring institution of therapy Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment HHV-6 infection (e.g., symptoms, cytopenias) requiring treatment BK viremia or viruria with clinical consequence requiring therapy (continuous bladder irrigation, antiviral therapy) and/or surgical intervention Enterocolitis with enteric (GI) viruses Lower tract respiratory viruses (excludes adenovirus, SARS-CoV-2 [COVID]) requiring low flow oxygen SARS-CoV-2 (COVID) infection requiring low flow oxygen Any viremia (virus not otherwise specified) requiring therapy	HSV infection with end organ involvement (encephalitis, hepatic, lung) Severe VZV infection with end organ involvement (coagulopathy, encephalitis, hepatic, lung, eye) CMV end-organ involvement (lung, intestines, eye) EBV PTLD Adenovirus with end-organ involvement, including pneumonitis, but excluding conjunctivitis and upper respiratory tract infections HHV-6 with end-organ involvement (such as encephalitis, hepatitis, pneumonitis) BK viremia or viruria with end organ damage (i.e., renal failure requiring dialysis) Lower tract respiratory viruses (excludes adenovirus, SARS-CoV-2 [COVID]) requiring or high flow oxygen Or positive pressure ventilation Any viral encephalitis, meningitis, or end organ disease

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Parasitic infections	Giardiasis or other parasitic gastrointestinal infection with diarrhea <1L / day (<5 episodes / day) (child < 20 mL/kg/day) Chronic strongyloidiasis treated with oral ivermectin or other oral therapies Toxoplasma DNAemia without organ involvement resolving spontaneously (without treatment)	Giardiasis or other parasitic gastrointestinal infection with diarrhea > 1 L / day (5 episodes/ day) (child > 20 mL/kg/day) or with abdominal pain Toxoplasma DNAemia without organ involvement requiring treatment	Strongyloides hyperinfection or disseminated infection CNS or other organ toxoplasmosis
Nonmicrobiologically defined infections	Pneumonia or bronchopneumonia not requiring supplemental oxygen Fever with negative cultures responding to treatment within 14 days Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia requiring low flow oxygen Sepsis without an identified organism (excluding patients receiving immune effector therapy diagnosed with cytokine release syndrome (CRS)) Typhlitis without severe sepsis, ileus, or need for surgical intervention	Any acute pneumonia requiring high flow oxygen or positive pressure ventilation Septic shock without an identified organism (excluding patients receiving immune effector therapy diagnosed with CRS) Typhlitis requiring surgical indication as grade 3

Sepsis (Adult) based on CDC's Sepsis Criteria:

a. Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.
b. Hypotension: A systolic blood pressure of ≤100 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension
c. Organ Dysfunction defined by Sequential Organ Failure Assessment (eSOFA) score: Any of the following
    i. Initiation of new vasopressor infusion
    ii. Initiation of mechanical ventilation (invasive or non-invasive)
    iii. Acute renal failure (only for patients without end-stage renal failure) defined as **Either:**
        a. Doubling of serum creatinine compared to baseline **OR**

b. Decrease in estimated glomerular filtration rate (eGFR) by ≥ 50% compared to baseline

iv. Hyperbilirubinemia defined as **BOTH**
   a. Total bilirubin ≥ 2mg/dl, **AND**
   b. Total bilirubin increase of ≥ 50% compared to baseline

v. Thrombocytopenia (only for patients with baseline platelet count >100 cell/μL) defined as **BOTH**
   a. Platelet count <100 cell/μL, **AND**
   b. Decrease in platelet count ≥50% compared to baseline

vi. Serum lactate ≥2 mg/dL

d. Adult Sepsis Criteria: Any organ dysfunction PLUS a source and or suspected source of infection

e. Adult Septic Shock: Sepsis plus vasopressors to maintain adequate blood pressure AND elevated lactate (>2mmol/L or >18 mg/dL).

Pediatric Sepsis based on International Pediatric Sepsis Consensus Conference (2005):

a. Pediatric SIRS definition: Two or more of the following, one of which must be abnormal temperature or leukocyte count
   i. Core temperature >38.5C or < 36C
   ii. Tachycardia, otherwise unexplained and persistent in the absence of external stimulus, chronic drugs, or painful stimuli; or bradycardia, in < 1 year old, otherwise unexplained and persistent.
   iii. Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
   iv. Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands

b. Pediatric Sepsis: Requires either Pediatric SIRS definition (supplemental table 2) plus suspected or proven infection

c. Pediatric Severe Sepsis: Sepsis plus either 1) cardiovascular dysfunction or ARDS; or 2) two or more other organ dysfunctions.

d. Pediatric Septic Shock: Sepsis and cardiovascular organ dysfunction (below)

e. Pediatric organ dysfunction criteria: (hematological criteria excluded)

I. Cardiovascular:
Despite administration of fluid bolus >40 ml/kg in 1 hour presence of
   a. Hypotension <5th percentile for age (or per supplemental table 2)
      OR
   b. Blood pressure elevation agents at any dose
      OR
   c. Two of the following:
      I. Capillary refill > 5 secs
      II. Core to peripheral temperature gap > 3^{o}C
      III. Urine output < 0.5 mL/kg/hr
      IV. Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
      V. Blood lactate > 2 x ULN

II. Respiratory:
   a. ARDS
      OR
   b. Intubated

OR

c. >50% FiO2 to maintain SaO2 or SpO2 ≥ 92%

III. Neurological:

a. Glasgow Coma Score ≤ 11

OR

b. Acute change in mental status with a decrease in GSC ≥3 pts from abnormal baseline

IV. Renal:

a. Serum creatinine ≥ 2 x ULN for age

OR

b. 2-fold increase in baseline creatinine

V. Hepatic:

a. Total bilirubin ≥4 mg/dL

OR

b. ALT >2 x ULN for age

Pediatric Systemic Inflammatory Response Syndrome Definitions and Laboratory Values Ranges for the four Pediatric Age Groups [1]

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia ($10^3/mm^3$WBC)	Hypotension Systolic BP mmHg
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<75
>1 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<74
>5 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<83
>12 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<90

[1] Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005 Jan;6(1):2-8. doi: 10.1097/01.PCC.0000149131.72248.E6. PMID: 15636651.

Disseminated Infections:

Two or more non-contiguous sites infected with the same organisms.

- For infections coded as “Disseminated” per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.
- It can occur at any level of severity, but most will be grade 2 or 3

Oxygen Supplementation definitions:

a. Low flow: oxygen by nasal cannula at ≤ 6L/minute
b. If patient requires supplemental oxygen at baseline (i.e., on 2L/minute) in the outpatient setting, an increase over the baseline oxygen needs (i.e increase to 3L/minute) is required to meet “low flow” definition
c. High flow: oxygen by nasal cannula at >6L/minute
d. Positive Pressure: Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), intubation with mechanical ventilation

Recurrence Intervals to Determine Whether an Infection is the Same or New:

Type of Infection	Recurrence Internal reflects a previously diagnosed Infection
Cytomegalovirus, Herpes simplex virus, Epstein-Barr virus, and Human herpes virus 6 related infections	2 months (< 60 days)
Varicella zoster virus	2 weeks (< 14 days)
Polyomavirus	2 months (< 60 days)
Bacterial, non-*C. difficile*	1 week (< 7 days)
Bacterial, *C. difficile*	1 month (< 30 days)
Yeast infections (non-cryptococcal)	2 weeks (< 14 days)
Invasive mold infections, dimorphic fungal infection, and cryptococcal infection	3 months (< 90 days)
Helicobacter pylori infection	1 year (< 365 days)
Respiratory viruses: Adenovirus, Enterovirus, Influenza A &B, Respiratory syncytial virus, Parainfluenza, Rhinovirus, and SARS-CoV-2 infections	3 months (<90 days)
Parasitic infections (excluding chronic strongyloidiasis)	3 months (< 90 days)
Chronic strongyloidiasis (defined as positive serologies without detection of larvae)	2 years

Invasive fungal disease (IFD) due to yeasts, yeast-like fungi, and dimorphic fungi

IFD type	Criteria for proven IFD	Criteria for evidence of IFD
Endemic mycoses (for example *Coccidioides*, *Blastomyces*, *Histoplasma*)	*At least one of these criteria:* • Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus, *or* • Culture of the fungus from blood or specimens from an affected site	Clinical diagnosis (pulmonary, cutaneous, osseous, GI, and/or CNS) and initiation of treatment for endemic mycosis *Plus at least one of these criteria:* • *Histoplasma* or *Blastomyces* antigen in urine, serum, or body fluid • Antibody to *Coccidioides* in cerebrospinal fluid • Two-fold rise of *Coccidioides* antibodies in 2 consecutive serum samples
Pneumocystis jirovecii pneumonia (PJP or PCP)	Detection of the organism microscopically in tissue, BAL fluid, or sputum using conventional or immunofluorescence staining	Clinical diagnosis of PJP with initiation of treatment • *Plus at least one of these criteria:* • ß-D-glucan (Fungitell®) ≥ 8 0 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell have been excluded) • Detection of *Pneumocystis jirovecii* DNA by PCR from a respiratory tract specimen

IFD type	Criteria for proven IFD	Criteria for evidence of IFD
Cryptococcal infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast consistent with *Cryptococcus* species (based on morphology or PCR) • Recovery of *Cryptococcus* by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with *Cryptococcus* • Positive cryptococcal antigen in cerebrospinal fluid or blood	Clinical diagnosis of cryptococcal infection (pulmonary, CNS, cutaneous, disseminated with initiation of treatment *Plus at least one of these criteria:* • Radiographic evidence of meningeal inflammation • Lesion on imaging consistent with cryptococcal disease
Candida and other yeast infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast • Recovery of yeast by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with yeast	*Applies to Candida only* *Candidemia within the previous 2 weeks with at least one of these criteria:* • Radiographic findings consistent with abscesses in liver, spleen, or brain • Meningeal enhancement • Progressive retinal exudates or vitreal opacities on ophthalmologic examination *Plus initiation of treatment and at least one of these criteria:* • ß-D-glucan (Fungitell®) ≥80 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell® have been excluded) • Positive T2Candida®

IFD due to *Aspergillus* and other molds

Proven mold infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a tissue specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage • Recovery of a mold by culture of a specimen obtained by a sterile procedure from a normally sterile site (with clinical or radiological evidence of an infection), excluding BAL fluid, sinus specimens, and urine • Blood culture that yields a mold in the context of a compatible infection • Identification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue		
Probable mold infection	Clinical feature **Pulmonary aspergillosis and other pulmonary mold infections** *At least one of these patterns are seen on CT imaging:* • Dense, well-circumscribed lesions • Air crescent sign • Cavity • Wedge-shaped, segmental, or lobar consolidation • Reverse halo sign (for molds other than *Aspergillus*) ***Aspergillus* or other mold tracheobronchitis** Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopy ***Aspergillus* and other mold sino-nasal disease** *At least one of these criteria:* • Acute localized pain • Nasal ulcer with black eschar • Extension from the paranasal sinus across bony barriers ***Aspergillus* and other mold CNS infection** Focal lesions or meningeal enhancement on imaging	AND	Mycologic evidence • *Aspergillus* or other mold recovered by culture from sputum, BAL, bronchial brush, or aspirate • Microscopic detection of mold from sputum, BAL, bronchial brush, or aspirate • *At least one of these criteria applied to Aspergillus galactomannan antigen:* ○ Single serum or plasma: ≥ 1.0 ○ BAL fluid: ≥ 1.0 ○ Single serum or plasma: ≥ 0.7 plus BAL fluid ≥ 0.8 ○ CSF: ≥ 1.0 • *At least one of these criteria applied to organism specific PCR (e.g., Aspergillus or Mucor):* ○ Plasma, serum, or whole blood: 2 or more consecutive PCR tests positive ○ BAL fluid: 2 or more PCR tests positive ○ At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

APPENDIX I

DIAGNOSIS AND SEVERITY SCORING FOR ACUTE AND CHRONIC GVHD

1. GvHD Clinical Staging

GVHD clinical staging will be according to the MAGIC criteria below
From BMT CTN Technical Document GvHD Guidance v1.0, dated March 13, 2023.

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Generalized erythroderma (>50% BSA) **plus** bullae and/or desquamation
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl
GI tract	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day	Severe abdominal pain +/- ileus, frank blood or melena (regardless of stool volume)
UGI		Severe/persistent nausea/vomiting/ anorexia			

- For GI GVHD, children is defined as <18 years of age and <50 kg weight
- Upper GI GVHD: in the absence of a biopsy, symptom severity and duration require nausea ≥3 days, and/or ≥ 2 vomiting episodes per day for at least two days, and/or anorexia with weight loss
- For stage 4 GI GVHD, severe abdominal pain is defined as (1) pain that requires opioid use **and** (2) pain that significantly impacts on performance status as determined by the treating physician

Overall Clinical Grade:
Grade 0 No stage 1-4 of any organ
Grade I Stage 1-2 skin and no liver or GI involvement
Grade II Stage 3 skin and/or Stage 1 liver and/or Stage 1 GI
Grade III Stage 0-3 skin with Stage 2-3 liver and/or Stage 2-3 GI
Grade IV Stage 4 in any target organ (skin, liver, GI)

2. Grading of Chronic GVHD (NIH Criteria)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

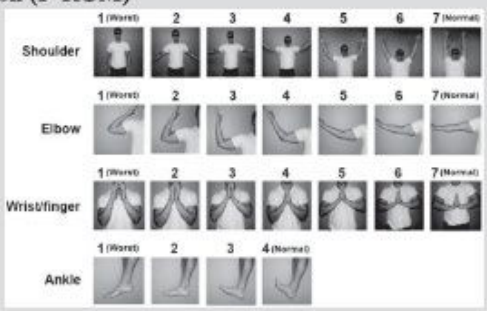
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



3. Categories of Acute and Chronic GVHD

Category	Time of Symptoms after HCT	Presence of Acute GVHD Features	Presence of Chronic GVHD Features*
Acute GVHD			
Classic acute GVHD	≤ 100 d	Yes	No
Late-onset acute GVHD	> 100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

*As defined in Section 4 (below)

4. Signs and Symptoms of Chronic GVHD

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GvHD)	Distinctive (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	Other Features (can be recognized as part of chronic GvHD if diagnosis is confirmed)	Common Features (seen with both acute and chronic GvHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting, or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric)		
Scalp and body hair		• New onset of scarring or non- scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse, or dull (not explained by other causes) • Premature gray hair	
Mouth	• Lichen-planus like changes	• Xerostomia • Mucocele • Mucosal atrophy • Pseudomembranes • Ulcers		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eyelids with edema)	
Genitalia *Females* *Males*	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or stenosis • Phimosis or urethral/meatus scaring or stenosis	• Erosions • Fissures • Ulcers		

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GvHD)	Distinctive (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	Other Features (can be recognized as part of chronic GvHD if diagnosis is confirmed)	Common Features (seen with both acute and chronic GvHD)
GI tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea, vomiting • Diarrhea • Weight loss • Failure to thrive
Liver				• Total bilirubin, ALP >2 x ULN ALT> 2 x ULN
Lung	• Bronchiolitis obliterans diagnosed lung biopsy • Bronchiolitis obliterans syndrome*	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia** • Restrictive lung disease**	
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis	• Edema • Muscle cramps • Arthralgia or arthritis	
Hemato poietic and immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • AIHA and ITP • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

APPENDIX J

PATIENT-REPORTED OUTCOME (PRO) QUESTIONS

Presented here are the individual question items for all PRO surveys. The schedule for each PRO domain or set of items is described in Sections 4.3.8.3 to 4.3.8.6. Patient-facing survey forms will be prepared for both electronic and paper survey administration.

Patient-facing survey forms will be developed and approved by the NMDP IRB as separate documents from this protocol. **This protocol appendix should not be printed and provided to patients**.

1. Pediatric (age 5-7) Parent/guardian proxy-report PROMIS assessments

1.1. PROMIS Anxiety

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
My child felt nervous	☐	☐	☐	☐	☐
My child felt scared	☐	☐	☐	☐	☐
My child felt worried	☐	☐	☐	☐	☐
My child felt like something awful might happen	☐	☐	☐	☐	☐
My child worried when he/she was at home	☐	☐	☐	☐	☐
My child got scared really easy	☐	☐	☐	☐	☐
My child worried about what could happen to him/her	☐	☐	☐	☐	☐
My child worried when he/she went to bed at night	☐	☐	☐	☐	☐

1.2. PROMIS Depressive symptoms

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
My child could not stop feeling sad	☐	☐	☐	☐	☐
My child felt everything in his/her life went wrong	☐	☐	☐	☐	☐
My child felt like he/she couldn"t do anything right	☐	☐	☐	☐	☐
My child felt lonely	☐	☐	☐	☐	☐
My child felt sad	☐	☐	☐	☐	☐
It was hard for my child to have fun	☐	☐	☐	☐	☐

1.3. PROMIS Anger

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
My child felt mad	☐	☐	☐	☐	☐
My child was so angry he/she felt like yelling at somebody	☐	☐	☐	☐	☐
My child was so angry he/she felt like throwing something	☐	☐	☐	☐	☐
My child felt upset	☐	☐	☐	☐	☐
When my child got mad, he/she stayed mad	☐	☐	☐	☐	☐

1.4. PROMIS Fatigue

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for my child to play or go out with friends as much as he/she would like	☐	☐	☐	☐	☐
My child felt weak	☐	☐	☐	☐	☐
My child got tired easily	☐	☐	☐	☐	☐
Being tired made it hard for my child to keep up with schoolwork	☐	☐	☐	☐	☐
My child had trouble finishing things because he/she was too tired	☐	☐	☐	☐	☐
My child had trouble starting things because he/she was too tired	☐	☐	☐	☐	☐
My child was so tired it was hard for him/her to pay attention	☐	☐	☐	☐	☐
My child was too tired to do sports or exercise	☐	☐	☐	☐	☐
My child was too tired to do things outside	☐	☐	☐	☐	☐
My child was too tired to enjoy the things he/she likes to do	☐	☐	☐	☐	☐

1.5. PROMIS Mobility

In the past 7 days…

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
My child could do sports and exercise that other kids his/her age could do	☐	☐	☐	☐	☐
My child could get up from the floor	☐	☐	☐	☐	☐
My child could keep up when he/she played with other kids	☐	☐	☐	☐	☐
My child could move his/her legs	☐	☐	☐	☐	☐
My child could stand up without help	☐	☐	☐	☐	☐
My child could stand up on his/her tiptoes	☐	☐	☐	☐	☐
My child could walk up stairs without holding on to anything	☐	☐	☐	☐	☐
My child has been physically able to do the activities he/she enjoys most	☐	☐	☐	☐	☐

1.6. PROMIS Cognition

In the past 7 days…

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Your child has to use written lists more often than other people his/her age so he/she will not forget things	☐	☐	☐	☐	☐
It is hard for your child to pay attention to one thing for more than 5-10 minutes	☐	☐	☐	☐	☐
Your child has trouble keeping track of what he/she is doing if he/she gets interrupted	☐	☐	☐	☐	☐
Your child has to read things several times to understand them	☐	☐	☐	☐	☐
Your child forgets things easily	☐	☐	☐	☐	☐
Your child has to work really hard to pay attention or he/she makes mistakes	☐	☐	☐	☐	☐
Your child has trouble remembering to do things like school projects or chores	☐	☐	☐	☐	☐

1.7. PROMIS Peer relationships

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
My child felt accepted by other kids his/her age	☐	☐	☐	☐	☐
My child was able to count on his/her friends	☐	☐	☐	☐	☐
My child was good at making friends	☐	☐	☐	☐	☐
My child and his/her friends helped each other out	☐	☐	☐	☐	☐
Other kids wanted to be my child"s friend	☐	☐	☐	☐	☐
Other kids wanted to be with my child	☐	☐	☐	☐	☐
Other kids wanted to talk to my child	☐	☐	☐	☐	☐

2. Pediatric (age 5-17) Parent/guardian proxy-report Occupational Function and Sociodemographic/social determinant of health items

2.1. Occupational function items

How many days per week does your child attend school?

Number of days attending school (please enter whole number): _____

In the past 30 days, how many days did your child miss school because of illness or injury?

Number of days of school missed (please enter whole number): _____

In the past 30 days, has your child attempted to go to school but found that he/she wasn't able to?

- Yes
- No

If yes, what prevents your child from going to school at the present time?

_____

_____

2.2. Sociodemographics/social determinants of health

What is your child's zip code? _____

Is your child Hispanic or Latino? *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Don't know

Which group(s) best describes your child? *(Select all that apply)*

- ☐ American Indian or Alaska Native
  - ☐ Alaskan Native or Aleut
  - ☐ North American Indian
  - ☐ American Indian, South or Central America
  - ☐ Caribbean Indian
- ☐ Asian
  - ☐ South Asian
  - ☐ Filipino (Pilipino)
  - ☐ Japanese
  - ☐ Korean
  - ☐ Chinese
  - ☐ Vietnamese
  - ☐ Other Southeast Asian
- ☐ Black or African American
  - ☐ African
  - ☐ African American
  - ☐ Black Caribbean
  - ☐ Black South or Central American
  - ☐ Other Black
- ☐ Native Hawaiian or Other Pacific Islander
  - ☐ Guamanian
  - ☐ Hawaiian
  - ☐ Samoan
  - ☐ Other Pacific Islander
- ☐ White
  - ☐ Eastern European
  - ☐ Mediterranean
  - ☐ Middle Eastern
  - ☐ North Coast of Africa
  - ☐ North American
  - ☐ Northern European
  - ☐ Western European
  - ☐ White Caribbean
  - ☐ White South or Central American
  - ☐ Other White
- ☐ Something else, please specify: _____
- ☐ Don't know

What type of health insurance coverage does your child have? *(Select all that apply)*

- ☐ No insurance
- ☐ Medicaid
- ☐ Medicare
- ☐ Medigap
- ☐ Indian Health Service
- ☐ Military-related healthcare
- ☐ Private health insurance (including through your employer)
- ☐ Disability insurance Other government program (please describe): _____
- ☐ Other health insurance coverage (please describe): _____
- ☐ Don't know

Was there any time during the past year when your child needed medical care but did not get it?

- ☐ Yes
- ☐ No

Was there any time during the past year that your child delayed getting medical care you felt he/she needed?

- ☐ Yes
- ☐ No

What is your family's total yearly HOUSEHOLD income from all sources, before taxes? *(Select one response)*

This includes money from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income received by ALL members of your household

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

What is your child's living situation today?

- ☐ My child has a steady place to live
- ☐ My child has a place to live today, but I am worried about losing it in the future
- ☐ My child has does not have a steady place to live

Think about the place your child lives. Are there problems with any of the following? *(Select all that apply)*

- ☐ Pests such as bugs, ants, or mice
- ☐ Mold
- ☐ Lead paint or pipes
- ☐ Lack of heat
- ☐ Oven or stove not working

3. Pediatric (age 8-17) Self-report PROMIS assessments

3.1. PROMIS Anxiety

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
I felt like something awful might happen	☐	☐	☐	☐	☐
I felt nervous	☐	☐	☐	☐	☐
I felt scared	☐	☐	☐	☐	☐
I felt worried	☐	☐	☐	☐	☐
I worried when I was at home	☐	☐	☐	☐	☐
I got scared really easy	☐	☐	☐	☐	☐
I worried about what could happen to me	☐	☐	☐	☐	☐
I worried when I went to bed at night	☐	☐	☐	☐	☐

3.2. PROMIS Depressive symptoms

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
I could not stop feeling sad	☐	☐	☐	☐	☐
I felt alone	☐	☐	☐	☐	☐
I felt everything in my life went wrong	☐	☐	☐	☐	☐
I felt like I couldn't do anything right	☐	☐	☐	☐	☐
I felt lonely	☐	☐	☐	☐	☐
I felt sad	☐	☐	☐	☐	☐
I felt unhappy	☐	☐	☐	☐	☐
It was hard for me to have fun	☐	☐	☐	☐	☐

3.3. PROMIS Anger

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
I felt fed up	☐	☐	☐	☐	☐
I felt mad	☐	☐	☐	☐	☐
I felt upset	☐	☐	☐	☐	☐
I was so angry I felt like throwing something	☐	☐	☐	☐	☐
I was so angry I felt like yelling at somebody	☐	☐	☐	☐	☐

3.4. PROMIS Fatigue

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for me to keep up with my schoolwork	☐	☐	☐	☐	☐
Being tired made it hard for me to play or go out with my friends as much as I"d like	☐	☐	☐	☐	☐
I felt weak	☐	☐	☐	☐	☐
I got tired easily	☐	☐	☐	☐	☐
I had trouble finishing things because I was too tired	☐	☐	☐	☐	☐
I had trouble starting things because I was too tired	☐	☐	☐	☐	☐
I was so tired it was hard for me to pay attention	☐	☐	☐	☐	☐
I was too tired to do sports or exercise	☐	☐	☐	☐	☐
I was too tired to do things outside	☐	☐	☐	☐	☐
I was too tired to enjoy the things I like to do	☐	☐	☐	☐	☐

3.5. PROMIS Mobility

In the past 7 days…

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
I could do sports and exercise that other kids my age could do	☐	☐	☐	☐	☐
I could get up from the floor	☐	☐	☐	☐	☐
I could keep up when I played with other kids	☐	☐	☐	☐	☐
I could move my legs	☐	☐	☐	☐	☐
I could stand up by myself	☐	☐	☐	☐	☐
I could stand up on my tiptoes	☐	☐	☐	☐	☐
I could walk up stairs without holding on to anything	☐	☐	☐	☐	☐
I have been physically able to do the activities I enjoy most	☐	☐	☐	☐	☐

3.6. PROMIS Cognition

In the past 7 days…

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
I have to use written lists more often than other people my age so I will not forget things	☐	☐	☐	☐	☐
It is hard for me to pay attention to one thing for more than 5-10 minutes	☐	☐	☐	☐	☐
I have trouble keeping track of what I am doing if I get interrupted	☐	☐	☐	☐	☐
I have to read things several times to understand them	☐	☐	☐	☐	☐
I forget things easily	☐	☐	☐	☐	☐
I have to work really hard to pay attention or I make mistakes	☐	☐	☐	☐	☐
I have trouble remembering to do things like school projects or chores	☐	☐	☐	☐	☐

3.7. PROMIS Peer relationships

In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
I felt accepted by other kids my age	☐	☐	☐	☐	☐
I was able to count on my friends.	☐	☐	☐	☐	☐
I was able to talk about everything with my friends.	☐	☐	☐	☐	☐
I was good at making friends.	☐	☐	☐	☐	☐
My friends and I helped each other out	☐	☐	☐	☐	☐
Other kids wanted to be my friend	☐	☐	☐	☐	☐
Other kids wanted to be with me	☐	☐	☐	☐	☐
Other kids wanted to talk to me	☐	☐	☐	☐	☐

4. Comprehensive Score of Financial Toxicity – COST (Adult self-report, Age 18+)

Below is a list of statements that other people with your illness have said are important. Please mark one response per line to indicate your response as it applies to the past 7 days.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I know that I have enough money in savings, retirement, or assets to cover the cost of my treatment.	☐	☐	☐	☐	☐
My out-of-pocket medical expenses are more than I thought they would be.	☐	☐	☐	☐	☐
I worry about the financial problems I will have in the future as a result of my illness or treatment.	☐	☐	☐	☐	☐
I feel I have no choice about the amount of money I spend on care.	☐	☐	☐	☐	☐
I am frustrated that I cannot work or contribute as much as I usually do.	☐	☐	☐	☐	☐
I am satisfied with my current financial situation.	☐	☐	☐	☐	☐
I am able to meet my monthly expenses.	☐	☐	☐	☐	☐
I feel financially stressed.	☐	☐	☐	☐	☐
I am concerned about keeping my job and income, including work at home.	☐	☐	☐	☐	☐
My cancer or treatment has reduced my satisfaction with my present financial situation.	☐	☐	☐	☐	☐
I feel in control of my financial situation.	☐	☐	☐	☐	☐
My illness has been a financial hardship to my family and me.	☐	☐	☐	☐	☐

5. Adult (age 18+) Self-report PROMIS assessments

5.1. Anxiety

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
My worries overwhelmed me	☐	☐	☐	☐	☐
I felt uneasy	☐	☐	☐	☐	☐
I felt nervous	☐	☐	☐	☐	☐
I felt like I needed help for my anxiety	☐	☐	☐	☐	☐
I felt anxious	☐	☐	☐	☐	☐
I felt tense	☐	☐	☐	☐	☐

5.2. Depression

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I felt worthless	☐	☐	☐	☐	☐
I felt helpless	☐	☐	☐	☐	☐
I felt depressed	☐	☐	☐	☐	☐
I felt hopeless	☐	☐	☐	☐	☐
I felt like a failure	☐	☐	☐	☐	☐
I felt unhappy.	☐	☐	☐	☐	☐
I felt that I had nothing to look forward to	☐	☐	☐	☐	☐
I felt that nothing could cheer me up	☐	☐	☐	☐	☐

5.3. Anger

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I was irritated more than people knew	☐	☐	☐	☐	☐
I felt angry	☐	☐	☐	☐	☐
I felt like I was ready to explode	☐	☐	☐	☐	☐
I was grouchy	☐	☐	☐	☐	☐
I felt annoyed	☐	☐	☐	☐	☐

5.4. Fatigue

During the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	☐	☐	☐	☐	☐
I have trouble starting things because I am tired	☐	☐	☐	☐	☐

In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
How run-down did you feel on average?	☐	☐	☐	☐	☐
How fatigued were you on average?	☐	☐	☐	☐	☐
How much were you bothered by your fatigue on average?	☐	☐	☐	☐	☐
To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
How often did you have trouble finishing things because of your fatigue?	☐	☐	☐	☐	☐

5.5. Physical function

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
Are you able to run errands and shop?	☐	☐	☐	☐	☐
Does your health now limit you in doing two hours of physical labor?	☐	☐	☐	☐	☐
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐	☐	☐	☐	☐
Does your health now limit you in lifting or carrying groceries?	☐	☐	☐	☐	☐
Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐	☐	☐	☐	☐

5.6. Cognition

In the past 7 days…

	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
My thinking has been slow	☐	☐	☐	☐	☐
It has seemed like my brain was not working as well as usual	☐	☐	☐	☐	☐
I have had to work harder than usual to keep track of what I was doing	☐	☐	☐	☐	☐
I have had trouble shifting back and forth between different activities that require thinking	☐	☐	☐	☐	☐
I have had trouble concentrating	☐	☐	☐	☐	☐
I have had to work really hard to pay attention or I would make a mistake	☐	☐	☐	☐	☐
I have had trouble forming thoughts	☐	☐	☐	☐	☐
I have had trouble adding or subtracting numbers in my head	☐	☐	☐	☐	☐

5.7. Ability to participate in social roles & activities

	Never	Rarely	Sometimes	Usually	Always
I have trouble doing all of my regular leisure activities with others	▢	▢	▢	▢	▢
I have trouble doing all of the family activities that I want to do	▢	▢	▢	▢	▢
I have trouble doing all of my usual work (include work at home).	▢	▢	▢	▢	▢
I have trouble doing all of the activities with friends that I want to do	▢	▢	▢	▢	▢
I have to limit the things I do for fun with others	▢	▢	▢	▢	▢
I have to limit my regular activities with friends	▢	▢	▢	▢	▢
I have to limit my regular family activities	▢	▢	▢	▢	▢
I have trouble doing all of the work that is really important to me (include work at home)	▢	▢	▢	▢	▢

6. Adult (age 18+) Parent/guardian proxy-report Occupational Function and Sociodemographic/social determinant of health items

6.1. Occupational Functioning

Which of the following best describes your current job status? *(Select all that apply)*

- ☐ Working full-time (30 or more hours per week)
- ☐ Working part-time (less than 30 hours per week
- ☐ Caring for home or family (not seeking paid work)
- ☐ Unemployed and looking for work (including laid off or furloughed)
- ☐ Unable to work due to illness or disability
- ☐ Retired
- ☐ Student
- ☐ Other, please specify: _____

What kind of work do you do at the present time or in your previous employment? *(Select all that apply)*

- ☐ Management, Business and Financial Occupations
- ☐ Computer, Engineering, and Science Occupations
- ☐ Education, Legal, Community Service, Arts, and Media Occupations
- ☐ Healthcare Practitioners and Technical Occupations
- ☐ Service Occupations
- ☐ Sales and Related Occupations
- ☐ Office and Administrative Support Occupations
- ☐ Farming, Fishing, and Forestry Occupations
- ☐ Construction and Extraction Occupations
- ☐ Installation, Maintenance, and Repair Occupations
- ☐ Production Occupations
- ☐ Transportation and Material Moving Occupations
- ☐ Military Specific Occupations
- ☐ Other, please specify: _____
- ☐ I am not currently and have not previously been employed

Please answer if you are currently a student:
How many days per week do you attend school?

Number of days attending school (please enter whole number): _____

In the past 30 days, how many days did you miss school because of illness or injury?

Number of days of school missed (please enter whole number): _____

Please answer if you are currently working:
At the present time, how many hours do you work each week (paid or unpaid)?

Number of hours worked (please enter whole number): _____

In the past 30 days, about how many days did you miss work because of illness or injury? (Do not include work missed for maternity/paternity leave)

Number of days missed (please enter whole number): _____

In the past 30 days, have you attempted to work/go to school but found that you weren't able to?

- ☐ Yes
- ☐ No

If yes, what prevents you from working/going to school at the present time?

_____
_____

How much have your disease and treatment experiences impacted your goals concerning work or school? *(Select one response)*

- ☐ Very negative impact
- ☐ Somewhat negative impact
- ☐ No impact
- ☐ Somewhat positive impact
- ☐ Very positive impact

6.2. Sociodemographics/social determinants of health

What is your zip code? _____

Are you Hispanic or Latino? *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Don't know

Which group(s) best describes you? *(Select all that apply)*

- ☐ American Indian or Alaska Native
  - ☐ Alaskan Native or Aleut
  - ☐ North American Indian
  - ☐ American Indian, South or Central America
  - ☐ Caribbean Indian
- ☐ Asian
  - ☐ South Asian
  - ☐ Filipino (Pilipino)
  - ☐ Japanese
  - ☐ Korean
  - ☐ Chinese
  - ☐ Vietnamese
  - ☐ Other Southeast Asian
- ☐ Black or African American
  - ☐ African
  - ☐ African American
  - ☐ Black Caribbean
  - ☐ Black South or Central American
  - ☐ Other Black
- ☐ Native Hawaiian or Other Pacific Islander
  - ☐ Guamanian
  - ☐ Hawaiian
  - ☐ Samoan
  - ☐ Other Pacific Islander
- ☐ White
  - ☐ Eastern European
  - ☐ Mediterranean
  - ☐ Middle Eastern
  - ☐ North Coast of Africa
  - ☐ North American
  - ☐ Northern European
  - ☐ Western European
  - ☐ White Caribbean
  - ☐ White South or Central American
  - ☐ Other White
- ☐ Something else, please specify:
- ☐ Don't know

What is your current relationship status? *(Select the one response that best describes your current relationship status)*

- ☐ Married
- ☐ Living with a partner
- ☐ Never married
- ☐ Separated
- ☐ Divorced
- ☐ Widowed
- ☐ Other, please describe:
  _____

What is the highest degree or level of school that you have completed? *(Select one response)*

- ☐ Up to 8th grade
- ☐ 9th –- 12th grade, no diploma
- ☐ High school diploma or equivalent (GED)
- ☐ Some college, no degree
- ☐ Vocational or Associate's degree
- ☐ College degree (B.A./B.S.)
- ☐ Advanced degree (e.g., Master's or Doctorate program)
- ☐ Don't know

What type of health insurance coverage do you have? *(Select all that apply)*

- ☐ No insurance
- ☐ Medicaid
- ☐ Medicare
- ☐ Medigap
- ☐ Indian Health Service
- ☐ Military-related healthcare
- ☐ Private health insurance (including through your employer)
- ☐ Disability insurance
- ☐ Other government program (please describe): _____
- ☐ Other health insurance coverage (please describe): _____
- ☐ Don't know

Was there any time during the past year when you needed medical care but did not get it?

- ☐ Yes
- ☐ No

Was there any time during the past year that you delayed getting medical care you felt you needed?

- ☐ Yes
- ☐ No

What is your total yearly HOUSEHOLD income from all sources, before taxes? *(Select one response)*

This includes money from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income received by ALL members of your household.

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

What is your living situation today?

- ☐ I have a steady place to live
- ☐ I have a place to live today, but I am worried about losing it in the future
- ☐ I do not have a steady place to live

Think about the place you live. Do you have problems with any of the following? *(Select all that apply)*

- ☐ Pests such as bugs, ants, or mice
- ☐ Mold
- ☐ Lead paint or pipes
- ☐ Lack of heat
- ☐ Oven or stove not working

How confident are you filling out medical forms by yourself?

- ☐ Not at all
- ☐ A little bit
- ☐ Somewhat
- ☐ Quite a bit
- ☐ Extremely

Do you currently need a caregiver (anyone who provides direct medical, financial or emotional support)?

- ☐ Yes
- ☐ No
- ☐ Don't know

Do you currently have a caregiver?

- ☐ Yes
- ☐ No

[If yes] Does your caregiver live with you?

- ☐ Yes
- ☐ No

APPENDIX K

CYTOKINE RELEASE SYNDROME GUIDANCE AND MANAGEMENT

Guidelines for Grading and Management of Suspected Cytokine Release Syndrome

Cytokine Release Syndrome (CRS): Transplantation of HLA-mismatched peripheral blood stem cells (PBSC) can be complicated by the development of CRS, usually within 7-10 days of transplantation. In many cases, clinical toxicities correlate with elevated inflammatory serum cytokine levels. The signs and symptoms most often experienced by patients include, but are not limited to, fever, fatigue, hypotension, tachycardia, acute renal failure, and neurological toxicities. Fever is usually the first toxicity to occur. Management of CRS should be per institutional practice. Steroids should be avoided.

CRS Grading: Grading will be based on the American Society for Blood and Marrow Transplantation (ASBMT) CRS Consensus Guidelines.[58] Generalized treatment guidelines are as outlined in the Table K1 below.

Table K1. Generalized Guidelines for Monitoring and Treatment of CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4^
Fever	≥ 38	≥ 38	≥ 38	≥ 38
With EITHER				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low flow nasal cannula‡ or blow-by	Requiring high flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)
Potential Interventions (General)	Supportive care, antipyretics. Consider Tocilizumab	Fluid bolus, notify the ICU, consideration of low dose pressors for prevention of fluid overload, Echo/CXR. Consider Tocilizumab	Tocilizumab with exception for grade 3 CRS with hypotension alone which is well managed on low dose pressors.**	Tocilizumab (per institutional standards) ***

Abbreviations: BiPAP: Bi-level Positive Airway Pressure; CPAP; Continuous Positive Airway Pressure; CRS: Cytokine Release Syndrome; CXR: Chest X-Ray; Echo: Echocardiogram; ICU: Intensive Care Unit

*Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low flow nasal cannula is classified as grade 3 CRS. ‡Low flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High flow nasal cannula is defined as oxygen delivered at >6 L/minute.

^Intubation may be indicated in patients who have a degree of neurotoxicity where there is concern for their ability to maintain a patent airway. This may occur either in the setting of CRS or after CRS has resolved. The decision for intubation should not be captured as a grade 4 CRS when the other criteria for such are not met. Intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not, by definition, grade 4 CRS.

**The definition of “High dose” vasopressors requires ≥ 3 hours of any of the following: norepinephrine monotherapy ≥ 20 mcg/kg/min; dopamine monotherapy ≥ 10 mcg/kg/min; phenylephrine monotherapy ≥ 200 mcg/kg/min; epinephrine monotherapy ≥ 10 mcg/kg/min; if on vasopressin: vasopressin + norepinephrine equivalent of ≥ 10 mcg/kg/min; and if on combination vasopressors (excluding vasopressin) ≥ norepinephrine equivalent (cumulative) ≥ 20 mcg/kg/min.

***Steroids should be avoided.

APPENDIX L

REFERENCES

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