Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP)

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BMT CTN PROTOCOL 1502
VERSION 4.0

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PROTOCOL SYNOPSIS – BMT CTN PROTOCOL #1502

Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP)

Study Chairpersons:	Amy E. DeZern, M.D., M.H.S. and Michael A. Pulsipher, M.D.
Primary Objective:	Assess overall survival (OS) at 1 year post-hematopoietic stem cell transplantation (HSCT) from a haploidentical marrow donor in patients with severe aplastic anemia (SAA).
Secondary Objectives:	Assess the proportion of patients alive and engrafted; neutrophil and platelet recovery; graft failure (primary and secondary); grades II-IV acute GVHD and chronic GVHD; immune reconstitution; incidence of CMV viremia/disease and EBV viremia/post-transplant lymphoproliferative disease (PTLD).
Correlative Studies:	ATG pharmacokinetic (PK) profile in transplant recipients; pre-HSCT telomere length in all consenting patients and consenting haplo donors.
Study Design:	This study is a prospective, multicenter phase II study with patients receiving haploidentical transplantation for SAA.
Accrual Objective:	The goal is to transplant 30 patients on the protocol. Additional patients may be screened, consented, and registered in order to reach accrual goals.
Accrual Period:	The estimated accrual period is 3 years.
Eligibility Criteria:	Diagnosis of SAA, without a fully matched related sibling donor available, but with a haplo marrow donor available. Exclusions include inherited bone marrow failure syndrome, previous hematopoietic stem cell or solid organ transplant, uncontrolled infection, inadequate organ function, and performance score < 60.
Treatment Description:	Patients will be treated with a preparative regimen of fludarabine (150 mg/m2), cyclophosphamide (29 mg/kg, low dose TBI (200 cGy), and Thymoglobulin® (4.5 mg/kg). GVHD prophylaxis will be with post-HSCT cyclophosphamide (100 mg/kg), tacrolimus, and mycophenolate mofetil (MMF).
Study Duration:	Patients will be followed for 1 year post-transplant.
Interim Analysis:	No formal interim analyses for efficacy or futility will be used.

Safety Monitoring: Graft failure and mortality are the key safety endpoints to be monitored on the study so that if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. The rate of graft failure including both primary graft failure and secondary graft failure by Day 56 post-transplant and the rate of mortality by Day 115 post ATG preparation will be monitored using a truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions. The safety boundary for graft failure was developed from an SPRT contrasting 15% versus 35% graft failure rate and the safety boundary for mortality was developed from an SPRT contrasting 10% versus 30% mortality rate.

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CHAPTER 1

1 BACKGROUND AND STUDY RATIONALE

1.1 Objectives

The primary objective of this phase II study is to assess overall survival in recipients of haploidentical (haplo) donor grafts at 1 year post-hematopoietic stem cell transplantation (HSCT) in patients with severe aplastic anemia (SAA).

Secondary endpoints include assessment of overall survival, rejection free survival, neutrophil and platelet engraftment, graft failure, grade II-IV acute GVHD, chronic GVHD, immune reconstitution, and infectious complications. Additional biological correlative studies include measurement of antithymocyte globulin (ATG) pharmacokinetics (PK) for correlation with engraftment, GVHD, immune reconstitution, and survival as well as measurement of telomere length for correlation with disease phenotype, engraftment, and survival.

1.2 Background

1.2.1 The Current Role of HSCT in SAA

Acquired SAA is a rare bone marrow failure disorder with an estimated annual incidence of 2 cases per million and with over 600 new cases in the United States each year.[1, 2] The majority of cases are thought to be related to autoimmune destruction of marrow microenvironment or hematopoietic stem cells; accordingly, the disease can be treated and often cured by either immune suppression or marrow replacement through transplantation.[3] HSCT from a human leukocyte antigen (HLA) matched sibling donor (MSD) has become the standard of care for younger, newly diagnosed patients[3, 4] with long-term survival rates close to 90% in patients under 20,[5, 6] and around 76% for patients older than 20.[6] However, if the patient has siblings, each of them only has a 25% chance of being a match based on HLA inheritance patterns.

Horse ATG and cyclosporine (CSA) immunosuppressive therapy (IST) is generally front-line treatment for SAA patients who lack matched sibling donors or are not good candidates for HSCT.[7] The hematopoietic response rate is 60-70%.[2] However, up to 40% of patients eventually relapse[8] and an additional 10-40% develop a secondary clonal disease.[9] For those whose disease is primary refractory or who relapse within 4-6 months after IST, most groups recommend unrelated donor HSCT if an appropriately matched unrelated donor is available.[10] Up to half of patients who initially respond to IST subsequently recur and either require long-term immune suppression or are refractory to subsequent courses of IST. Unrelated donor HSCT can be considered as a reasonable alternative for SAA patients in these clinical scenarios.

Recent improvements in survival after unrelated donor transplant for SAA have been noted using reduced doses of total body irradiation (TBI),[11] the substitution of a portion of the cyclophosphamide dosing with fludarabine,[12] and selecting donors who are better HLA-matched to patients. These approaches have helped to lower graft failure, overall mortality, and graft versus host disease (GVHD). Some studies suggest that outcomes using HSCT with a fully matched unrelated donor (MUD) are similar to HSCT using a MSD.[13-17] Results of the BMT

CTN 0301 trial for unrelated donor HSCT in SAA shows that of the 4 cyclophosphamide dose levels tested, 50 and 100 mg/kg in combination with ATG, fludarabine, and TBI (200 cGy) lead to better outcomes than the 0 mg/kg or 150 mg/kg dose.[12] Additionally, it is well-recognized that bone marrow (BM) is the preferred source of stem cells over peripheral blood stem cells (PBSC) in the unrelated donor setting, similar to MSD HSCT for SAA.[18-20]

Unfortunately, fully matched unrelated donors (HLA-A, B, C, DRB1) from worldwide registries can be identified for about 80% of Caucasians and for much lower percentages of persons of other races and/or ethnicities.[21] Outcomes using unrelated adult donors mismatched at a single HLA-locus (7/8 HLA-matched) have proven inferior to outcomes with fully matched unrelated donors (MUD), though allowing a single HLA-locus mismatched transplant greatly expands donor availability.[21, 22] With a sizable population of SAA patients who could benefit from unrelated donor HSCT who do not have fully matched donors, the need for improved alternative donor approaches has been identified as a key priority by an international working group on SAA convened by the BMT CTN in 2010.[23]

Registry data for alternative donor HSCT for SAA shows inadequate outcomes. Unpublished data from the CIBMTR for transplants performed between 2009 and 2013 in the US are summarized in Table 1 and show overall survival for each type of alternative donor transplant utilized for patients with SAA. The following sections will show more promising data associated with specific approaches to haplo HSCT that inform our proposal.

Table 1: Overall Survival in SAA by Donor Source

MUD BM 1-year OS	MUD PBSC 1-year OS	MMURD 1-year OS	UCB 1-year OS	Haplo*
Number=260 85% (95% CI 80-89%)	Number=72 72% (95% CI 61-82%)	Number=121 66% (95% CI 56-74%)	Number=45 58% (95% CI 43-72%)	Number=19 12 alive (12 of 19; 63%)

MUD = matched unrelated donor, MMURD = mismatched unrelated donor, MMRD = mismatched related donor (1 HLA-locus), Haplo = Haplo, UCB = unrelated cord blood, BM = bone marrow, PBSC = peripheral blood stem cells, OS = overall survival (95% CI = 95% confidence interval)
*Too few patients to calculate 1-year overall survival using the Kaplan-Meier estimator

1.2.2 **Haplo Donor Transplants in SAA**

The use of haplo donors for SAA transplantation has only more recently been attempted and accordingly there are only limited published data regarding outcomes with this approach. In small case series, rejection has been between 6% and 25%, acute GVHD between 12% and 30%, chronic GVHD between 20% and 40%, and overall survival between 62.5% and 84.6%.[24-26]

We pooled newer, unpublished data from Brazil, Johns Hopkins, and the Fred Hutchinson Cancer Research Center using a reduced intensity regimen with post-transplant cyclophosphamide in 29 patients. Results are promising and are shown below. All patients received a uniform conditioning regimen of TBI 200, fludarabine 150 mg/m^2 and Cy 29 mg/kg. Ten patients received ATG. Patients received Cy 100 mg/kg post-transplant in addition to methotrexate or calcineurin inhibitors for GVHD prophylaxis. There were 4 graft failures and 6

deaths. Twenty-three of 29 patients are alive with variable follow up: 10 patients were followed for less than 6 months after transplantation, 4 patients have been followed between 6 and 12 months, and 9 patients have been followed for longer than 12 months.

Table 2: Haplo Donor Transplants in SAA

Patient #	Conditioning	Engraftment	Last Follow-Up	Status
1	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	36 months	Alive
2	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	13 months	Alive
3	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	18 months	Alive
4	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	7 months	Alive
5	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	17 months	Alive
6	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	3 months	Alive
7	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	44 months	Alive
8	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	6 months	Alive
9	Cy29/Flu150/TBI200	Primary Graft Failure	2 months	Died
10	Cy29/Flu150/TBI200	Yes, 100% donor	28 months	Alive
11	Cy29/Flu150/TBI200	Yes, 100% donor	9 months	Alive
12	Cy29/Flu150/TBI200	Yes, 100% donor	24 months	Alive
13	Cy29/Flu150/TBI200	Yes, 100% donor	17 months	Alive
14	Cy29/Flu150/TBI200	Yes, 100% donor	11 months	Died
15	Cy29/Flu150/TBI200	Yes, 100% donor	6 months	Alive
16	Cy29/Flu150/TBI200	Yes, 100% donor	3 months	Alive
17	Cy29/Flu150/TBI200	Primary Graft Failure	4 months	Died
18	Cy29/Flu150/TBI200	Primary Graft Failure	1 month	Alive
19	Cy29/Flu150/TBI200	Yes, 100% donor	3 months	Died

20	Cy29/Flu150/TBI200	Primary Graft Failure	1 month	Died
21	Cy29/Flu150/TBI200	Yes, 100% donor	29 months	Alive
22	Cy29/Flu150/TBI200	Yes, 94% donor	2 months	Alive
23	Cy29/Flu150/TBI200	Yes, 100% donor	5 months	Died
24	Cy29/Flu150/TBI200	Yes, 100% donor	3 months	Alive
25	Cy29/Flu150/TBI200	Yes, 100% donor	1 month	Alive
26	Cy29/Flu150/TBI200	Yes, 100% donor	2 months	Alive
27	Cy29/Flu150/TBI200	Yes, 100% donor	1 month	Alive
28	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	4 months	Alive
29	Cy29/Flu150/TBI200/ATG	Yes, 100% donor	3 months	Alive

Eight of the 29 patients received early low dose ATG (4.5mg/kg starting on Day -9). The eight patients had documented acquired disease and received grafts from 5/10 HLA-A, B, C, DR, DQ matched related donors. Six had failed ATG-containing regimens previously and two had relapsed after high dose cyclophosphamide as IST. Two additional patients had inherited syndromes: one with Diamond Blackfan who received a graft from a 5/10 related donor and one with telomeres less than the first percentile in length with a presumed familial syndrome who received a 9/10 unrelated graft. Median follow-up time is 17.5 months (range 5-49). The median age was 34 years (range 17-54) with 6 patients greater than age 30 years and 50% were males. Median time to neutrophil engraftment was 18 days (range 16-24). Median time to red cell engraftment was 25 days (range 16-48). Median time to platelet engraftment was 27.5 days (range 22-108). At the time of BMT, six patients had PNH clones and all were eliminated. All patients are alive and well, fully engrafted with 100% donor chimerism in blood and marrow. Two patients had grade I-II skin acute GVHD. These two patients also had mild chronic GVHD of the skin/mouth requiring systemic steroids. One patient was able to come off all immunosuppression by 15 months and the other by 17 months. Based on these results, early low dose ATG will be used in this protocol.[2]

1.2.3 **Evolving Role of ATG Exposure in HSCT**

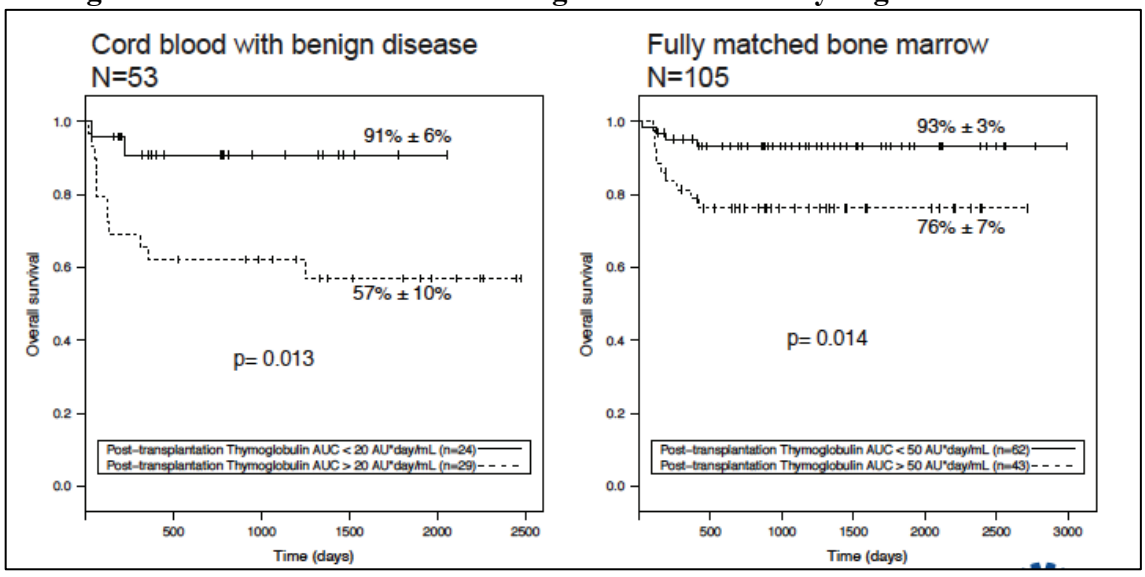
ATG is commonly used in HSCT regimens to prevent graft failure and GVHD, especially for nonmalignant diseases.[27-30] There are data to suggest that the rabbit preparation of ATG (rATG – Thymoglobulin®) results in improved outcomes compared to the horse preparation (hATG – Atgam®) when used in HSCT for SAA. In a CIBMTR study presented in abstract form, grades II-IV acute GVHD at Day 100 were lower with rATG compared to hATG for unrelated donor

transplants. This advantage was not seen for hematopoietic recovery, chronic GVHD, or overall survival.[31]

We know a great deal about pharmacokinetics (PK) of medications in HSCT, such as busulfan, where doses are individualized based on levels.[32] Less is known about the PK and pharmacodynamic interactions of ATG in the HSCT setting, which can be even more variable in children and adolescents.[33] Some reports show that prolonged exposure may lead to delayed immune reconstitution and more infections, while short exposure may lead to limited protection against GVHD.[34, 35] Recently, a population PK model has been created for the Thymoglobulin® preparation of ATG. This model allows for individualized dosing that can achieve target area under the curve (AUC) ATG exposures pre- and post-HSCT. Dosing is based upon body weight and absolute lymphocyte count measured just prior to starting the HSCT preparative regimen.[33]

Recent publications have demonstrated a link between pre-HSCT and post-HSCT AUC of ATG and outcomes. Admiraal and colleagues in the Netherlands demonstrated in 251 patients (mostly children, n = 116 malignant disease, n = 69 benign disease, n = 15 marrow failure, and n = 51 immune deficiency) that when the post-HSCT AUC was < 20 AU*day/mL there was improved immune reconstitution as shown by recovery of CD4 counts ($p < 0.0001$ on logistic regression fitting).[36] One hundred and eighteen patients received bone marrow grafts, 36 received peripheral blood, and 96 received cord blood. Successful immune reconstitution was in turn associated with improved overall survival compared to unsuccessful immune reconstitution (56% vs. 75%, $p < 0.001$). A low ATG post-HSCT AUC (< 20 AU*day/mL in UCB or < 50 AU*day/mL in marrow) was itself associated with improved overall survival for patients with benign diseases receiving a cord blood graft (91% vs. 57%, $p = 0.013$) and for all patients that received matched bone marrow or PBSC graft (93% vs. 76%, $p = 0.014$) as seen in Figure 1.

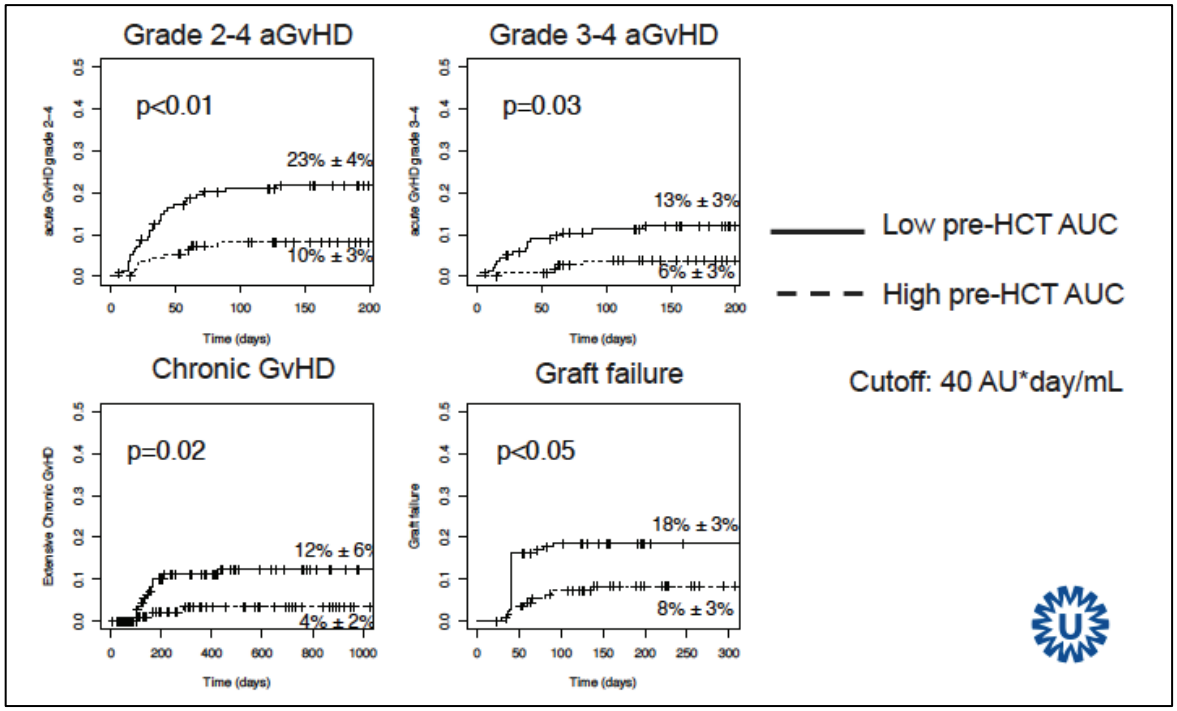
Figure 1: Overall Survival According to Post-HSCT Thymoglobulin® AUC



With all stem cell sources included, the ATG post-HSCT AUC did not have an influence on GVHD. When looking at cord blood transplants alone, with lower ATG post-HSCT AUC there was a higher rate of grades II-IV acute GVHD, but no difference in grades III-IV acute GVHD

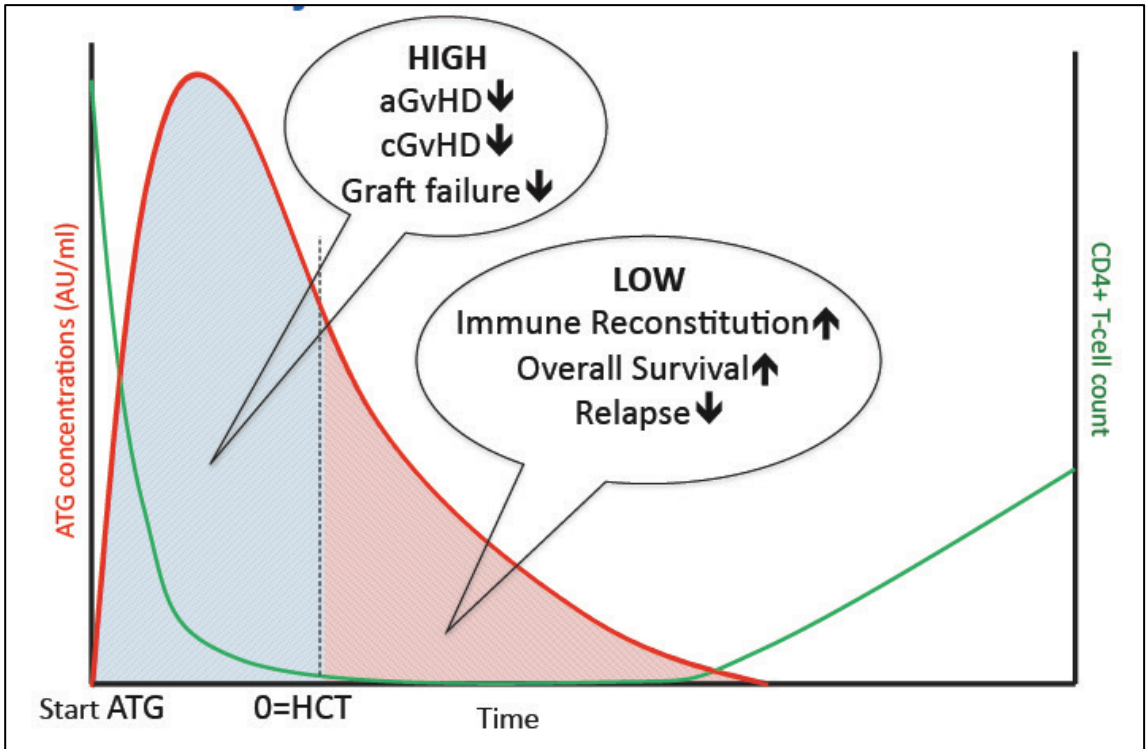
and no difference in extensive chronic GVHD. This increase in only grade II acute GVHD is balanced with the benefits of high ATG pre-HSCT exposure, which reduced grades II-IV acute GVHD (10% vs. 23%, $p < 0.01$), chronic GVHD (4% vs. 12%, $p = 0.02$), and graft failure (8% vs. 18%, $p < 0.05$) as shown in Figure 2.[36]

Figure 2: GVHD and Graft Failure According to Pre-HSCT Thymoglobulin® AUC



These results suggest that early and targeted ATG could improve outcomes in HSCT as depicted in Figure 3, although these data are primarily in children and with a limited population of SAA patients. Given that haplo donors have been a very small part of the data set to date and with the encouraging outcomes to date using a fixed ATG dose level of 4.5mg/kg in the Johns Hopkins single center experience, we will use a fixed ATG dosing in this haplo cohort study. However, we will perform ATG PK testing on the haplo cohort as well to assess whether the pre- and post-AUC levels achieved with fixed dosing correlate with outcomes.

Figure 3: Depiction of Thymoglobulin® Exposure and Impact on HSCT



1.2.4 Summary

In conclusion, a major challenge in treating acquired SAA is the management of patients who are refractory to IST or have relapsed after IST. HSCT is the only curative option for these patients but many are ineligible because they lack a suitable donor. Here we seek to increase options for these patients by using novel therapeutic strategies of GVHD prophylaxis with PTCY to expand the donor pool to include haploidentical donors. We hypothesize that this approach will result in improved survival through reduction of transplant complications including graft failure and GVHD.

1.2.5 Protocol History

Version 1.0 of the protocol included a cord blood cohort in addition to the haploidentical cohort, and sites chose which cohort they would enroll their patients on. The intent was for these two cohorts to accrue in parallel and be evaluated separately. Six months after accrual had begun, only a few sites expressed interest in the cord blood cohort and no cord blood patients had been enrolled. As a result, the cord blood cohort was removed from the protocol for Version 2.0, which was released on June 19, 2018.

CHAPTER 2

2 STUDY DESIGN

2.1 Study Overview

This study is a phase II study of haploidentical transplant to assess overall survival (OS) at one-year post-HSCT in patients with SAA.

2.2 Hypotheses and Objectives

2.2.1 Hypotheses

Primary Hypothesis:

Using the regimens described below, OS at one-year post-HSCT will be ≥ 75% in patients who receive a bone marrow transplant from a haplo donor for SAA.

2.2.2 Objectives

Primary Objective:

Assess OS at one year post-HSCT in patients who receive haploidentical transplant for SAA.

Secondary Objectives:

1) Estimate the probability of being engrafted (i.e., without primary or secondary graft failure) and alive at 1-year post-HSCT.

2) Estimate neutrophil recovery at Day 28 and Day 56 and platelet recovery at Day 100.

3) Estimate the probability of primary or secondary graft failure at 1-year post-HSCT.

4) Estimate grades II-IV and grade III-IV acute GVHD at Day 100 and chronic GVHD at 1-year post-HSCT.

5) Determine the pace and quality of immune reconstitution by measuring CD4, CD19, and CD56 counts pre-HSCT and at Day 91, Day 180, and Day 365 post-HSCT.

6) Determine the rate of specific infectious complications (CMV viremia and disease, EBV viremia, and PTLD) within the first year after HSCT.

2.3 Eligibility Criteria for Enrollment

2.3.1 Patient Inclusion Criteria

1. Patient is ≤ 75 years of age at time of enrollment.
2. Confirmed diagnosis of SAA defined as:[37]

a. Bone marrow cellularity < 25% **or** marrow cellularity < 50% but with < 30% residual hematopoietic cells.

b. Two out of three 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 sibling donor (6/6 match for HLA-A and B at intermediate or high resolution and DRB1 at high resolution using DNA-based typing) available.

4. Failed at least one trial of immunosuppressive therapy (IST) by being refractory (persistence of severe cytopenias and fulfillment of SAA disease criteria at least 3 months after initial IST)[41] or having relapsed (initial improvement of cytopenias after first-line IST but then a later return to fulfillment of SAA disease criteria when IST is decreased or ceased)[41]. IST could have included ATG based regimens, calcineurin inhibitors and/or other higher dose therapy directed at the treatment of primary SAA.

5. 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. See Section 2.4 for additional information.

6. Patient and/or legal guardian must sign informed consent for HSCT.

7. The haplo donor and/or legal guardian must be able to sign informed consent documents.

8. The potential haplo donor must be willing and able to donate bone marrow.

9. The weight of the haplo donor must be ≥ 20 kg.

10. Adequate organ function defined as:

a. Cardiac: Left ventricular ejection fraction (LVEF) at rest ≥ 40%. For patients aged < 13 years, shortening fraction (SF) ≥ 26% by echocardiogram or MUGA may be substituted for LVEF.

b. Hepatic: Total bilirubin < 3.0 x the upper limit of normal (ULN) for age (patients who have been diagnosed with Gilbert's Disease are allowed to exceed this limit) and AST and ALT < 5.0 x ULN for age.

c. Renal:

i. For patients ≥ 13.0 years of age at the time of enrollment: estimated creatinine clearance > 50 mL/minute (using the Cockcroft-Gault formula[1] and actual body weight). Please refer to Body Weight calculations in Appendix E.

ii. For patients < 13.0 years of age at enrollment: GFR estimated by the updated Schwartz formula[2] ≥ 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 patients ≥ 13.0 years of age: DLCO (corrected/adjusted for hemoglobin) > 40% **and** FEV1 > 50% predicted (without administration of bronchodilator) **and** FVC > 50% predicted.

ii. For patients < 13.0 years of age unable to perform PFTs due to age or developmental ability: (1) no evidence of dyspnea at rest **and** (2) no need for supplemental oxygen **and** (3) O2 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%)).

11. Karnofsky or Lansky performance status ≥ 60%.
12. 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 Patient Exclusion Criteria

1. Inherited bone marrow failure syndromes such as Fanconi anemia must be ruled out according to center standards.
2. Clonal cytogenetic abnormalities consistent with pre-myelodysplastic syndrome (pre-MDS) or MDS on marrow examination (e.g. Monosomy 7).
3. Diagnosis of myelodysplastic syndrome (MDS).
4. Presence of anti-donor HLA antibodies (positive anti-donor HLA antibody is defined as a positive cross-match test of any titer by complement-dependent cytotoxicity or flow cytometric testing or the presence of anti-donor HLA antibody to the high expression loci HLA-A, B, C, DRB1, or DPB1 with mean fluorescence intensity (MFI) > 1000 by solid phase immunoassay).
5. Prior allogeneic stem cell transplant.

[1] Cockcroft-Gault formula, based on ideal body weight (IBW): $CrCl = \frac{(140 - age) \times IBW\ (kg)}{P_{Cr} \times 72} \times 0.85$ for females

[2] Schwartz equation: 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

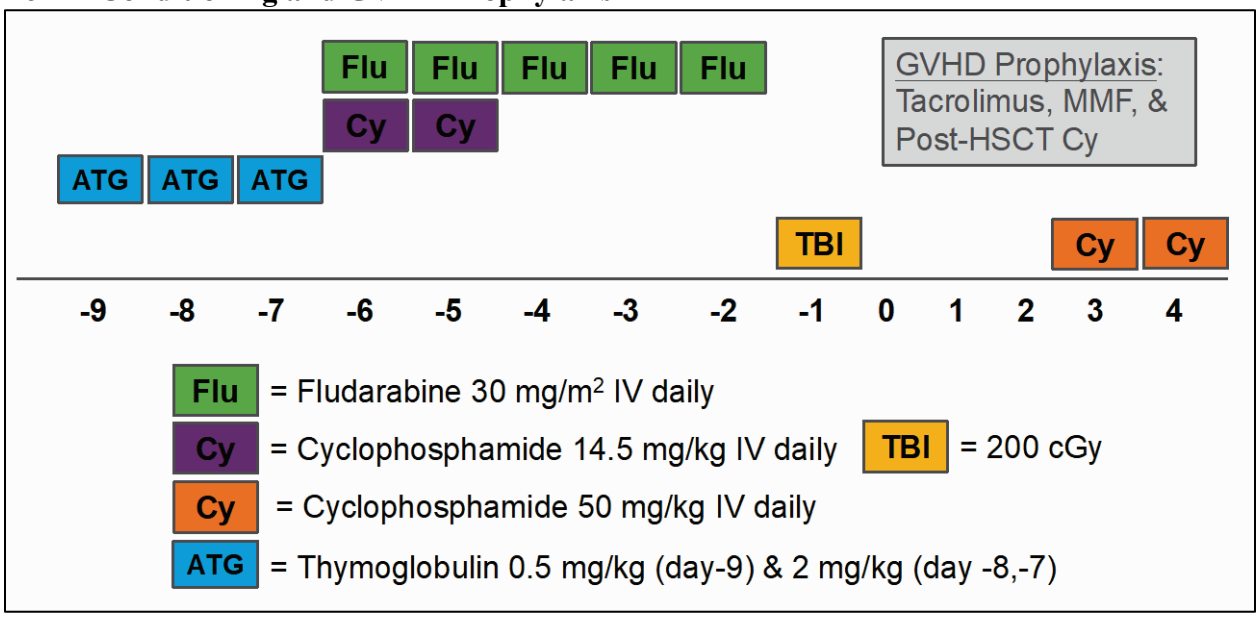
6. Prior solid organ transplant.
7. Known life-threatening reaction (i.e., anaphylaxis) to Thymoglobulin® that would prohibit use for the patient as this study requires use of the Thymoglobulin® preparation of ATG.
8. Uncontrolled bacterial, viral, or fungal infection at the time of enrollment. Uncontrolled is defined as currently taking medication and with progression or no clinical improvement on adequate medical treatment.
9. Seropositive for the human immunodeficiency virus (HIV).
10. Active Hepatitis B or C determined by a detectable viral load of HBV or HCV.
11. Female patients who are pregnant (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.
13. Alemtuzumab or ATG within 2 weeks of enrollment.

2.4 Donor Selection Criteria

1. Haplo donor selection is based on HLA typing and relationship to recipient (Section 2.3.1).
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 cross-match incompatibility or a medical reason to select otherwise. 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 in cross-match testing 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.[38]
3. If there is more than one donor with the least amount of HVG allele mismatches, the suggested prioritization in order of importance includes ABO compatibility, CMV status (use a sero-negative donor for a sero-negative recipient or use a sero-positive donor for a sero-positive recipient), younger age and lighter weight (this rule applies down to the age of 18, however, children may also be used as donors if appropriate), and sex of the donor (if all else is equal, males are preferred over nulliparous females over multiparous females).

2.5 Treatment Plan

2.5.1 Conditioning and GVHD Prophylaxis



2.5.1.1 Conditioning for Haplo Bone Marrow Recipients

2.5.1.1.1 Fludarabine

Fludarabine dose will be 30 mg/m^2 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 patient is < 125% of ideal body weight (IBW). For patients ≥ 125% of IBW, fludarabine will be dosed on body surface area based upon the recipient's adjusted ideal body weight (AIBW). For patients who have an estimated or measured creatinine clearance < 70 mL/min/1.73 m^2, or 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. Fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

2.5.1.1.2 Pre-HSCT Cyclophosphamide

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 hour infusion (total dose received 29 mg/kg). Cyclophosphamide dosing should be based on recipient's total body weight (TBW) in all patients < 125% of IBW, and adjusted ideal body weight (AIBW) in all patients ≥ 125% of IBW as per Appendix E. 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.

2.5.1.1.3 Total Body Irradiation

TBI is to be delivered in a single dose of 200 cGy on Day -1. TBI may be delivered from either linear accelerator or Cobalt sources (per institutional practice).

2.5.1.1.4 **Thymoglobulin®**

Thymoglobulin® preparation of ATG will be dosed upon actual body weight. The dose will be 0.5 mg/kg IV on Day -9 over 6 hours and 2 mg/kg IV on Days -8 and -7 over 4 hours. Premedication should follow local institutional practice with suggested minimum of 1 mg/kg methylprednisolone in children and up to 100 mg in adults prior to the infusion (equivalent steroid allowed), preferably repeated in 3-4 hours during the infusion. **Note: Thymoglobulin® is the required preparation of ATG for this study. Patients will not be eligible if the treating center plans to use other preparations of ATG.** Pharmacokinetic corollary labs should be drawn as outlined in Appendix C.

2.5.1.2 **Haplo Marrow Product Handling & Infusion**

Patients 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 bone marrow will be harvested with a target yield of 4 $x10^8$ nucleated cells per kilogram of recipient IBW, and a recommended minimum yield of 2.5 $x10^8$ 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 total nucleated cell 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 G for additional bone marrow harvesting guidelines.

The protocol team will begin implementing a review process in regards to bone marrow harvesting at participating sites. As a requirement for site activation, a copy of the site's SOP for bone marrow harvest will be collected along with total nucleated cell dose/kilogram patient weight and product volume for the last 2 harvests performed at the site. This is to ensure that participating sites are experienced in bone marrow harvesting and the recommended TNC can be attained for all patients enrolled on 1502.

Note: The patient 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 medical emergency (e.g., treatment of anaphylaxis). In the event that a patient requires steroids, please notify the Emmes Protocol Coordinator.

2.5.1.3 **GVHD Prophylaxis for Haplo Recipients**

2.5.1.3.1 **Post-HSCT Cyclophosphamide**

Cyclophosphamide 50 mg/kg IV daily will be given for 2 days, Days +3 to +4 (total dose received 100 mg/kg) after transplantation. Cyclophosphamide and mesna given post transplant will be dosed based on IBW, unless actual body weight is less than IBW, in which case use actual body weight. If the patient weighs $\geq$ 125% of IBW, cyclophosphamide will be dosed according to the adjusted IBW. 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 doses.

Recommended Ideal Body Weight Calculation for Children Age 1-17 Years (who are less than 60 inches in height):

IBW = ((Height in cm)^2 x 1.65)/1000

Recommended Ideal Body Weight Calculation for Adults Age ≥ 18 Years:

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg
IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

Dose Adjustment for Patients Weighing More Than 125% of IBW:

Adjusted ideal body weight = IBW + 0.25(Actual weight – IBW)

2.5.1.3.2 Tacrolimus

Tacrolimus IV or 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 level of 10-15 ng/mL. The recommended IV starting dose is 0.03 mg/kg/day based on actual body weight with PO equivalent acceptable. May change to oral dosing once therapeutic levels are achieved or per institutional standards. If tacrolimus is not tolerated, cyclosporine may be substituted IV or PO starting on Day +5 and administered per institutional standards to maintain a level of 200-400 ng/mL by HPLC method or 250-500 ng/mL by TDX method. Recommended starting doses range from 3-6 mg/kg/day IV bolus dosing q12 hours or 6 mg/kg/day PO divided BID. The calcineurin inhibitor 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.

2.5.1.3.3 MMF

MMF dose will be 15 mg/kg PO TID up to 1 gm TID (or IV equivalent) starting on Day +5 (max dose 3000mg/day) and will be discontinued after the last dose on Day +35 or may continue if active GVHD is present.

2.5.2.3.4 Growth factor

G-CSF will be given IV or SQ starting on Day +5 for the haplo cohort at 5 mcg/kg/day (rounded to nearest vial size) until ANC is > 1500 for 3 days. Additional G-CSF may be administered as warranted. Pegfilgrastim (Neulasta®) and GM-CSF are not permitted.

2.5.2 GVHD Treatment

In the event of the development of either acute or chronic GVHD, therapy will be at the discretion of treating centers.

2.5.3 Supportive Care

2.5.3.1 Infectious disease prophylaxis

Antifungal prophylaxis will be administered according to institutional practices. It is important to follow levels of cyclosporine and tacrolimus for patients receiving one of the azole antifungal medications. The combination of both drugs can raise the levels of the immunosuppressant to toxic levels. If a patient on cyclosporine or tacrolimus is started on an azole antifungal

medication, a dose reduction of the cyclosporine or tacrolimus is required and levels should be obtained to ensure they are not in the toxic range.

Pneumocystis jiroveci pneumonia (PJP) prophylaxis will be administered according to institutional practices. Recommendations include starting approximately one month post-HSCT (or later if WBC not recovering) and continuing until at least three months off of all immunosuppressive medications.

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 one year post-HSCT and while on immunosuppressive medications.

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

2.5.3.2 **Infectious disease monitoring**

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

EBV viremia as tested by DNA PCR will be monitored at minimum weekly after transplant until Day +100. If the patient becomes viremic with a DNA PCR level of 1000 copies/mL or higher on two consecutive occasions, the recommendation is to use Rituximab (375 mg/m^2 IV x1) or treat according to institutional practice. If the patient develops persistent EBV viremia or signs/symptoms of EBV-related post-transplant lymphoproliferative disease (PTLD) despite rituximab administration, treatment is recommended according to institutional practice.

HHV-6 viremia as tested by DNA PCR is recommended to be monitored weekly until Day +60. If the patient becomes viremic they are treated according to institutional practices.

In addition, all Grade 2 and 3 infections will be reported according to the BMT CTN MOP.

2.5.3.3 **Management of graft failure**

Patients experiencing primary or secondary graft failure are managed according to institutional practices.

For this protocol, lineage-specific, myeloid and T cell chimerisms are required. Myeloid engraftment might not proceed at the same rate as T cell engraftment. If myeloid has greater than or equal to 5% donor, even if T cell compartment does not, this is not considered primary graft failure.

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.

Management of graft failure as defined in this protocol is per institutional standards. Fixed chimerism not defined as graft failure should be managed per Appendix H.

2.5.3.4 **Management of ATG Intolerance**

Patients experiencing a new, severe, or life-threatening reaction to ATG and 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 as per local institutional preference or practice with documentation of the deviation.

2.5.4 **Risks and Toxicities**

2.5.4.1 **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, or viral (including CMV, BK virus) infection; severe mucositis; severe GVHD; hepatic veno-occlusive disease; pulmonary toxicities; hemorrhagic cystitis; bleeding without hemodynamic compromise.

2.5.4.2 **Drug Information**

2.5.4.2.1 **Fludarabine**

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

1) Neurotoxicity: Agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy, or weakness have been reported. Severe neurologic effects, including blindness, coma, and death may occur; severe CNS toxicity is rarely seen with doses in the recommended range for non-transplant therapy. The dose used in this study is approximately 1.5 times the usual one-course dose given in non-transplant settings. Doses and schedules similar to those used in this study have been used in adult and pediatric patients without observed increase in neurotoxicity.
2) Anemia: Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported after one or more cycles of therapy in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission. Corticosteroids may or may not be effective in controlling these episodes. The majority of patients re-challenged developed a recurrence of the hemolytic process.
3) Cardiovascular: Deep venous thrombosis, phlebitis, transient ischemic attack, and aneurysm (1%) are reported.
4) Fever: 60% develop fever.
5) Rash: 15% develop a rash, which may be pruritic.
6) Digestive: Gastrointestinal side effects include: nausea/vomiting (36%), diarrhea (15%), stomatitis (9%), anorexia (7%), GI bleeding and esophagitis (3%), mucositis (2%), liver failure, abnormal liver function test, constipation, dysphagia (1%) and mouth sores.
7) Some other side effects include: Chills (11%), peripheral edema (8%), myalgias (4%), osteoporosis (2%), pancytopenia, arthralgias (1%), dysuria (4%), urinary tract infection and hematuria (2%); renal failure, abnormal renal function test, and proteinuria (1%); and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

Dose adjustments of fludarabine are required for renal insufficiency (Sections 2.5.1 and 2.5.2).

2.5.4.3 **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: nausea, vomiting, diarrhea, headache, dizziness, hemorrhagic cystitis, fluid weight gain/edema, SIADH, transaminitis, cardiomyopathy, pericarditis, rash, mucositis, alopecia, cytopenias, sterility, and, rarely, secondary myelodysplastic syndrome and anaphylaxis.

Dose adjustments for cyclophosphamide will not be made.

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 equal to 80% of the total daily dose of cyclophosphamide.

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

2.5.4.4 **Thymoglobulin®**

Thymoglobulin® is a rabbit preparation of anti-thymocyte globulin (ATG). Common side effects include nausea, fever, chills, diarrhea, rash, dizziness, headache, and tiredness. More serious side effects can include severe allergic reaction, serum sickness, easy bleeding/bruising, fast/irregular heartbeat, joint/muscle pain, stomach/abdominal pain, and weakness. Because this drug works by weakening the immune system, it lowers the ability to fight infections, including some viral infections such as cytomegalovirus (CMV) Epstein Barr virus (EBV), and Human Herpes Virus 6 (HHV-6). No dose adjustments are required.

2.5.4.5 **Mycophenolate Mofetil (MMF)**

MMF is an ester prodrug of the active immunosuppressant mycophenolic acid (MPA).

Side effects include: pancytopenia, infection (including sepsis, CMV, HSV, VZV, and Candida), nausea, vomiting, diarrhea, allergic reactions, hypertension, headache, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, and leg cramps/bone pain.

Drug interactions: MMF activity is decreased with oral antacids and cholestyramine. There are no pharmacokinetic 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 mycophenolic acid (MPA) level should be checked. If the level is greater than 2, it will require a

dose reduction.

2.5.4.6 **Cyclosporine (CSA):**

Cyclosporine (CSA) is a calcineurin inhibitor used for immunosuppression. Administration may cause nephrotoxicity, seizures, tremors, headaches, abdominal pain or indigestion, edema, confusion, muscle cramps, dizziness, hemolytic anemia, hypertension, hirsutism, thrombotic microangiopathy, electrolyte imbalances, paresthesia/neuropathy, gingival hyperplasia, hypertriglyceridemia, diarrhea, transient blindness, renal dysfunction, and hepatic dysfunction.

Drug interactions & Dose adjustments: CSA is adjusted to maintain a serum trough level of 200-400 ng/mL by HPLC method or 250-500 ng/mL by TDX method. Patients with hepatic or renal insufficiency should receive doses at the lower end of therapeutic concentrations. No dose adjustments are required in patients undergoing hemodialysis. There are interactions between the azole antifungal medications and CSA such that the dose of CSA should be empirically lowered when an azole medication is initiated and levels of CSA should be checked to ensure it remains in the proper therapeutic window.

2.5.4.7 **Tacrolimus**

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

Toxicities: There is a spectrum of well-described toxicities of tacrolimus. Toxicities include renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, nausea, diarrhea, headache, neurologic toxicity including tremor and leukoencephalopathy, infection, and rarely thrombotic thrombocytopenic purpura (TTP).

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. Patients with hepatic or renal insufficiency should receive doses at the lower end of concentrations (5-10ng/mL). No dose adjustments are required in patients 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 the table below. Dose adjustments for therapy with other azoles may be indicated. However, the initial tacrolimus dose (on Day 5) remains fixed.

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 the table 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 2.1: Suggested preemptive dose reduction of tacrolimus when azoles are initiated at steady state levels of tacrolimus

Antifungal	Tacrolimus	
	Dose ↓	Comment
Voriconazole	67%	Strongly advised
Posaconazole	67%	Advised
Itraconazole	50%	Advised
Fluconazole	25%	Consider

2.5.4.8 **Filgrastim (G-CSF)**

Administration of G-CSF can cause bone pain, increased levels of liver enzymes and uric acid in the blood, thrombocytopenia, headaches, fatigue, local irritation at injection site, nausea, bleeding, fever, allergic reaction, splenomegaly or rupture of the spleen, worsening of pre-existing skin rashes, temporary hair loss, and inflammation of a blood vessel in the skin.

2.5.4.9 **Total Body Irradiation**

TBI can cause nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema (usually within 24 hours, resolving in 48-72 hours), hyperpigmentation, fever, mucositis, alopecia, and pancytopenia. Late effects include: cataracts (10-20%), hypothyroidism, nephropathy, interstitial pneumonitis, veno-occlusive disease, carcinogenesis, and sterility.

2.5.4.10 **Toxicity Grading**

Toxicities are graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

2.5.5 **Health Related Quality of Life (HR-QoL) Assessments**

2.5.5.1 **Instruments**

MOS SF-36: The Medical Outcomes Study Short Form 36 is a 36-item general assessment of HR-QoL with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of HR-QoL. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data. These summary scores are derived by multiplying the z-score for each scale by its respective physical or mental factor score coefficient and summing the products. Resulting scores are then transformed into T-scores (mean = 50; standard deviation = 10). The SF-36 takes 6 minutes to complete.

PedsQL: The PedsQL™ Stem Cell Transplant Module is a 46-item instrument that measures HR-QoL in children and adolescents undergoing hematopoietic stem cell transplant, and is developmentally appropriate for self-report in ages 8 through 18 years.

2.5.5.2 **Administration**

The self-report questionnaires will be completed at Baseline, then at Day 100, Day 180, and Day 365 post-transplant or until death. Only English- and Spanish-speaking adult patients and English-speaking pediatric patients are eligible to participate in the HR-QoL component of this trial. Patients >18 years will complete the MOS SF-36. Patients 8 years through 18 years will complete the PedsQL™ Stem Cell Transplant Module. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. The method of survey completion, the date, and the language will be recorded in the database. **Surveys may not be completed by surrogates**.

Table 2.2 – Required Patient-Reported Outcomes Data Collection

Instrument	Number of Items	Baseline	Day 100	Day 180	Day 365
MOS SF-36	36	X	X	X	X
PedsQL™ SCT Module	46	X	X	X	X

CHAPTER 3

3 STUDY ENDPOINTS AND DEFINITIONS

3.1 Primary Endpoint

3.1.1 Overall Survival (OS)

The primary endpoint is overall survival (OS) at 1 year post-HSCT in patients with SAA. OS is defined as the time interval from date of transplant to death or to last follow-up, whichever occurs first.

3.2 Secondary Endpoints

3.2.1 Neutrophil Recovery

Neutrophil recovery is achieving an ANC > 0.5 $x10^9$/L for three consecutive measurements on different days, with the first of the three days being defined as the day of neutrophil engraftment.

3.2.2 Platelet Recovery

Platelet recovery is defined by achieving a platelet count > 20 x 10^9/L with no platelet transfusions in the preceding seven days. The first day of the sustained platelet count will be defined as the day of platelet engraftment.

3.2.3 Alive with Sustained Engraftment

Being alive and engrafted is defined as not having experienced death, primary graft failure, or secondary graft failure.

Donor cell engraftment is defined as donor chimerism greater than or equal to 5% on or after Day 56 after transplantation. Chimerism may be evaluated in whole blood or blood cell fractions, including CD3 and CD33 or CD15 fractions. For this protocol, lineage-specific, myeloid, and T cell chimerisms are required.

3.2.3.1 Primary Graft Failure

Primary graft failure is defined by the lack of neutrophil engraftment by Day +56 post-HSCT or failure to achieve at least 5% donor chimerism (whole blood or marrow) on any measurement up to and including Day +56.

For this protocol, lineage-specific, myeloid, and T cell chimerisms are required. Myeloid engraftment might not proceed at the same rate as T cell engraftment. If myeloid has greater than or equal to 5% donor, even if T cell compartment does not, this is not considered primary graft failure.

3.2.3.2 Secondary Graft Failure

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

1. Initial neutrophil engraftment (ANC greater than or equal to 0.5 $x10^9$/L measured for three consecutive measurements on different days) followed by sustained subsequent

decline in ANC to less than 0.5 x 10^9/L for three consecutive measurements on different days;
2. Initial whole blood or marrow donor chimerism greater than or equal to 5%, but then declining to less than 5% on subsequent measurements;
3. Second infusion/transplant given for graft failure.

3.2.3.3 **Alive with Autologous Recovery**

Autologous recovery is defined as ANC > 0.5 x 10^9/L and transfusion independence but with < 5% donor chimerism (whole blood or marrow).

3.2.4 **GVHD**

Acute and chronic GVHD are graded according to the BMT CTN Manual of Procedures (MOP).

3.2.5 **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-transplant.

3.2.6 **Infection**

All Grade 2 and 3 infections will be reported according to the BMT CTN MOP. CMV viremia and disease, EBV viremia, HHV-6, and PTLD will be collected as per section 2.5.4.2.

3.2.7 **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-transplant using two instruments: the MOS SF-36 for adult patients (> 18 years), and the PedsQL™ Stem Cell Transplant Module for pediatric patients (8 years through 18 years). The instruments will be scored according to the recommendations of the developers. See Section 2.5.6 for detailed descriptions of the instruments. The SF-36 will be summarized by the Physical Component Summary (PCS) and Mental Component Summary (MCS). HR-QoL will be described for each treatment arm over time. Only adult patients able to read and speak in English or Spanish and pediatric patients able to read and speak in English are eligible to participate in the HR-QoL component of this trial.

CHAPTER 4

4 PATIENT ENROLLMENT AND EVALUATION

4.1 Enrollment Procedures

Patients will be registered using the BMT CTN Electronic Data Capture System (AdvantageEDC™). 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 Segment 0 Enrollment Form in AdvantageEDC, at which point a study number will be generated. After patient is enrolled on Segment 0, the authorized user should complete the HLA Forms to verify an eligible HLA match score. This eligibility screening includes a question confirming that the patient (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 patient on Segment A using the Segment A Enrollment Form. **The patient is not officially enrolled on study and may not begin study treatment until they are enrolled on Segment A.**
3. A visit schedule based on transplant date is displayed for printing and is referred to as "Segment A Follow-up".

4.2 Study Monitoring

4.2.1 Follow-up Schedule

The follow-up schedule for study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the BMT CTN 1502 Forms Guide.

Table 4.2.1: Follow-Up Schedule

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

12 week	84 ± 3 days
13 week	91 ± 3 days
100 day	100 ± 3 days
6 month	180 ± 28 days
12 month	365 ± 45 days

4.2.2 **Case Report Forms**

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Forms Guide. Forms that are not entered into AdvantageEDC™ within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into AdvantageEDC ™ and integrated into the Data Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Forms Guide.

Reporting Patient Deaths: Recipient death information must be entered into AdvantageEDC ™ within 24 business hours of knowledge of the patient'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 AdvantageEDC ™.

CIBMTR Data Reporting: Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants 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 US allotransplant recipients.) Enrollment on BMT CTN #1502 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post-transplant Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule. Patients not undergoing HCT are not required to have their information reported to the CIBMTR.

Weekly GVHD Monitoring: GVHD should be monitored in accordance with BMT CTN guidelines as specified in the Manual of Procedures. Patients should be assessed weekly until Day +100 post-transplant for GVHD. After Day +100, patients 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 4.2.1.

4.2.3 **Adverse Event Reporting**

4.2.3.1 **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.

Expectedness: An adverse event can be Expected or Unexpected

- **Expected adverse events** are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered

expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

- **Unexpected adverse events** are those that vary in nature, intensity or frequency from information in the current adverse event list, the Investigator's Brochure, the package insert, or when it is not included in the informed consent document as a potential risk.

Serious Adverse Event: A serious adverse event (SAE), as defined by per 21 CFR 312.32, is any adverse event 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 or convulsions that do not result in inpatient hospitalization, or 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 subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a Serious Adverse Event). Any event is considered a Serious Adverse Event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

4.2.3.2 **Required Adverse Event Reporting**

Adverse event reporting will be consistent with BMT CTN procedures (BMT CTN Administrative Manual of Procedures, Chapter 6). It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of study treatment. Unexpected, serious adverse events (SAEs) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, life-

threatening and fatal SAEs must be reported within 24 hours of knowledge of the event. All other unexpected SAEs must be reported within three business days of knowledge of the event. Events entered in AdvantageEDC will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals as defined on the Form Submission Schedule. Any expected life-threatening SAE not collected on another study form must be reported through the expedited AE reporting system via AdvantageEDC.

The Data and Safety Monitoring Board will receive summary reports of all unexpected SAEs on a semi-annual basis.

4.2.4 Patient Evaluations

Table 4.2.4 summarizes patient clinical assessments over the course of the study.

4.2.4.1 *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 (weight within 7 days prior to planned ATG infusion to ascertain ATG dosing).
2. Karnofsky or Lansky performance status.
3. Hematopoietic cell transplantation- comorbidity index (HCT-CI)
4. CBC with differential and platelet count and chemistries (creatinine, bilirubin, alkaline phosphatase, AST, ALT, ferritin). Please note that the absolute lymphocyte count is required within 7 days prior to planned ATG infusion to ascertain ATG dosing for UCB transplant recipients.
5. HLA typing (patient and donor) and anti-donor antibody testing (if not already performed). HLA typing may be done more than 30 days prior to enrollment.
6. Infectious disease titer for human immunodeficiency virus (HIV) by local standard of care.
7. Hepatitis B and C determined by serology and/or NAT.
8. LVEF or, for patients aged < 13.0 years, shortening fraction measurement by echocardiogram or MUGA.
9. Pulmonary function testing: FEV1, FVC, and DLCO (corrected for Hb). For patients aged < 13.0 years and patients unable to perform PFTs due to age or developmental ability, pulse oximetry is an acceptable alternative.
10. Bone marrow aspirate/biopsy with cytogenetics within 60 days prior to enrollment.
11. Diepoxybutane (DEB) testing on peripheral blood or comparable testing on marrow for Fanconi Anemia (at any time prior to enrollment).
12. Pregnancy test for females of childbearing potential (testing per institutional practice).
13. Study-required blood samples as described in Appendix C (all patients):
    a. Thymoglobulin pharmacokinetics (5 time points, 5 mL each time):

i. Upon completion of 1st dose of ATG (within 60 minutes)
ii. Prior to infusion of 2nd dose (within 60 minutes)
iii. Upon completion of 2nd dose of ATG (within 60 minutes)
iv. Upon completion of 3rd dose of ATG (within 60 minutes)
v. Day 0 (any time prior to infusion of graft)

CBC including absolute lymphocyte count should also be collected on Day 0 (if possible) along with this PK sample and results documented in AdvantageEDC; the timing of the sample (d-m-y hh:mm) should also be documented

14. Optional blood samples as described in Appendix C:
    a. Telomere length assay (all patients and haplo donors; collected pre-conditioning for patients, pre-donation for donors)
        i. Children < 20 kg: 12 mL in EDTA tubes
        ii. Adults: 24 mL in EDTA tubes
    b. Future research (all patients): 3mL whole blood prior to conditioning
15. Absolute lymphocyte numbers by flow cytometry for lymphocyte subpopulations to include CD4, CD19, and CD56.
16. Serum quantification of IgG, IgM, and IgA.
17. Baseline peripheral blood samples for chimerism analysis by molecular methods (patient and donor).
18. Health Related Quality of Life (HR-QoL): Patient 'self-reported' assessments to include the Medical Outcomes Study Short Form 36 (MOS SF-36) for English and Spanish speaking adult patients (> 18 years). English-speaking pediatric patients (ages 8 through 18 years) will complete the PedsQL™ Stem Cell Transplant Module.

4.2.4.2 ***Post-transplant evaluations***

1. 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 to be in keeping with the BMT CTN MOP. Chronic GVHD Provider Survey to be completed by an MD, NP, or PA at the time of patient assessment. For scheduling purposes, a target day range has been provided in Table 4.2.1.
2. Karnofsky or Lansky performance status at Day +365.
3. CBC at least three times a week (or as per institution's standard practice) from Day 0 until ANC > 0.5 x 10^9/L for 3 consecutive measurements over 3 or more days. Thereafter, CBC at least twice per week (or as per institution's standard practice) until Day +28, then weekly until Day +100, then at Day +180 and Day +365.
4. 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 (or as per institution's standard practice). 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 (or as per institution's standard practice).

5. Toxicity assessments at Day +28, +56, +100, +180, and +365.
6. Absolute lymphocyte numbers by flow cytometry for lymphocyte subpopulations to include at minimum CD4, CD19, and CD56 at Day +100, +180, and +365.
7. Serum quantification of IgG, IgM, and IgA at Day +365.
8. Quantification of peripheral blood (whole blood and CD3) or marrow chimerism (including lineage-specific, myeloid, and T cell chimerisms) 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.**
9. EBV DNA quantitative PCR testing and CMV 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 patient is off of all immunosuppression.
10. Study-required blood samples as described in Appendix C (all patients):
    a. Thymoglobulin pharmacokinetics (1 time point, 5 mL):
        i. Day +7 (no time restrictions)
11. Health Related Quality of Life (HR-QoL): Patient 'self-reported' assessments at Day +100, Day +180, and Day +365 post-transplant to include the Medical Outcomes Study Short Form 36 (MOS SF-36) for English- and Spanish-speaking adult patients (> 18 years). English-speaking pediatric patients (ages 8 through 18 years) will complete the PedsQL™ Stem Cell Transplant Module.

Table 4.2.4: Summary of Assessments

Study Assessments / Testing	Baseline (Pre-conditioning)	During conditi-oning	0	7	14	21	28	35	42	49	56	63	70	77	84	91	100	180	365
History, Physical Exam, Weight, and Height	X																		
Karnofsky/Lansky Performance Status	X																		X
CBC[1], Differential, Platelet Count, and Blood Chemistries[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HLA Typing & Anti-Donor Antibody Testing	X																		
Infectious Disease Titers[3]	X																		
LVEF or Shortening Fraction for < 13 years	X																		
Pulmonary Function Tests[4]	X																		
Bone Marrow Aspirate for Pathology and Cytogenetics[5]	X																		
Testing for Fanconi Anemia[6]	X																		
Pregnancy Test (females only)	X																		
Study-required Blood Samples[7]		X	X	X															
Optional Blood Samples[8]	X																		
CD4, CD19, and CD56 Counts	X																X	X	X
Serum Quantification of IgG, IgM, and IgA	X																		X
Peripheral Blood Chimerism[9]	X						X				X						X	X	X
CMV & EBV DNA Quantitative PCR Testing[10]				X	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 & HR-QoL	X																X	X	X

[1] CBC performed three times weekly from Day 0 until ANC > 0.5 x 10^9/L for three consecutive measurements on different days. CBC then performed twice per week until Day +28, then weekly until Day +100, then at Day +180 and Day +365. CBC including absolute lymphocyte count should be collected on Day 0 along with the PK sample (if possible).

[2] Blood chemistries include: creatinine, bilirubin, alkaline phosphatase, AST, ALT, Ferritin (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] Infectious disease titers include: hepatitis panel (HepB SAb, HepB SAg, HepB Core Ab, HepC Ab) and HIV.

[4] DLCO (corrected for Hb), FEV1, and FVC or pulse oximetry for patients aged < 13.0 years if unable to perform standard PFT.

[5] Bone marrow aspirate and biopsy (cytogenetics is required, local MDS panel recommended) within 60 days prior to enrollment.

[6] Results of Diepoxybutane (DEB) testing on peripheral blood or comparable testing on marrow for Fanconi anemia at any time prior to enrollment.

[7] Study-required blood draws include 6 samples for Thymoglobulin® pharmacokinetics in all patients (4 samples during ATG dose days, 1 sample on Day 0, and 1 sample on Day +7).

[8] Optional blood draws include a baseline sample for telomere length assay collected from all consenting patients pre-conditioning and consenting haplo donors pre-donation as well as 1 sample for future research collected from all consenting patients pre-conditioning.

[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).

[10] EBV and CMV 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 an MD, NP, or PA at the time of patient assessment.

CHAPTER 5

5 STATISTICAL CONSIDERATIONS

5.1 Study Overview

This study is designed as a multi-center, Phase II trial to assess the safety and efficacy of HSCT using haploidentical bone marrow with Thymoglobulin® (ATG)-containing preparative regimens in patients with severe aplastic anemia. The target enrollment is to get 30 transplanted patients.

5.1.1 Accrual

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

5.1.2 Primary Endpoint

The primary objective is to assess overall survival probability at one year post-transplant. Death from any cause is the event for this endpoint. The time to event is time from transplant to death or last follow-up, whichever occurs first.

5.2 Sample Size Calculations

The sample size for this study is 30 patients. Overall survival probability will be estimated. Ninety-five percent confidence intervals were calculated for varying probabilities based on a sample size of 30. Table 5.2 provides confidence intervals for a variety of underlying proportions. Of particular interest is where the OS probability is 75%, which is our targeted one-year survival probability. For this setting, the confidence interval length is 31% with the lower limit of 59.5%, which is above previous estimates. As presented in the background, CIBMTR one year survival of patients using haplo was 63%, very close to the 59.5% 95% confidence interval if the OS probability is 75%. If we achieve survival > 75%, we will have high confidence (p = 0.05) that outcomes have improved compared to this historical control. The percentages above and below 75% are meant to represent other plausible survival rates.

TABLE 5.2 POSSIBLE 95% CONFIDENCE INTERVAL FOR VARIOUS UNDERLYING OVERALL SURVIVAL RATES WITH N = 30

Overall Survival Rate (%)	Possible 95% Confidence Intervals (%)		Length of 95% Confidence Interval
85	**72.2**	**97.8**	**25.6**
80	**65.7**	**94.3**	**28.6**
75	**59.5**	**90.5**	**31.0**
70	53.6	86.4	32.8
65	47.9	82.1	34.1
60	42.5	77.5	35.0
55	37.2	72.8	35.6
50	32.1	67.9	35.8

The OS probability estimate will be based on the Kaplan-Meier product limit estimator. In the absence of censoring, the Kaplan-Meier estimate reduces to the binomial proportion.

5.3 Interim Analysis and Pausing Guidelines

There will be no interim analyses for efficacy or futility. Patients will be monitored for key safety endpoints including graft failure and mortality. Graft failure will be monitored including both primary graft failure and secondary graft failure. Primary graft failure will be determined by Day 56 post-transplant in all patients receiving a transplant. Secondary graft failure will be determined by Day 56 post-transplant in all patients achieving the initial engraftment. Mortality will be monitored up to 115 days from the first day of preparative regimen (Day -9) in all patients receiving the first dose of ATG. The rationale for monitoring mortality from the first day of ATG preparation in all patients receiving the first dose of ATG is to guard against excessive early mortality including death due to the intervention in patients 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-transplant evaluation for patients receiving a transplant.

Graft failure and mortality will be monitored so that if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The pausing guidelines serve as a trigger for consultation with the DSMB for additional review and are not formal “stopping rules” that would mandate automatic closure of study enrollment.

A truncated Sequential Probability Ratio Test (SPRT) based on a binomial test of proportions will be used to monitor each safety endpoint as described below. This sequential testing procedure conserves type I error across all of the monitoring looks for each endpoint, but not across endpoints. The SPRT can be represented graphically. At each interim analysis, the number of patients evaluable for the endpoint is plotted against the total number of patients who have experienced the event. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive graft failure or mortality. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that graft failure or mortality is higher than predicted by the number of patients on study. Otherwise, the SPRT continues until enrollment reaches the target goal.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be slightly lower than the nominal level.

5.3.1 Graft Failure by Day 56 Post Transplant

Graft failure will be monitored up to Day 56 post-transplant in all patients who proceed to transplant. Events for this safety endpoint include both primary graft failure and secondary graft failure. The safety boundary for graft failure was developed from an SPRT contrasting 15% versus 35% graft failure by Day 56 post-transplant, with nominal type I and II errors of 10% and 14%, respectively. The slope of the line for monitoring excessive graft failure is 0.240 and the intercept is 1.929. The stopping rule is summarized in Table 5.3.1A.

TABLE 5.3.1A PAUSING GUIDELINES FOR DAY-56 GRAFT FAILURE

Number of Patients Proceed to Transplant	Pause if Graft Failure Occurs in
3 – 4	3
5 – 8	4
9 – 12	5
13 – 16	6
17 – 21	7
22 – 25	8
26 – 29	9
30	10

The actual operating characteristics of the truncated test, shown in Table 5.3.1B, were determined in a simulation study with 10,000 replications. The simulation assumed uniform accrual of 30 patients over a three-year time period.

TABLE 5.3.1B OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR DAY-56 GRAFT FAILURE FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

True Day-56 rate	15%	20%	25%	30%	35%
Probability reject the null hypothesis	0.07	0.20	0.41	0.63	0.80
Mean month stopped	36.6	34.1	30.2	25.6	21.0
Mean # endpoints in 56 days	4.4	5.4	6.0	6.0	5.7
Mean patients evaluable for endpoints	28.9	26.9	23.7	20.0	16.3

Graft failure will be monitored in all patients who actually receive a BM infusion. The SPRT rejects the null hypothesis in favor of the alternative 7% of the time when the true Day-56 rejection rate is 15%, and 80% of the time when the true Day-56 rejection rate is 35%. This corresponds to a type I error rate $\alpha = 0.07$ and a type II error rate $\beta = 0.20$. When the true Day-56 rejection rate is 35%, on average, the DSMB will be consulted 21 months after opening, when 6 events have been observed in 17 patients. Note that the SPRT procedure is adequately powered to distinguish between a rejection rate of 15% and 35%.

5.3.2 Mortality by Day 115 Post ATG Preparation

Mortality will be monitored up to 115 days from the first day of ATG preparation (~100 days post-transplant for patients receiving a transplant). Mortality will be monitored in all patients receiving the first dose of ATG. The safety boundary for mortality was developed from an SPRT contrasting 10% versus 30% mortality rate, with nominal type I and type II errors of 8% and 15%, respectively. The slope of the line for monitoring excessive mortality is 0.186 and the intercept is 1.751. The stopping rule is summarized in Table 5.3.2A.

TABLE 5.3.2A PAUSING GUIDELINES FOR 115 DAY MORTALITY

Number of Patients Started ATG Preparation and Evaluable for Mortality by 115 Days	Pause if Mortality Occurs in
3 – 6	3
7 – 12	4

13 – 17	5
18 – 22	6
23 – 28	7
29 – 30	8

The actual operating characteristics of the truncated test, shown in Table 5.3.2B, were determined in a simulation study with 10,000 replications. The simulation assumed uniform accrual of 30 patients over a three-year time period.

TABLE 5.3.2B OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FOR DAY 115 MORTALITY FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

True Day-115 rate	**10%**	**15%**	**20%**	**25%**	**30%**
Probability reject the null hypothesis	0.05	0.20	0.43	0.67	0.84
Mean month stopped	38.7	35.9	31.4	26.0	21.4
Mean # endpoints	2.9	4.1	4.6	4.8	4.6
Mean patients with 115 days follow-up	29.1	26.9	23.2	18.9	15.2

Mortality will be monitored in all patients starting the preparative regimen. The SPRT rejects the null hypothesis in favor of the alternative 5% of the time when the true Day-115 mortality is 10%, and 84% of the time when the true Day-115 mortality is 30%. This corresponds to a type I error rate $\alpha = 0.05$ and a type II error rate $\beta = 0.16$. When the true Day-115 mortality is 30%, on average, the DSMB will be consulted 21.4 months after opening, when 5 events have been observed in 16 patients**.** Note that the SPRT procedure is adequately powered to distinguish between a mortality rate of 10% and 30%.

5.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be described for all patients. 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 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 Analysis Plan

Analysis of all endpoints will be conducted for transplanted patients.

5.5.1 Analysis of the Primary Endpoint

The primary analysis will consist of estimating the one-year overall survival probability using the Kaplan-Meier estimator. The event for this endpoint is death from any cause. The time to this event is the time from transplant to death or last follow-up, whichever occurs first. The one-year OS probability and its 95% confidence interval will be estimated.

5.5.2 Analysis of Secondary Endpoints

Proportion of Patients Alive and Engrafted

The proportion of patients alive and engrafted at one year will be estimated along with a 95% confidence interval.

Neutrophil Engraftment

Cumulative incidence of neutrophil engraftment at Day 28 will be estimated with a 95% confidence interval using the cumulative incidence function with death prior to neutrophil engraftment as the competing risk.

Platelet Engraftment

Cumulative incidence of platelet engraftment at Day 100 will be estimated with a 95% confidence interval using the cumulative incidence function with death prior to platelet engraftment as the competing risk.

Primary and Secondary Graft Failure

The frequency and proportion of patients experiencing primary graft failure by Day 56 and the proportion of patients who have engrafted and subsequently experience secondary graft failure will be described with 95% confidence interval.

Grade II – IV Acute GVHD

Cumulative incidence of Grade II – IV acute GVHD at Day 100 will be estimated with a 95% confidence interval using the cumulative incidence function with death prior to Grade II – IV acute GVHD as the competing risk.

Chronic GVHD

Cumulative incidence of chronic GVHD at one year will be estimated with a 95% confidence interval using the cumulative incidence function with death prior to chronic GVHD as the competing risk. This will include analysis of the severity of chronic GVHD using the NIH criteria.

Immunologic Reconstitution

Immune reconstitution assays including CD4, CD19, and CD56 will be measured pre-HCT and at Day 91, Day 180, and Day 365 post-HCT. These will be summarized at each time point using descriptive statistics.

Incidence of Infectious Complications

The number of specific infections (documented bacteremia with organism, CMV, and EBV) and the number of patients experiencing infections will be tabulated. Incidences of CMV viremia and disease, EBV viremia, and PTLD will be reported.

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-transplant using two instruments: the MOS SF-36 (both PCS and MCS) for English- and Spanish-speaking adult patients (> 18 years) and the PedsQL^{TM} Stem Cell Transplant Module for English-speaking pediatric patients (8 years through 18 years). HR-QoL at each time point will be summarized using simple descriptive statistics (mean, SD). Analysis will be done separately for each instrument using a Bonferroni adjusted significance level (0.05/4). All models will be adjusted for baseline HR-QoL.

APPENDIX A:

HUMAN SUBJECTS

APPENDIX A:

HUMAN SUBJECTS

1. Subject 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 patient 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 Institutional Review Board (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 patient identifier code. The code relaying the patient'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 Data and Coordinating Center 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 severe aplastic anemia in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

APPENDIX B:

CONSENT FORMS

Patient Informed Consent Template for the BMT CTN 1502 Study

Optimizing Haploidentical Aplastic Anemia Transplantation

Your Name: _____

Study Title: Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP)

Protocol: BMT CTN #1502

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Principal Investigator: *Insert local PI information*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. You're being asked to join because you:

- Have a diagnosis of severe aplastic anemia (SAA), and
- Your SAA can be treated with an **allogeneic transplant.** You don't have a completely matched **related** or **unrelated donor**, but you do have a half-matched family (**haploidentical**) bone marrow donor

This study will take at least 3 years and will include 30 participants. Your participation will last for **1 year** after your transplant.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), is providing staff support and money for this research study. The BMT CTN and the NIH will make decisions together about how to manage the study.

An **allogeneic transplant** uses blood-making cells from a **related donor** (family member) or an **unrelated donor** (not a family member) to replace your diseased blood cells. Before your transplant, you will get chemotherapy with radiation to destroy the diseased cells.

After chemotherapy, the healthy cells from your donor are given to you. The new cells go into your bloodstream through an intravenous (IV) catheter (or tube). It's just like getting blood or medicine through an IV. The donor cells find their way into your marrow where most often they grow and start to make healthy new red blood cells, white blood cells, and platelets.

For this study, the cells used for your transplant will come from **bone marrow** (related donor), which is soft, spongy tissue inside of bones. The bone marrow will come from a half-matched (haploidentical) family member such as a sister, brother, child or parent. This means that you and

the donor have one set of genes (out of two possible) that are the same, or are half-matched. This is called a **haploidentical transplant**. 'Haplo' means half.

3. Study Purpose

We invite you to take part in this study because you have severe aplastic anemia (SAA) and an allogeneic transplant is a treatment option for you. We're doing this study to learn how well SAA patients do with transplants that use haploidentical bone marrow.

4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or if you want to leave the study, please contact:

[insert contact info]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

If you join the study, we will check your health before you start treatment, while you receive treatment, and for 1 year after your transplant.

Before Your Treatment

You will need to have several check-ups and tests to see if you can be in the study. These check-ups and tests are part of your regular care. They would be done even if you were not part of this study. These tests include:

- Medical history
- Physical exam, height, and weight
- Blood and urine tests
- Heart function tests
- Lung (pulmonary) function tests; for children, pulse oximetry test to measure how much oxygen is in your blood.
- Bone marrow tests. These tests are called aspirates or biopsies. Samples of your marrow will be taken from your hip bone with a large needle.
- A pregnancy test if you are a woman and able to have children (if you are pregnant, you will not be able to join this study).

During Your Treatment

If the check-ups and tests show that you can be in the study, you'll get a bone marrow transplant from a half-matched (haplo-identical) family member.

Before Your Transplant:

The conditioning regimen is the combination of chemotherapy drugs (chemo) and radiation you'll receive before you get your donor cells. This helps the donor cells start to grow and make new cells in your bone marrow (engraft).

A common side effect of allogeneic transplant is Graft versus Host Disease (GVHD). It's a medical condition that can be very serious (see Risks and Toxicities Related to Transplant under **Section 6: Risks and Discomfort**).

GVHD happens because of differences in your immune cells (host) and your donor's immune cells (graft). The donor cells might see your cells as foreign and attack them, causing GVHD to happen. Your doctor will give you drugs to help prevent GVHD from happening.

Your doctor will use the following drugs and radiation to prepare your body for transplant:

- **Thymoglobulin®, also known as anti-thymocyte globulin, rabbit ATG and rATG** (helps the donor cells engraft in your body and is also a GVHD prevention drug)
- **Fludarabine** and **Cyclophosphamide** (chemotherapy drugs)
- **Total body irradiation, TBI** (radiation therapy given to the whole body to help weaken your immune system and prevent rejection of transplanted stem cells)

The schedule of drugs you will receive to prepare your body for transplant is as follows:

- We'll give you Thymoglobulin® each day for 3 days, starting 9 days before your transplant (Day -9 through Day -7).
- Then we'll give you Fludarabine each day for 5 days, starting 6 days before your transplant (Day -6 through Day -2).
- You'll also get Cyclophosphamide for 2 days, starting 6 days before your transplant (Day -6 and Day -5).
- Last, you'll get a low dose of TBI the day before your transplant (Day -1).

After your transplant, you'll also get drugs to help prevent GVHD:

- You'll get **Cyclophosphamide** for 2 days, starting 3 days after your transplant (Day +3 and Day +4). Your doctor will give you this drug in your vein (IV).
- We'll give you **Tacrolimus** daily starting 5 days after your transplant (Day +5). Your doctor will either give you this drug in your vein (IV) or you will take a pill.

- Then we'll give you **Mycophenolate mofetil** (MMF) daily starting 5 days after your transplant (Day +5). Your doctor will either give you this drug in your vein (IV) or you will take a pill.
- You will continue to take Tacrolimus (or a similar drug called Cyclosporine) for about 6 to 12 months, and MMF for about 5 weeks after your transplant or until there are no signs of GVHD.

After your transplant, you will also get drugs to help speed up the recovery of white blood cells.

- We'll give you **Filgrastim** (G-CSF) through your catheter or by injection under your skin 5 days after your transplant (Day +5). You'll get Filgrastim every day until your blood counts are at a safe level and then continue for three additional days before stopping.

See Table 1 below for a schedule of when you'll get these drugs**.**

Table 1: Schedule of Drugs

Drugs	**Days -9 to -7**	**Days -6 to -2**	**Days -6 & -5**	**Day -1**	**Day 0 (Transplant day)**	**Days +3 & +4**	**Days +5 to +180**	**Days +5 to +35**	**Days +5 to +7 or more**
Thymoglobulin (ATG)	X								
Fludarabine		X							
Cyclophosphamide			X						
Total body irradiation (TBI)				X					
Transplant day (infusion of bone marrow)					X				
Cyclophosphamide						X			
Tacrolimus or cyclosporine							X		
Mycophenolate mofetil (MMF)								X	

Filgrastim									X

Your Transplant:

On your transplant day (Day 0), the donor cells from your haploidentical family member will be given to you through your catheter just like a blood transfusion. The cells will travel to your bone marrow where they will start to make new, healthy blood cells.

Health Evaluations:

We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

After Your Treatment

Health Evaluations after Transplant:

- Routine blood tests (cell counts and liver and kidney function) two or three times per week until Day 28, then weekly until Day 100, and then at Days 180 and 365.
- One of six protocol-required 5 mL (~1 teaspoon) blood samples from a vein in your arm on Day 7 (4 of the other protocol-required samples will be taken pre-transplant on the days you receive ATG and 1 will be taken on the day of your transplant).
- Blood tests to see how well your immune system is working at Day 100, 180, and 365.
- Blood tests to find the amount of donor cells in your body on Days 28, 56, 100, 180, and 365. This is called chimerism.
- Blood tests to find out if you have any infections weekly until Day 100.
- Physical exam to look for toxicities on Days 28, 56, 100, 180, and 365.
- Physical exam to look for GVHD weekly until Day 100 and then at Days 180 and 365.
- Health-Related Quality of Life Questionnaires: If you speak English and are 8 years of age or older or if you speak Spanish and are 19 years of age or older, you will be asked to complete a questionnaire about your quality of life before your transplant and then at Day 100, Day 180, and Day 365.

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to very serious. The risks listed in this section might happen from transplant. These risks might happen if you have a transplant as part of this study or as standard care. Your doctor will give you drugs to help lower the side effects, such as feeling sick to your stomach (nausea). In some cases, side effects

can be long lasting or may never go away. The chemotherapy drugs can cause leukemia years later, but this is rare. These "secondary cancers" are often very hard to treat and can cause death.

Risks and Toxicities Related to Transplant:

The following problems may happen because of your transplant. These risks may happen if a transplant was done as part of the study or not. The risks are:

Death due to infection or transplant complications: Patients undergoing transplant for severe aplastic anemia are at risk of fatal complications due to several complications listed below (infection, organ damage, graft versus host disease, etc.). Although approaches to haploidentical transplant included in this study may improve outcomes, in past studies, as many as 20-40% of patients have had fatal complications using this stem cell source.

Slow recovery of blood counts: The red blood cells, white blood cells, and platelets can be slow to recover after a bone marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions and you will be at risk for bleeding and infections. You'll receive Filgrastim to speed the recovery of the white cells as much as possible.

Graft failure: The stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10 - 15% chance of graft failure. If graft failure occurs, you could have low blood counts for a long period of time. If your counts don't recover, you may need to receive a second transplant. Graft failure can be fatal.

Graft-Versus-Host Disease (GVHD): GVHD happens when the donor cells recognize your body as foreign and attack it. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it.

Acute GVHD, which can happen 0 – 3 months after transplant, may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD, which can happen 3 months or later after transplant, may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

Damage to the vital organs in your body: The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys, bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections or the chemotherapy and radiation.

Serious infections: Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will be prescribed certain drugs to reduce the chance of those infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant.

Although most infections can be successfully treated, some infections may result in death.

Recurrence of disease or a new blood cancer: Your severe aplastic anemia may come back even if the transplant is successful at first. In rare cases, a new blood cancer may develop from the donor cells. Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). These blood cancers usually develop 2 - 10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic transplant is probably less than 2%. If cancer develops in your blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

Risk to the unborn: The treatments in this study have not been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must use effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD, and for 1 year after transplant. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (abstinence)
2. Consistent use of birth control pills
3. Injectable birth control methods (Depo-Provera, Norplant)
4. Tubal sterilization or male partner who has undergone a vasectomy
5. Placement of an IUD (intrauterine device)
6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Reproductive Risks:

The drugs used in this research study may damage your reproductive organs, affect your ability to have children, or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of the study. Women may also want to talk to their doctors about freezing eggs prior to transplant.

- If you are a woman and can become pregnant:

  You will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use an effective method of birth control during your transplant and continue until 1 year after transplant.

  Additional Information about MMF:

  - MMF could be damaging to an unborn baby if you are pregnant or become pregnant

while receiving the drug.

- MMF can make birth control pills less effective and increase your chances of becoming pregnant while you are taking it.
- If you can become pregnant, you must use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for 6 weeks after stopping MMF.
- In this study, you will be assigned to receive MMF for about 5 weeks, so you should not become pregnant during that time. If you think you might become pregnant or could become pregnant during the upcoming 5 weeks, you should not join the study.

- If you are a man:

  Your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant. You must still use an effective method of birth control during your transplant and continue until 1 year after transplant.

Please check with your doctor to understand more about these risks.

Unforeseen Risks:

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about these types of transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

Other Treatments or Medications:

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes over-the-counter drugs, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to these medications during your participation in the study.

For more information about risks and side effects, ask your study doctor.

Risks and Toxicities Related to Medications:

Likely	What it means: This type of side effect is expected to happen in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to happen in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not happen often – in fewer than 2% of patients – but is serious when it happens. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Possible Side Effects of Study Drugs

The most common side effects of the treatments used in this study are listed below. There is also the risk of very uncommon or unknown side effects. All chemotherapy drugs in this study are commonly used in transplant.

Fludarabine (Fludara®) – Chemotherapy drug

Likely	Less Likely	Rare, but Serious
▪ Infection ▪ Anemia (low red blood cell count) ▪ Tiredness ▪ Nausea ▪ Vomiting ▪ Pneumonia ▪ Mouth sores ▪ Fever ▪ Swelling of hands and feet ▪ Weakened immune system ▪ Pain ▪ Low number of white blood cells ▪ Low number of platelets in the blood ▪ Electrolyte imbalances	▪ Diarrhea ▪ Numbness and tingling in hands and/or feet ▪ Changes in vision ▪ Skin rash ▪ Cough ▪ Changes in heartbeat ▪ Loss of appetite ▪ Chills ▪ Lung inflammation	▪ Agitation or nervousness ▪ Confusion ▪ Difficulty breathing ▪ Weakness ▪ Severe brain injury and death ▪ Bleeding due to decreased number of platelets ▪ Kidney damage that could require dialysis ▪ Coma ▪ New (secondary) cancers

Thymoglobulin® (rabbit ATG, antithymocyte globulin rabbit) - Helps engraft cells and prevent GVHD

Likely	Less Likely	Rare, but Serious
▪ Fever/chills ▪ Hives ▪ Nausea ▪ Headache ▪ Body swelling ▪ Skin rash, joint aches and pain ▪ Shivering ▪ Serum sickness ▪ Low white blood cell count	▪ Severe or life-threatening allergic reaction ▪ Lymphomas (i.e., cancers of the immune system)	▪ Anaphylaxis ▪ Acute kidney failure ▪ High potassium

Cyclophosphamide (Cytoxan®) - Chemotherapy drug, helps prevent GVHD

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with increased risk of infection ▪ Temporary hair loss ▪ Nausea ▪ Vomiting ▪ Loss of appetite ▪ Sores in mouth or on lips ▪ Diarrhea ▪ Stopping of menstrual periods in women ▪ Decreased sperm production in men ▪ Decreased platelet count (mild) with increased risk of bleeding ▪ Blood in urine	▪ Low red blood cell count (anemia) ▪ Temporary tiredness ▪ Damage to the fetus if you become pregnant while taking drug	▪ Scarring of lung tissue, with cough and shortness of breath ▪ Severe heart muscle injury and death at very high doses ▪ New (secondary) cancers

Filgrastim (G-CSF; Neupogen®) – helps speed up recovery of white blood cells

Likely	Less Likely	Rare, but Serious
▪ Ache or pain inside of bones ▪ Increased levels of liver enzymes and uric acid in the blood ▪ Low number of platelets in the blood ▪ Headache ▪ Tiredness	▪ Local irritation (skin) at the injection site ▪ Nausea ▪ Bleeding ▪ Fever	▪ Allergic reaction ▪ Enlargement or rupture of the spleen ▪ Worsening of pre-existing rashes ▪ Temporary hair loss ▪ Inflammation of a blood vessel in the skin

Mycophenolate Mofetil (MMF: CellCept®) – helps prevent GVHD

Likely	Less Likely	Rare, but Serious
▪ Miscarriage ▪ Birth defects ▪ Diarrhea ▪ Damage to unborn baby ▪ Limited effectiveness of birth control ▪ Stomach pain ▪ Nausea ▪ Vomiting ▪ Headache ▪ Tremors ▪ Low white blood cell count with increased risk of infection ▪ Swelling of the hands, feet, ankles or lower legs	▪ Low red blood cell count (anemia) ▪ Rash ▪ Difficulty falling asleep or staying asleep ▪ Dizziness ▪ Uncontrollable hand shakes	▪ Difficulty breathing ▪ Unusual bruising ▪ Fast heartbeat ▪ Excessive tiredness ▪ Weakness ▪ Blood in stool ▪ Bloody vomit ▪ Change in vision ▪ New (secondary) cancers ▪ Progressive Multifocal Leukoencephalopathy (a disease that damages the white/gray parts of the brain)

Total Body Radiation (TBI) – helps to weaken your immune system and prevent rejection of transplanted stem cells

Likely	Less Likely	Rare, but Serious
▪ Fever ▪ Fatigue ▪ Hair loss ▪ Loss of appetite ▪ Mouth sores ▪ Nausea ▪ Diarrhea ▪ Stomach cramps ▪ Vomiting (throwing up) ▪ Painful swelling of the salivary glands under the ears for a few days ▪ Low red blood cell count (anemia) ▪ Infection ▪ Bleeding ▪ Cataracts ▪ Hormone problems (such as thyroid disease or diabetes) ▪ Mouth sores	▪ Skin pigmentation (reversible) ▪ Sterility (inability to have children) ▪ Slow growth	▪ Lung fibrosis ▪ New (secondary) cancers

Tacrolimus (FK506, Prograf®) – GVHD drug

Likely	Less Likely	Rare, but Serious
▪ High blood pressure ▪ High blood sugar ▪ Low red blood cell count (anemia) ▪ High or low potassium levels ▪ Low magnesium and calcium levels ▪ Loss of appetite ▪ Diarrhea ▪ Nausea ▪ Fever ▪ Headache	▪ Hair loss ▪ Vomiting ▪ Tingling sensation in the extremities ▪ Itching ▪ Rash ▪ Abdominal pain	▪ Confusion ▪ Painful joints ▪ Increased sensitivity to light ▪ Change in vision ▪ Insomnia (trouble sleeping) ▪ Infection ▪ Jaundice (skin yellowing) ▪ Kidney injury ▪ Seizures ▪ RPLS/PRES[1]

[1] Reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES). In transplant patients, it can be caused by some of the drugs used to prevent or treat GVHD. It can often, but not always, be prevented by very careful control of blood pressure.

It is very important that you DO NOT eat grapefruit or drink grapefruit juice while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

7. Other Treatments

It's optional to join this study. If you choose not to take part, you may still receive treatment with alternative immune suppressing therapy, new agents, or an allogeneic transplant to treat your disease. The transplant treatment and evaluations you would receive could be very similar to what you would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with a partially-matched related or unrelated donor or another alternative donor source
- Treatment with other drugs to suppress the immune system without a transplant
- Treatment with drugs aimed at temporarily boosting your blood counts or other new agents under investigation
- Treatment with blood transfusions only
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about transplants for SAA. It could also help people with SAA that may need a transplant in the future.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to meet your needs and medical conditions.

10. Privacy, Confidentiality, and Use of Information

Your confidentiality is one of our main concerns. Study records that have your name will be kept private as required by law. You will not be identified by name in the central study records. Your records will be given a unique code number. The key to the code will be kept in a locked file in the Principal Investigator's office.

All necessary steps will be taken to avoid you being identified in any public presentations. The results of this study treatment may be published in scientific journals in the future, but no patients (including you) will be identified.

Information about your transplant course may be reviewed or transmitted to national and international transplant registries, including:

- [Institution]
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- U.S. government agencies that are responsible for overseeing research such as The Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state, and local health departments
- The Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study
- Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC), including:
    - The Center for International Blood and Marrow Transplant Research (CIBMTR)
    - The National Marrow Donor Program (NMDP)
    - Emmes, who are coordinating the studies of the BMT CTN
- Study investigators:
    - Dr. Amy DeZern, Co-Principal Investigator
    - Dr. Michael Pulsipher, Co-Principal Investigator

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this clinical trial has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Data regarding your clinical situation, including follow-up after 1 year, may be obtained from the CIBMTR, which captures information on all U.S. transplants.

For questions about access to your medical records, please contact:

[Insert name and phone number].

Expiration date for retention of records:

Information about the study results will stay in your research file at [insert institution] for at least 6 years or until after the study is completed, whichever is longer. At that time, either the research information not already in your medical record will be destroyed or your name and other identifying information will be removed from such study results. Research information in your medical record will be kept indefinitely.

11. Ending Your Participation

Being in this study is voluntary. You can choose to not be in this study or to leave this study at any time. If you choose not to take part in or leave this study, your regular medical care will not be affected in any way. Tell your doctor in writing if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing will be most helpful to you.

The study doctor or the study sponsor may stop the study at any time and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.

- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

If you decide to leave this study after taking the study treatment or are asked to leave by your doctor for medical reasons, you'll need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, [investigator's name(s)], or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at [telephone number].

You will get medical treatment if you're injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

13. Compensation or Payment

You will not be paid for your participation in this research study. You will not be compensated or reimbursed for any extra costs (travel, meals, etc.) from taking part in this study.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care for your allogeneic transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for tests that are only done for research on this study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. Ethical Review

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

16. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert names and contact details]

17. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in this study, or if you have any complaints about any aspect of the study, the way it is being conducted, or any questions about your rights as a research participant, you may contact:

[Insert appropriate contact details]

For questions about your rights while taking part in this study, call the [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at [telephone number].

18. OPTIONAL Blood Samples for Trial-Related and Future Research Studies

This section of the Consent Form is about collection of optional blood samples for trial-specific and future research studies from people who are taking part in the study.

You can choose to give blood samples for optional trial-specific and future research studies if you want to. You can still be a part of the main study even if you say "no" to giving optional blood samples for these studies. Please mark your choice at the end of this section.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide optional blood samples, here is what will happen:

- We'll take 24 mL (about 5 teaspoons) from your catheter or by a vein in your arm if you are an adult , or 12 mL (about 2.5 teaspoons) if you're a child (< 20kg). We'll collect this sample when you have your 1st check-up, before treatment starts.
    - This blood sample will be shipped on the day of collection to a qualified research laboratory that is partnering with the clinical trial team physicians for an important study related to this trial. This study wants to look at your telomeres, which are caps at the end of DNA strands to protect them. DNA is in your blood, so we can study telomeres using blood samples.
- At the same time, we will collect one additional 3 mL (about ⅔ teaspoon) blood sample.
    - This blood sample will be sent to the BMT CTN Biorepository for processing and storage for future genomic research studies. A repository is a place that protects, stores, and sends out samples for approved research studies. All research samples will be given a bar code that cannot be linked to you by future researchers testing your samples. A link to this code does exist. The link is stored at the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC). The staff at the Repository where your sample is being stored does not have a link to this code. Your research samples will continue to be stored at the BMT CTN Repository until they are used up for approved research.
    - These samples will be kept and may be used in research to learn more about immune recovery, GVHD, severe aplastic anemia, cancer, and other diseases. When the samples are given to investigators for research, no information about your name, address, phone number, or other information that will let the researchers know who you are will be provided.
    - DNA from your stored blood samples and your health information might be used in genome-wide association (GWA) studies for a future project either done or supported

by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

- If your coded samples are used in such a study, the researchers are required to add your test results and sample information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples. However, the results of genetic studies could, in theory, include identifying information about you.

  Your name and other information that could directly identify you (such as address or social security number) will not be placed into any scientific database. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is small, but may grow in the future. Researchers have a duty to protect your privacy and to keep your information confidential.

Benefits

The research that may be done with your blood samples is not designed specifically to help you. The benefits of research using blood samples include learning more about what causes GVHD, severe aplastic anemia, cancer, and other diseases, how to prevent them, and how to treat them.

Risks

There is a small risk of an infection or fainting from the blood draw.

A possible risk is the loss of confidentiality about your medical information. We will do our best to make sure that your personal information is kept private. The chance that this information will be given to someone else is very small.

Some general things to think about when letting us store your blood samples for research are:

- The choice to let us collect and/or store blood samples for future research is up to you. No matter what you decide to do, it will not affect your care.
- If you decide now that your blood samples can be collected and stored for research, you can change your mind at any time. Just contact your study doctor in writing and let him or her know that you do not want us to continue storing your blood samples. His/her mailing address is on the first page of this form. Then any unused blood samples that remain will no longer be stored for research. However, samples and information that have already been shared with researchers cannot be taken back or destroyed.
- In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the

researchers reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, you will not be told of the results and the results will not be put in your health records.

- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.
- Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Genetic Information Nondiscrimination Act

A new federal law (2009) called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research.

This means that they must not use your genetic information when making decisions about your insurance. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at [telephone number].

No matter what you decide to do, it will not affect your care.

You can change your mind at any time about allowing us to use your samples and health information for research. However, samples and information that have already been shared with researchers cannot be taken back or destroyed.

Statement of Consent for Optional Blood Samples for Trial-Related and Future Research Studies

The purpose of collecting, storing optional blood samples, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep. I understand that I do not have to allow the collection and storage of my blood samples for study-specific and future research studies. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that optional blood samples may be collected and that my blood samples and related information can be stored indefinitely by the BMT CTN Biorepository for research to learn about, prevent, or treat GVHD, severe aplastic anemia, cancer, or other health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

Telomere Research Study

- ❑ I do agree to give blood samples for a telomere research study.
- ❑ I do not agree to give blood samples for a telomere research study.

Future Genomic Research Studies

- ❑ I do agree to give blood samples for future genomic research.
- ❑ I do not agree to give blood samples for future genomic research.

_____ _____

Signature Date

Health Insurance Portability and Accountability Act 1 (HIPAA)[13] authorization to use and disclose individual health information for research purposes:

A. **Purpose**:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study, *Optimizing Cord Blood and Haploidentical Aplastic Anemia Transplantation*.

B. **Individual Health Information to be Used or Disclosed**:

My individual health information that may be used or disclosed for this research includes:

- Demographic information (for example: date of birth, sex, weight).
- Medical history (for example: diagnosis, complications with prior treatment).
- Findings from physical exams.
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results).

C. **Parties Who May Disclose My Individual Health Information**:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*].

D. **Parties Who May Receive or Use My Individual Health Information**:

The individual health information disclosed by parties listed in Item C and information I disclose during the course of the research may be received and used by the following parties:

- Principal Investigators and the researcher's staff:
  - Dr. Amy DeZern, Co-Principal Investigator
  - Dr. Michael Pulsipher, Co-Principal Investigator
- Study Sponsors:
  - National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH);
  - Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC), including the National Marrow Donor Program (NMDP), the Center for International Blood and Marrow Transplant Research (CIBMTR), and Emmes;

[3] HIPAA is the Health Insurance Portability and Accountability Act of 1906, a federal law related to privacy of health information.

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP);
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state, and local health departments.
- The Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study

E. **Right to Refuse to Sign this Authorization**:

I do not have to sign this Authorization. If I decide not to sign this Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting for abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

TITLE: BMT CTN 1502: Optimizing Haploidentical Aplastic Anemia Transplantation

Principal Investigator:

Name: Phone:

Address 1: Fax:

Address 2: Email:

For patients under 18, consent must be provided by the Legally Authorized Representative and Patient Assent is required (see **Assent Section** on the next page).

- I have had the chance to ask questions and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

_____ _____

Participant's Signature (if 14 years or older) Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Name of Counseling Physician/Staff	Date
Signature of Counseling Physician/Staff	Date
Name of Interpreter	Date
Signature of Interpreter	Date

Pediatric Patient Assent

Study Title: **Optimizing Haploidentical Aplastic Anemia Transplantation**

Protocol: **BMT CTN 1502**

- **Why am I here?**

We invite you to join this research study because you need a transplant to treat your severe aplastic anemia. We will replace your unhealthy blood cells with blood cells from one of your family members. The new cells will travel to your bones and start making healthy cells in your body.

For this study, we will ask you for information about your health (health information) and for extra blood samples.

- **Why are you doing this study?**

We're doing this study to learn how well patients with severe aplastic anemia do with transplants that use haploidentical bone marrow.

- **What will happen to me if I join the study?**

If you say you want to be in the study, we will:

- Before your transplant:
    - Give you drugs to help your body get ready for the transplant. The drugs might make you feel sick. Your doctor will watch your health closely.
    - We will collect extra blood (about 1 teaspoon) 4 times before your transplant and 1 time on the day of your transplant. We will use a small needle to collect the blood from a vein in your arm, unless you have a central line in which case the samples will be collected through that central line. We will try to collect the extra samples at the same time as you have other blood tests done.
- After your transplant:
    - We will collect extra blood (about 1 teaspoon) one week after your transplant.
    - We will also give you drugs to help your body adjust to the new cells. The drugs might make you feel sick. Your doctor will keep watching your health after your transplant.

You will be in the study for 1 year after your transplant. About 30 people will be in the study.

- **Will the blood draw hurt?**

When we collect your blood from a vein in your arm, it may feel like a pinch. It will hurt for a minute and the place where the needle went might be red and sore. You might get a little bruise from the needle, but it goes away in a few days.

- **What if I have questions?**

You can ask any questions that you have about the study. If you forget to ask a question and think of it later, you can call me:

[insert office number].

You can also ask your question the next time you see me.

You can call the study office at any time to ask questions about the study.

- **How will you use my health information and blood samples?**

Your health information and blood samples will be used for this study and for future research about transplant in patients with severe aplastic anemia.

- **How will you store my health information and blood samples**?

Your blood samples will be sent to a qualified research lab for an important study.

All research samples will be tied to a number. This number will not be linked to your name or other identifying information.

A. Will the study help me?

We don't know if this study will help you or not. It may help other people who need a transplant in the future.

B. Will I be paid to be in the study?

No, you will not be paid to be in the study. It will not cost you anything to be in the study.

C. Do I have to be in this study?

If you don't want to be in this study, you need to tell us and your parent or guardian.

Your doctor will not be angry or upset if you do not want to join. You will still need to have treatment for your disease.

You can say yes now and change your mind at any time.

Please talk this over with your parents before you decide if you want to be in the study. We will also ask your parents to give their permission for you to join this study.

TITLE: BMT CTN 1502: Optimizing Haploidentical Aplastic Anemia Transplantation

Writing your name on this page means that you agree to join this study and know what will happen to you.

- I've been told what I will be asked to do if I am in this study.
- I've been told that I don't have to be in this study. I may quit the study at any time, and no one will be mad at me.
- If I want to quit the study, all I have to do is tell the person in charge.
- I've had a chance to discuss the study and ask questions. My questions have been answered.
- I agree to be in the study and do what I am asked to do for as long as I am in the study.
- My parents and I will get a copy of this form after I sign it.

_____	_____	_____
Patient's Name (if less than 14 years)	Date	Age (years)
_____	_____	_____
Signature of Child	Date	Age (years)

I have explained the purposes, procedures, and risks involved in this research study in detail to:

_____

Print name(s) of Parents/Authorized Consenting Party

AND

_____

Print child's name

Who in my opinion: _____IS _____IS NOT capable of assenting to participate in this study.

_____ _____

Signature of Person Conducting Assent Date

Donor Informed Consent to Participate in Research

Optimizing Haploidentical Aplastic Anemia Transplantation

Your Name: _____

Study Title: Optimizing Haploidentical Aplastic Anemia Transplantation (CHAMP)

Protocol: BMT CTN #1502

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Principal Investigator: *[Insert local PI information]*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. You're being asked to join because you're a bone marrow donor for a family member who is going to receive a haploidentical (half-matched) transplant in the main study, BMT CTN 1502.

This consent form is about a research study to learn how patients' DNA changes after they get cells from a donor (transplant). We will compare your DNA to your family member's DNA

before and after their transplant. In order to do this study, we will need extra blood samples from you.

It's your choice to give blood samples. Even if you say 'no' to giving samples for this research study, your family member can still receive a transplant from you as part of the main study. If you agree to give blood samples, we will collect them at the same time you have routine blood tests done.

This Consent Form will tell you about the purpose of the samples for research, the possible risks and benefits, other options available to you, and your rights as a research participant.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.
- You will not directly benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you give blood samples for future research, you can change your mind at any time.
- If you decide to quit the study, it will not affect your care or the care of your family member at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to provide blood samples for future research. If you decide to join, please sign and date the end of the Consent Form.

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are giving staff support and money for this research study.

The BMT CTN will lead the research study and, along with the NIH, will make decisions about how to manage the study.

2. Study Purpose

We are collecting extra blood samples because we want to learn more about **telomere** length in donors and how it relates to outcomes (results) for transplant recipients, including engraftment and survival. **Telomeres** are caps at the end of DNA strands to protect them**.** DNA is in your blood, so we can study telomeres using blood samples.

3. Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a study participant or you want to leave the study, please contact:

[insert contact info]

Giving blood samples for research is voluntary. You can choose not to give samples or change your mind at any time.

If you choose not to take part or change your mind, it will not affect your donation process or the treatment of your family member in the main study in any way.

If you change your mind, any unused blood samples will be destroyed. However, samples and information that have already been shared with researchers cannot be taken back or destroyed.

Your study doctor and study staff will be available to answer any questions that you may have.

4. Study Treatments and Tests

If you agree to give blood samples, here is what will happen:

a.) We will collect an extra blood sample at the same time you have routine blood tests done.

For adults and children who weigh 44 pounds (20kg) or more:

- We will collect **4 extra blood sample**s at one time prior to your donation to look at your telomeres. The amount of blood collected from you will be about 24 mL (about 5 teaspoons).

For children who weigh less than 44 pounds (20 kg):

- We will collect **2 extra blood sample**s at one time prior to your donation to look at your telomeres. The amount of blood collected from you will be 12 mL (about 2.5 teaspoons).

b.) The blood samples will be sent to the Johns Hopkins laboratory for processing and storage. All samples will be given a unique bar code that cannot be linked to you by researchers testing your samples.

5. Risks and Discomforts

There are no major risks to having your blood drawn. It can be uncomfortable to have your blood taken and it can sometimes leave a bruise. You might faint, but this is unlikely to happen. Only trained people will take your blood.

Information about the bone marrow donation process for this study can be found in a separate consent form. The transplant doctor or study coordinator will give you a copy of the donation consent form.

6. Possible Benefits

You will not directly benefit from taking part in this study. The information from this study will help doctors learn more about how well transplant recipients do with a haploidentical (half-matched) donor.

This information could help other people with blood cancers and disorders who may need a transplant in the future.

7. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential.

[Name of Transplant Center] and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- U.S. government agencies that are responsible for overseeing research such as The Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state, and local health departments
- The Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study
- Blood and Marrow Transplant Clinical Trials Network Data and Coordinating Center (BMT CTN DCC), including:
    - The Center for International Blood and Marrow Transplant Research (CIBMTR)
    - The National Marrow Donor Program (NMDP)
    - Emmes, who is coordinating the studies of the BMT CTN
- Study investigators:
    - Dr. Amy DeZern, Co-Principal Investigator
    - Dr. Michael Pulsipher, Co-Principal Investigator

Individuals authorized by the organizations above will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to these inspections. You also consent to allow authorized individuals to copy parts of your records, if required by these organizations.

We may give out your personal information if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

For questions about access to your medical records, please contact [name] at [number].

8. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the blood draw. The study sponsor may decide to end the study at any time. If we ask you to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You become unable to donate bone marrow to your family member.
- The study is stopped for any reason.

9. Physical Injury as a Result of Participation

It's important that you tell your doctor, [investigator's name(s)], or study staff if you feel that you have been injured because you provided blood samples for research. You can tell the doctor in person or call him/her at [telephone number].

You will get all available medical treatment if you are injured as a result of providing blood samples for future research.

You, your health plan, or your family member's health plan will be charged for this treatment for injury. The study will not pay for medical treatment.

In case of injury resulting from providing blood samples for this study, you do not lose any of your legal rights to seek payment by signing this form.

10. Payment and Study Costs

You will not be paid for your participation in the research study or for providing blood samples for research.

You will not be compensated or reimbursed for any extra costs (for example, travel and meals) from taking part in this study.

The visits at which these samples will be collected are standard for bone marrow donors and will be billed to your family member's insurance company.

Your family member's insurance will not be charged for the collection of these optional samples or for the research tests done with these samples. The costs of shipping and storing your blood samples will be paid by the BMT CTN.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number.

11. For More Study Information

If you need more information about providing blood samples for research, or if you have problems while you are participating in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:

[Insert name and contact details].

12. Contact Someone About Your Rights

If you wish to speak to someone not directly involved in the study, if you have any complaints about the study, or would like more information about your rights as a research participant, you may contact:

[Insert appropriate contact details].

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

For more information about your rights when providing blood samples for research, call the [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at [telephone number].

Health Insurance Portability and Accountability Act (HIPAA)[4] Authorization to use and disclose research purposes:

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study, *Optimizing Cord Blood and Haploidentical Aplastic Anemia Transplantation*.

B. Individual Health Information to be Used or Disclosed:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history
- Findings from physical exams
- Laboratory test results obtained at the time of work up

C. Parties Who May Disclose My Individual Health Information:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

D. Parties Who May Receive or Use My Individual Health Information:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigators and the researcher's staff:
  - Dr. Amy DeZern, Co-Principal Investigator
  - Dr. Michael Pulsipher, Co-Principal Investigator
- Study Sponsors:
  - National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
  - Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center

[4] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state, and local health departments.
- The Data and Safety Monitoring Board (DSMB), not part of [Institution]
- Institutional Review Boards (IRBs) responsible for this study

E. Right to Refuse to Sign this Authorization:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting for abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

I. This authorization does not have an expiration date.

TITLE: BMT CTN 1502: Optimizing and Haploidentical Aplastic Anemia Transplantation

Principal Investigator: Name: Phone:

Address 1: Fax:

Address 2: Email:

For donors under 18, consent must be provided by the Legally Authorized Representative and Donor Assent is required (see **Assent Section** on the next page).

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I will not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my family member's current care or prevent my family member from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____ _____

Participant Name Date

_____ _____

Participant's Signature (if 18 years or older) Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____	_____
Name of Counseling Physician/Staff	Date
_____	_____
Signature of Counseling Physician/Staff	Date
_____	_____
Name of Interpreter	Date
_____	_____
Signature of Interpreter	Date

Pediatric Donor Assent to Participate in Research

Study Title: **Optimizing Haploidentical Aplastic Anemia Transplantation**

Protocol: **BMT CTN 1502**

D. Why am I here?

If you give us your permission, we would like to have an extra sample of your blood. We would collect the extra sample at the same time you have other blood tests done.

E. Why are you doing this study?

We are collecting blood samples from donors, like you, to learn more about how the ends of DNA in donors affects how patients do after their transplants. DNA is in your cells and carries all the information about how your body works. We will keep all of the extra samples private and store them in a place called a biorepository. Your name will not be on the samples.

F. What will happen to me if I join the study?

If you say you want to be in the study, we will ask you for:

- **1 extra blood sample:** We'll collect about 2.5 teaspoons of blood (if you weigh less than 20kg) or 5 teaspoons of blood (if you weigh 20kg or more) 1 time.

We will use a small needle to collect the blood from a vein in your arm.

G. Will the blood draw hurt?

When we collect your blood from a vein in your arm, it may feel like a pinch. It will hurt for a minute and the place where the needle went might be red and sore. You might get a little bruise from the needle but it goes away in a few days. We will collect the extra samples at the same time as you have other blood tests done.

H. What if I have questions?

You can ask any questions that you have about this study. If you forget to ask a question and think of it later, you can call me at: [insert office number].

You can also ask your question the next time you see me. You can call the study office at any time to ask questions about the study.

I. How will you use my health information and blood samples?

Your health information and blood samples will be used for a study about transplant in patients with severe aplastic anemia.

J. How will you store my health information and blood samples?

Your blood samples will be kept at a laboratory at Johns Hopkins

All research samples will be tied to a number. This number will not be linked to your name or other identifying information.

K. Will the study help me?

This study will not help you or your family member, but it may help other people who need a transplant in the future.

L. Will I be paid to be in the study?

No, you will not be paid to be in the study. It will not cost you anything to be in the study.

M. Do I have to be in this study?

If you don't want to be in this study, you need to tell us and your parent or guardian.

Your doctor will not be angry or upset if you do not want to join. You can still give bone marrow to your family member who needs it. They will still get the exact same care.

You can say yes now and change your mind at any time.

Please talk this over with your parents before you decide if you want to give an extra blood sample for research. We will also ask your parents to give their permission for you to give an extra sample for research.

TITLE: BMT CTN 1502: Optimizing Haploidentical Aplastic Anemia Transplantation

Principal Investigator:

Name: Phone:

Address 1: Fax:

Address 2: Email:

Writing your name on this page means that you agree to give an extra blood sample and know what will happen.

If you want to quit the study, all you have to do is tell the person in charge.

You and your parent or guardian will get a copy of this form after you sign it.

_____

Signature of Child Date

_____

Signature of Person Conducting Assent Date

APPENDIX C:

LABORATORY PROCEDURES

APPENDIX C:

PROTOCOL-BASED LABORATORY PROCEDURES

There is one protocol-required correlative laboratory study associated with the BMT CTN 1502 trial. Study patients and consenting haplo-donors will also be provided the opportunity to participate in an optional correlative study. And finally, an optional opportunity will be offered to study patients to provide a single sample to be stored and used for future research.

1) REQUIRED: Thymoglobulin® Pharmacokinetics (PK)

The objective of the first lab correlate to the clinical trial will be to collect PK samples for Thymoglobulin® and to determine pre- and post-HSCT exposure levels (area under the curve, AUC) in all patients. These exposure levels will then be correlated with clinically relevant metrics, including engraftment, rejection, GVHD, immune reconstitution, and survival.

The PK assessment of Thymoglobulin® will be performed at UMC Utrecht in the laboratory of Jaap Jan Boelens and Rick Admiraal. Thymoglobulin® concentrations will be determined from plasma samples.

5 mL of blood for PK samples will be collected in an EDTA (lavender top) tube at 6 time points:

1.) Upon completion of first dose infusion (within 60 minutes)
With this draw, the start and end of the first Thymoglobulin® infusion (d-m-y hh:mm) and the timing of the sample (d-m-y hh:mm) must be documented

2.) Prior to infusion of second dose (within 60 minutes)
With this draw, the timing of the sample (d-m-y hh:mm) must be documented

3.) Upon completion of second dose infusion (within 60 minutes)
With this draw, the start and end of the second Thymoglobulin® infusion (d-m-y hh:mm) and the timing of the sample (d-m-y hh:mm) must be documented

4.) Upon completion of third dose infusion (within 60 minutes)
With this draw, the start and end of the second Thymoglobulin infusion (d-m-y hh:mm) and the timing of the sample (d-m-y hh:mm) must be documented

5.) On day 0 (any time prior to stem cell infusion)
CBC including absolute lymphocyte count should be collected on Day 0 (if possible) along with the PK sample and results documented in AdvantageEDC; the timing of the sample (d-m-y hh:mm) should also be documented

6.) On day 7 (no time restrictions)
With this draw, the timing of the sample (d-m-y hh:mm) must be documented

All blood samples should be placed on ice after collection and promptly taken for processing into

plasma within 6 hours of collection. Samples should be maintained cold while handling and final samples should be frozen. Please see the protocol-specific Research Sample Information Guide for detailed processing, aliquot labeling, and frozen sample shipping procedures.

Frozen samples will be batch-shipped on a biannual basis to the BMT CTN Biorepository managed by the NMDP. Once the trial is complete and all PK samples obtained, they will then be transported together to UMC Utrecht for laboratory analysis.

2) OPTIONAL: Telomere Length Analysis

The objective of the second lab correlate to the clinical trial will be to collect whole blood samples from consenting patients and each available consenting donor to measure leukocyte telomere length. The telomere lengths will then be correlated with clinically relevant metrics, including disease phenotype, engraftment, and survival for research purposes.

The telomere length will be measured by a CLIA-certified flow cytometry and FISH assay (Baerlocher Nature Protocols 2006) that is operated within the Johns Hopkins Pathology Laboratories (Armanios). Subpopulations of leukocytes will include granulocytes and lymphocytes.

The blood required from the patient (pre-HSCT conditioning) and donor (pre-donation) at a single time point will include:

Adults: 4 EDTA purple tops (6cc mL, 24cc total)
This will ensure yields for leukopenic patients especially if it will be shipped on Fridays.

Children less than 20kg: 2 EDTA purple tops (6cc mL, 12cc total)

Please see the protocol-specific Research Sample Information Guide for detailed sample labeling and same-day sample shipping procedures.

The blood tubes will be shipped on the day of collection to the Johns Hopkins project laboratory by Priority Overnight FedEx courier. No additional information will be provided to the patients or their treating physicians during the trial. Clinical correlations will be made in a retrospective fashion.

3) OPTIONAL: Research Sample to Support Future Genomic Studies

The objective of the optional research sample banking is to collect 3 mL of whole blood from all consenting patients pre-conditioning to support future genomic research. Blood samples will be collected and processed at the clinical sites into three 1 mL cryovial aliquots and frozen. Please see the protocol-specific Research Sample Information Guide for detailed processing, aliquot labeling, and frozen sample shipping procedures. Frozen whole blood samples will be batch-shipped on a biannual basis, along with the Thymoglobulin® PK samples, to the BMT CTN Biorepository managed by the NMDP.

Required - Thymoglobulin® Pharmacokinetics Correlative Study Research Samples						
Subjects	**Sample Type**	**Sample Collection Time Points**	**Stored Material**	**Sample Processing & Storage Site**	**Aliquots Stored**	**Purpose**
Patients	Peripheral Blood **5 mL EDTA**	• Completion of first dose infusion • Prior to infusion of second dose • Completion of second dose infusion • Completion of third dose infusion • On Day 0 (prior to stem cell infusion) • On Day +7 post-stem cell infusion	EDTA Plasma	Samples processed on the day of collection by the clinical sites and frozen for future batch-shipment to the BMT CTN Biorepository.	Four 0.5 mL EDTA plasma aliquots; stored at -80º C	**Thymoglobulin® Pharmacokinetics (PK)**

Optional - Telomere Length Analysis Correlative Study Research Samples					
Subjects	**Sample Type**	**Sample Collection Time Point**	**Sample Collection Summary**	**Shipping Specifications**	**Shipping and Testing Location**
Patients and Haplo-Donors	Peripheral Blood EDTA **24 mL (adults) 12 mL (children)**	**Patient**: pre-HSCT conditioning **Haplo-donor:** pre-HSC donation	Collect the peripheral blood sample and place into four (two for children) 6 mL Vacutainer tubes, containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant.	Blood sample tubes will be shipped at ambient temperature, on the day of collection, to JHMI laboratory by priority overnight FedEx® delivery.	**Telomere Length Analysis** Johns Hopkins Laboratory

Optional - Future Research Samples						
Subjects	**Sample Type**	**Sample Collection Time Point**	**Stored Material**	**Sample Processing & Storage Site**	**Aliquots Stored**	**Purpose**
Patients	Peripheral Blood **3 mL EDTA**	pre-HSCT conditioning	Whole Blood EDTA	Samples processed on the day of collection by the clinical sites and frozen for future batch-shipment to the BMT CTN Biorepository.	Three 1.0 mL whole blood aliquots; stored at -80º C	Undefined Future Research **(Genomic DNA Isolation)**

APPENDIX D:
WEIGHT CALCULATIONS

APPENDIX D:

WEIGHT CALCULATIONS

All chemotherapy doses will be calculated using weights determined as described below.

Dosing should be based on total body weight (TBW), if < 125% of IBW, and adjusted ideal body weight (AIBW) in all patients ≥ 125% of IBW.

Adjusted Ideal Body Weight (AIBW) Formula:
AIBW = IBW + [(0.25) x (actual body weight – IBW)]

Ideal Body Weight (IBW) for Patients greater than 17 Years of Age and older (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 patients 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 patients less than 152.4 cm feet, subtract 2.3 kg/2.54 cm

Ideal Body Weight (IBW) for Patients 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:
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:

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 E:

CAMITTA CRITERIA FOR SAA

APPENDIX E:

CAMITTA 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)
Bone Marrow Cellularity	< 25%	< 25%	< 25%
Absolute Neutrophil Count		< 500 / ml	< 200 / ml
Platelet Count		< 20,000 / ml	
Reticulocyte Count		< 1.0% corrected **or** < 60,000 / ml	

APPENDIX F:

ABBREVIATIONS

APPENDIX F:

ABBREVIATIONS

AdvantageEDC™ – Proprietary electronic data capture system
AE – Adverse Event
AIBW: Adjusted Ideal Body weight
aGVHD – Acute Graft Versus Host Disease
ALT – Alanine Aminotransferase
ANC – Absolute Neutrophil Count
AST – Aspartate Aminotransferase
ATG – Antithymocyte globulin
AUC – Area under the curve
BK – BK Virus
BM – Bone Marrow
BMT – Bone Marrow Transplant
BMT CTN – Blood and Marrow Transplant Clinical Trials Network
CBC – Complete Blood Count
CD4 – Cluster of Differentiation 4
CD34 – Cluster of Differentiation 34
CD19 – Cluster of Differentiation 19
CD56 – Cluster of Differentiation 56
cGVHD – Chronic Graft Versus Host Disease
cGY – Centigray
CIBMTR – Center for International Blood and Marrow Transplant Research
CMV – Cytomegalovirus
CNI – Calcineurin inhibitor
CNS – Central Nervous System
CSA – Cyclosporin A
CTCAE – Common Terminology Criteria for Adverse Effects
CYP3A4 – Cytochrome P450 3A4
DEB – Diepoxybutane
DLCO – Diffusing Capacity of the Lung for Carbon Monoxide
DMSO – Dimethyl Sulfoxide
DNA – Deoxyribonucleic Acid
EBV – Epstein Barr Virus
FEV1 – Forced Expiratory Volume 1
FVC – Forced Vital Capacity
G-CSF – Granulocyte Colony Stimulating Factor
GM-CSF – Granulocyte Macrophage Colony Stimulating Factor
GVHD – Graft Versus Host Disease
HCT-comorbidity – Hematopoietic Cell Transplant Comorbidity
HIV – Human Immunodeficiency Virus
HLA – Human Lymphocyte Antigen
HSCT – Hematopoietic Stem Cell Transplantation
HSV – Herpes Simplex Virus

HVG – Host Versus Graft
IBW – Ideal Body Weight
IST – Immunosuppressive Therapy
IV – Intravenous
IVIG – Intravenous Immunoglobulin
MDS – Myelodysplastic Syndrome
MMF – Mycophenolate Mofetil
MMRD – Mismatched related Donor
MMURD – Mismatched Unrelated Donor
MOP – Manual of Procedures
MPA – Mycophenolic Acid
MSD – Matched Sibling Donor
MUD – Matched Unrelated Donor
NAT – Nucleic Acid Testing
NCI – National Cancer Institute
OS – Overall Survival
PBSC – Peripheral Blood Stem Cells
PCR – Polymerase Chain Reaction
PFT – Pulmonary Function Testing
PJP – Pneumocystis Jiroveci Pneumonia
PK – Pharmacokinetics
PO – Per Os (by mouth)
PTLD – Post-Transplant Lymphoproliferative Disease
SAA – Severe Aplastic Anemia
SIADH – Syndrome of Inappropriate Antidiuretic Hormone
SQ – Subcutaneous
TBI – Total Body Irradiation
VZV – Varicella Zoster Virus
WBC – White Blood Cell

APPENDIX G:

BONE MARROW HARVEST GUIDELINES

APPENDIX G:

BONE MARROW HARVEST GUIDELINES [39]

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 bone marrow 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-bone marrow 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^{o}. 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 x 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 is 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 total nucleated cells: A x B = TNC. (Example: if marrow count is 27 and peripheral white cell count is 6, then the marrow mononuclear cell counts would be 21 = B)
3. TNC should then be divided by ideal body weight to determine TNC/kg achieved (target 4 x 10^8 nucleated cells/kg recipient ideal body weight).

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 bone marrow)

APPENDIX H:

GUIDANCE FOR MIXED CHIMERISM

APPENDIX H:

GUIDANCE FOR MIXED CHIMERISM

Chimerism measurements should be assessed as per protocol requirements (Table 4.2.4). Primary and secondary graft failure are also defined (Section 3.2.3 and 4.2.4.2). There will be patients who meet criteria for mixed chimerism post-transplant who require special attention.

Any donor chimerism below 99% 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 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 avoid, and if it occurs, treat mixed chimerism:

1. Optimize all possible cell counts in the donor harvest to achieve at least a goal of 3×10^8 mononuclear cells/kg recipient weight.
2. Ensure optimal compliance with all post-transplant immunosuppression.
    a. Mycophenolate mofetil should be given intravenously in patients in whom the oral preparation is not well tolerated
    b. Monitor levels of tacrolimus (as often as daily) to ensure therapeutic troughs of 10-15ng/mL.
3. If post-Day 28, Day 56, or Day 100 chimerism is low, increase frequency of monitoring per protocol (table 4.2.4), with monthly chimerisms until stable or resolved.
4. Do not stop immunosuppression. Consider increasing levels to upper end of goal range for tacrolimus or CSP.
5. Do not give DLI for chimerism. For patients with poor graft function and established donor chimerism, CD34+ selected cell boosts can be considered.
6. Rule out additional immune phenomenon such as large granular lymphocytosis.
7. Rule out contribution of infections or their treatments (e.g. valganciclovir for CMV, other treatments for EBV, HHV6, etc.).
8. Continue close clinical follow up.
9. Notify protocol chairs or medical monitor with questions or concerns.

APPENDIX I:

REFERENCES

APPENDIX I:

REFERENCES

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