BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

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BMT CTN Protocol 1503
Version 5.0

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PROTOCOL SYNOPSIS – BMT CTN 1503
v5.0
A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Co-Principal Investigators: Lakshmanan Krishnamurti, MD, Mark C. Walters, MD

Study Design: This study is designed as a phase II, multi-center trial of hematopoietic cell transplantation (HCT) versus standard of care in adolescents and young adults with severe sickle cell disease (SCD). Eligible participants are biologically assigned to HCT or standard of care based on the availability of HLA-matched related or unrelated donor after confirmation of clinical eligibility. Insurance coverage and donor availability are not known at referral or consultation.

Primary Objective: The primary objective is to compare the overall survival (OS) at 2 years after biological assignment between those assigned to the donor arm and to the no donor arm. Those assigned to the donor arm are expected to undergo HCT and those on the no donor arm, to receive standard of care supportive therapy.

Secondary Objectives: Secondary objectives will compare changes in SCD related events (pulmonary hypertension, cerebrovascular events, renal function, avascular necrosis, leg ulcer) and functional outcomes [6-minute walk distance (6MWD), health-related quality of life (HRQoL), cardiac function, pulmonary function, and mean pain intensity as assessed by a multidimensional electronic pain diary from baseline to 2-years after assignment to treatment arms. Additionally, some outcomes will also be measured at 1 year. Baseline, 1- and 2-year assessments will be done at the same sites to minimize variability. Secondary objectives for the donor arm include neutrophil recovery, platelet recovery, graft failure, chimerism, acute and chronic graft-versus-host disease, idiopathic pneumonia syndrome, veno-occlusive disease, and central nervous system toxicity.

Eligibility Criteria: Eligible patients are ≥ 15 and < 41years of age with severe sickle cell disease [any clinically significant sickle genotype, for example, Hemoglobin SS (Hb SS), Hemoglobin SC (Hb SC), Hemoglobin S Beta thalassemia (Hb Sβ), or Hemoglobin S-OArab genotype] with at least one of the following manifestations:

a. Clinically significant neurologic event (stroke) or neurological deficit lasting > 24 hours;
b. History of two or more episodes of acute chest syndrome (ACS) in the 2-year period preceding enrollment or referral despite adequate supportive care measures (i.e. asthma therapy);
c. An average of three or more pain crises per year in the 2-year period preceding enrollment or referral (required intravenous pain management in the outpatient or inpatient hospital setting);
d. Administration of regular red blood cell (RBC) transfusion therapy, defined as 8 or more transfusion events per year (in the 12 months before enrollment) to prevent vaso-occlusive clinical complications (i.e. pain, stroke, or acute chest syndrome);
e. An echocardiographic finding of tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec.
f. Ongoing high impact[1] chronic pain on a majority of days per month for ≥ 6 months as defined as ONE or more of the following: Chronic pain without contributory SCD complications[2], OR Mixed pain type in which chronic pain is occurring at site(s) (arms, back, chest, or abdominal pain) unrelated to any sites associated with Contributory SCD complications[2] (e.g. leg ulcers and/or avascular necrosis).

Adequate physical function as defined by all of the following**:**

a. Karnofsky/Lansky performance score ≥ to 60;
b. Cardiac function: Left ventricular ejection fraction (LVEF) > 40%; or LV shortening fraction > 26% by cardiac echocardiogram or by MUGA scan;
c. Pulmonary function: Pulse oximetry with a baseline O2 saturation of ≥ 85% **and** DLCO > 40% (corrected for hemoglobin);
d. Renal function: Serum creatinine ≤ 1.5x the upper limit of normal for age as per local laboratory **and** one of the following: creatinine clearance > 70 mL/min calculated using the CockcroftGault calculator, creatinine clearance >

[1]High impact chronic pain is identified as those reporting "severe interference" with life activities OR "usually or always" experiencing a limitation of their life or work activities including household chores. (See guidelines for identifying HICP in the BMT CTN 1503 Manual of Procedures)
[2]Contributory SCD complications are defined as clinical signs (e.g. presence of leg ulcers) or clinical assessments (e.g. imaging confirmation of splenic infarct or avascular necrosis). Chronic pain attributed solely to contributory SCD complications is excluded.

70 mL/min by 24 hour urine (preferred), **or** GFR > 70 mL/min/1.73 m2 by radionuclide GFR;

e. Hepatic function: ALT and AST < 5 times upper limit of normal as per local laboratory; serum conjugated (direct) bilirubin ≤ 2x upper limit of normal for age as per local laboratory Participants are not excluded if the serum conjugated (direct) bilirubin is >2x the upper limit of normal for age as per local laboratory **and**: There is evidence of a hyperhemolytic reaction after a recent RBC transfusion, **OR** there is evidence of moderate direct hyperbilirubinemia defined as direct serum bilirubin < 5 times ULN and not caused by underlying hepatic disease.

Additional inclusion required for donor arm participants to proceed with transplant:

a. Liver MRI (≤ 90 days prior to initiation of transplant conditioning) to document hepatic iron content is required for participants who are currently receiving ≥8 packed red blood cell transfusions for ≥1 year or have received ≥20 packed red blood cell transfusions (cumulative). Participants who have hepatic iron content ≥7 mg Fe/ g liver dry weight by liver MRI must have a liver biopsy and histological examination/documentation of the absence of cirrhosis, bridging fibrosis[1], and active hepatitis (≤ 90 days prior to initiation of transplant conditioning).

b. Lack of clinical or radiologic evidence of a recent neurologic event (such as stroke or transient ischemic attack) by Cerebral MRI/MRA within 30 days prior to initiating transplant conditioning. Subjects with clinical or radiologic evidence of a recent neurologic event will be deferred for ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation

c. Documentation of participant's willingness to use approved contraception method until discontinuation of all immunosuppressive medications is to be documented in the medical record corresponding with the consent conference.

Exclusion Criteria:

1. HLA typing with donor search prior to referral (consultation with HCT physician).

[1]The absence of bridging fibrosis will be determined using the histological grading and staging scale as described by Ishak and colleagues as described in the Manual of Operating Procedures.

a. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time, and also did not have an unrelated donor search, the patient will be considered eligible.
b. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
c. If a subject has had HLA typing with no related donor search and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
d. Subjects with a known HLA-identical sibling or HLA-matched unrelated donor are excluded

2. Uncontrolled bacterial, viral or fungal infection;
3. Seropositivity for HIV;
4. Previous HCT or solid organ transplant;
5. Participation in a clinical trial in which the patient receives an investigational drug or device must be discontinued prior to date of enrollment;
6. A history of substance abuse as defined by version IV of the Diagnostic & Statistical Manual of Mental Disorders (DSM IV);[1]
7. Demonstrated lack of compliance with prior medical care as determined by referring physician;
8. Pregnant or breast feeding females;
9. Inability to receive HCT due to alloimmunization, defined as the inability to receive packed red blood cell (pRBC) transfusion therapy;

Treatment Description: **Donor arm:** All donor arm patients receiving an unrelated donor HCT will receive busulfan, fludarabine, and r-ATG as their preparative regimen using a bone marrow graft. For donor arm

[1]American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. (4th ed.). Washington, DC American Psychiatric Association.

patients receiving a related donor HCT, there are 3 acceptable preparative regimens for this study:

a. Regimen A: Busulfan/Fludarabine/r-ATG using a bone marrow graft (preferred regimen)
b. Regimen B: Alemtuzumab/TBI 300 cGy using a peripheral blood graft
c. Regimen C: Alemtuzumab/Fludarabine/Melphalan using a bone marrow graft

The preparative regimen to be used for HLA-identical sibling transplants must be declared to the DCC by the site and used for all HLA-identical sibling transplants at that site.

GVHD prophylaxis

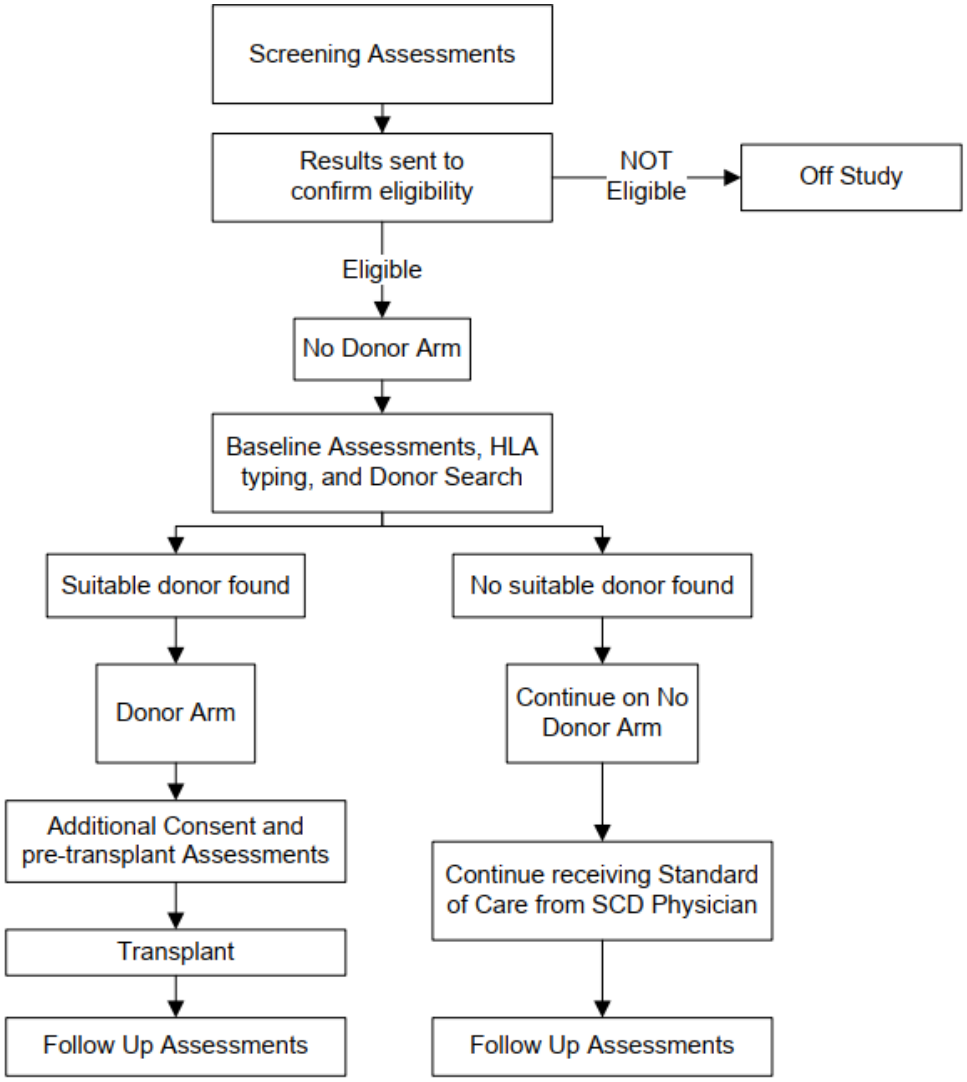
a. GVHD prophylaxis for patients receiving an unrelated donor transplant or Conditioning Regimen A: Tacrolimus commences on day -3 and extends through day +180 after transplantation, with methotrexate (MTX) administered intravenously on days +1 (15mg/m^2), +3 (10mg/m^2), +6 (10mg/m^2) and +11 (10mg/m^2). Patients unable to tolerate tacrolimus may receive cyclosporine.
b. GVHD prophylaxis for Conditioning Regimen B: Sirolimus commences on day -1 and extends through day +180 after transplantation or until donor CD3+ chimerism >50%, whichever is later
c. GVHD prophylaxis for Conditioning Regimen C: Tacrolimus commences on day -3 and extends through day +180 after transplantation, with methotrexate (MTX) 7.5 mg/m^2 administered intravenously on days +1, +3, and +6. Patients unable to tolerate tacrolimus may receive cyclosporine.

No-donor arm: Will continue with standard of care per their SCD physician.

Primary Endpoint: The primary endpoint is a comparison of the difference in the observed proportion of patients surviving at 2 years post biological assignment between the two treatment arms. Biologic assignment will occur ≤ 180 days after eligibility is confirmed by enrollment or the eligibility review committee (ERC). Participants will remain in their assigned treatment arm for analysis of all endpoints (intent-to-treat [ITT] principle).

Secondary Endpoints:	Comparison of SCD-related events and functional assessments by administering the 6MWD test, HRQoL and a 28-day e-pain diary to capture mean pain intensity. The secondary endpoints will examine changes between baseline, 1- year, and 2-years between participants on the donor and no donor arms. All baseline, 1-, and 2-year tests will be conducted at the same institution (to minimize variability).
Accrual Objective:	The sample size for the donor arm is fixed at 60 participants. Based on donor availability for ~30% of participants the sample size for the no donor arm is anticipated to be 140.
Accrual Period:	3 years.
Study Duration:	Participants will be followed for 2 years from time of biological assignment. Overall survival outcomes will continue to be measured between years 3 and 10.
Interim Analysis:	There will be no interim analyses for efficacy.
Stopping Guidelines:	Patients on the donor arm will be monitored for mortality at day 100 and 1-year post transplant and graft rejection at day 100 post transplant. The stopping rules for unacceptable day 100 mortality considers all patients together and for 1-year mortality, separately for HLA-matched related and unrelated donor transplants. For day 100 graft rejection, patients will be considered separately for HLA-matched related and unrelated donor transplants.

Study Design



Treatment Schema – Donor Arm

Unrelated Donor Transplant Conditioning Regimen,
and HLA-identical Sibling Transplant Conditioning Regimen A

Days	Treatment
-8	IV busulfan 3.2 mg/kg
-7	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2
-6	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, r-ATG 0.5 mg/kg
-5	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, r-ATG 1.0 mg/kg
-4	IV fludarabine 35 mg/m^2, r-ATG 1.5 mg/kg
-3	IV fludarabine 35 mg/m^2, r-ATG 1.5 mg/kg
-2	r ATG 1.5 mg/kg
-1	Rest day
0	Infusion of bone marrow

GVHD Prophylaxis for the Unrelated Donor Transplant Conditioning Regimen
and HLA-identical Sibling Transplant Conditioning Regimen A

Days	Prophylactic Agent
-3 through +180	Tacrolimus, begin taper +180 per institutional guidelines
0	Infusion of bone marrow
+1	IV methotrexate 15 mg/m^2
+3	IV methotrexate 10 mg/m^2
+6	IV methotrexate 10 mg/m^2
+11	IV methotrexate 10mg/m^2

HLA-identical Sibling Transplant Conditioning Regimen B

Days	Treatment
-7	IV Alemtuzumab: 0.03 mg/kg
-6	IV Alemtuzumab: 0.1 mg/kg
-5	IV Alemtuzumab: 0.3 mg/kg
-4	IV Alemtuzumab: 0.3 mg/kg
-3	IV Alemtuzumab: 0.3 mg/kg
-2	TBI 300 cGy with testicular shielding
-1	Rest day

0	Infusion of mobilized PBSC

GVHD Prophylaxis for Conditioning Regimen B

Days	Prophylactic Agent
-1 through +180	Sirolimus, begin taper +180 per institutional guidelines if donor CD3+ >50%

HLA-identical Sibling Transplant Conditioning Regimen C

Days	Treatment
-22	IV Alemtuzumab: 3 mg test dose
-21	IV Alemtuzumab: 10 mg
-20	IV Alemtuzumab: 15 mg
-19	IV Alemtuzumab: 20 mg
-8	IV Fludarabine 30 mg/m^2
-7	IV Fludarabine 30 mg/m^2
-6	IV Fludarabine 30 mg/m^2
-5	IV Fludarabine 30 mg/m^2
-4	IV Fludarabine 30 mg/m^2
-3	IV Melphalan 140 mg/m^2
-2	Rest Day
-1	Rest day
0	Infusion of bone marrow

GVHD Prophylaxis for Conditioning Regimen C

Days	Prophylactic Agent
-3 through +180	Tacrolimus, begin taper +180 per institutional guidelines
0	Infusion of bone marrow
+1	IV methotrexate 7.5 mg/m^2
+3	IV methotrexate 7.5 mg/m^2
+6	IV methotrexate 7.5 mg/m^2

ABBREVIATIONS

ACA	Affordable Care Act
ACS	Acute Chest Syndrome
AE	Adverse Event
AjBW	Adjusted Body Weight
ANC	Absolute Neutrophil Count
ATG	Anti-thymocyte Globulin
AUC	Area Under Curve
BMT	Bone Marrow Transplant
BU	Busulfan
CBC	Complete Blood Count
CCC	Clinical Coordination Center
CIBMTR	Center for International Blood and Marrow Transplant Research
CMS	Center for Medicare and Medicaid Services
CMV	Cytomegalovirus
CNS	Central Nervous System
CR1	Complete Remission 1
Css	Concentration at Steady State
CTCAE	Common Terminology for Adverse Events
CTN	Clinical Trials Network
CY	Cyclophosphamide
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Committee
EBV	Epstein-Barr Virus
EDC	Electronic Data Capture
EFS	Event Free Survival
ERC	Eligibility Review Committee
FEV1	Forced Vital Capacity 1 second
FLU	Fludarabine
FVC	Forced Vital Capacity
GEE	Generalized Estimating Equation
GVHD	Graft-versus-Host Disease
HbSC	Hemoglobin SC
HbSS	Hemoglobin SS
HbSβ	S Beta thalassemia (Sβ) genotype
HCT	Hematopoietic Cell Transplantation
HLA	Human Leukocyte Antigen
HRQoL	Health-Related Quality of Life
HU	Hydroxyurea
IBW	Ideal Body Weight
ICU	Intensive Care Unit
ITT	Intent to Treat
IPS	Idiopathic Pneumonia Syndrome
IV	Intravenous
MOP	Manual of Procedures
MSH	Multicenter Study of Hydroxyurea
6MWD	6 Minute Walk Distance
NHLBI	National Heart Lung & Blood Institute
NIH	National Institutes of Health
NMA	Non-myeloablative
NMDP	National Marrow Donor Program
OS	Overall Survival
PCR	Polymerase Chain Reaction
PFT	Pulmonary Function Test
PI	Principal Investigator
PRES	Posterior Reversible Encephalopathy Syndrome
RCT	Randomized Clinical Trial
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SCD-EOSI	Sickle Cell Disease related event of special interest
SPRT	Sequential Probability Ratio Test
STRIDE	Sickle Cell Transplantation to Prevent Disease Exacerbation in Young Adults
TBI	Total Body Irradiation
TLC	Total Lung Capacity
TRJV	Tricuspid Regurgitant Jet Velocity
TRM	Transplant Related Mortality
UCB	Umbilical Cord Blood
URD	Unrelated Donor
VOD	Veno-occlusive Disease

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Introduction

Sickle cell disease (SCD) is a hereditary anemia that affects approximately 100,000 Americans and millions of individuals worldwide. It is associated with early mortality and a diminished quality of life, with intermittent episodes of pain that are accompanied by progressive damage to vital organs, such as the lung, brain, spleen and kidney. Supportive health care measures instituted during childhood, which include newborn screening and pneumococcal prophylaxis, the administration of HU and regular RBC transfusions, have decreased the risk of serious infections and other life-threatening complications, resulting in improved survival to adulthood. This has shifted the demographics of SCD to a growing proportion of young adults with chronic health impairments. As an alternative to chronic supportive care, hematopoietic cell transplantation (HCT) from a human leukocyte antigen (HLA)-identical sibling donor has been used sparingly in children, but is curative in the majority of children treated[1]. This experience has been broadened to include alternate donors and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) recently completed a multicenter trial of unrelated donor HCT for children with severe SCD. However, there is limited experience with HCT in adults, even though the clinical need in this group of individuals is expanding rapidly. The possibility of conducting HCT more safely in young adults is strongly suggested by recent successful reports in young adults with thalassemia major and other hematological disorders using a reduced toxicity regimen that contain busulfan (Bu) or treosulfan in the preparative regimen[2-5]. Based in part on these results and results in our own pilot investigation, it is reasonable to project an acceptable safety profile after HLA-identical sibling and HLA-matched unrelated HCT in young adults with severe SCD, which in the long-term is projected to improve survival compared to adults who receive standard supportive care.

1.2. Rapid Disease Progression in Adults with SCD

1.2.1. Improved Survival of Children with SCD has Uncovered the Natural History of the Disease in Adults

In 1960, SCD was a disease of childhood and few survived to adulthood. Health care initiatives such as newborn screening, penicillin prophylaxis against pneumococcal sepsis and comprehensive programs with a focus on family education together dramatically improved outcomes in children with SCD. Currently, 90% of US newborns with SCD survive to 20 years of age. However, with improved survival to adulthood, chronic health impairments caused by progressive organ damage from SCD and the associated risk of premature death have become the dominant targets of clinical intervention for this disorder[6-12].

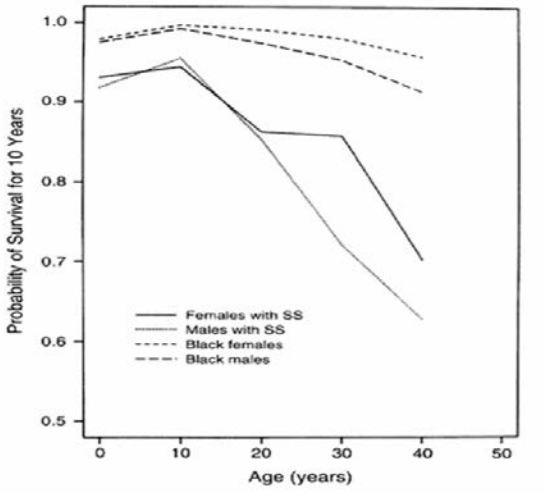


Figure 1. Steep decline in probability of survival in adulthood in patients with sickle cell disease

Natural history studies show that in contrast to the improvements in outcomes in childhood, there is a rapid progression in organ damage, morbidity and premature mortality in adulthood. Progression of organ damage in adulthood is marked by progressive organ impairment as a consequence of hemolysis and vaso-occlusion. In 3 large screening studies, approximately 30% of patients had a tricuspid valve regurgitant jet velocity (TRV) >2.5 m/s and 10% had a TRV >3 m/s. In all the epidemiological studies performed to date, the risk ratio of early death in adults with a TRV > 2.5 m/s ranged from 9.24 to 15.9 fold[9,13]. Renal insufficiency with proteinuria occurs in 70% of adults and progresses to renal failure in 11%. Abnormal pulmonary function occurs in 90% and progression to irreversible organ damage in 50% of patients by 50 years of age[8]. One third develop chronic pain syndrome and only 20% are employed[14,15]. Patients who experience a hemorrhagic stroke have a 26% risk of mortality within the first two-week period following the stroke.[16] Death in adulthood is frequently related to organ damage which is not preventable or easily managed with current medical measures[8]. SCD related complications such as leg ulcers, stroke, priapism, avascular necrosis, anxiety, and depression further worsen the health related quality of life. The mortality rate of patients with SCD is 5.8-20% in the first 10 years after transition to adult care[14,15]. Premature death occurs at a median age of 38 years, a statistic that has not changed in 20 years[8,17,18] (Figure 1). In a long-term follow-up study of patients with symptomatic SCD who were eligible to participate in the multicenter study of hydroxyurea (MSH), the annual mortality rate was 4.4 per 100 person-years among adults with SCD who satisfied eligibility criteria, which is 4.4%[13]. In another recent report, mortality was higher among those who have >4 pain crisis per year or those with a higher organ severity score[19]. Thus, if the 2-year mortality rate after HCT in adults is <15%, it is very likely that transplantation will confer a long-term survival advantage in these recipients.

1.3. Lack of Curative -Treatments for Adults with SCD

Myeloablative HLA-matched sibling HCT has excellent outcomes in children 16 years of age and younger. Following successful HCT there is a resolution of complications related to SCD with protection from episodes of pain, stroke, or acute chest syndrome and in most patients, a stable appearance of cerebral magnetic resonance imaging and pulmonary function tests and regeneration of the spleen[20]. The prevailing framework of clinical research in SCD shifts in the transition from childhood to adulthood. Among pediatric hematologists, the dominant view is that survival to adulthood is excellent, and that children, on average, have a very good quality of life as a result of supportive care measures such as antibiotics, family education, and the judicious use of transfusions. In addition, a great deal of effort has focused on identifying children who have high-risk features, so that the risk of any specific intervention might be balanced by the severity of disease in that individual.

In contrast, the prevailing view among clinicians who care for adults is that SCD is, on average, a severe disease with a significant risk of sudden death and the development of chronic medical problems and that supportive care options for young adult patients are not adequate to address the overwhelming nature of this disease. Thus, clinical studies in adults with SCD have focused on interventions that prolong survival and improve the quality of life. Unlike children, adults with SCD are much more likely to have a debilitating complication. As a result, the risk/benefit ratio of HCT may be more favorable in adults, particularly if an approach to HCT that defines an

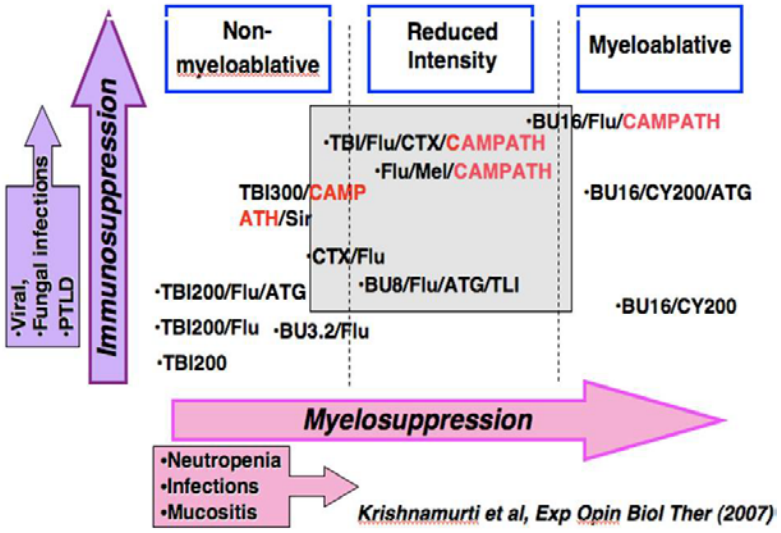
acceptable level of toxicity can be established. If successful, such an approach could significantly improve the outlook of many adults with SCD and broaden the therapeutic choices.

1.4. Rationale for Proposed Study

1.4.1. Novel Approaches to HCT for Hemoglobinopathies Based on a Combination of Reduced Intensity Conditioning and Immunosuppression

Non-myeloablative (NMA) and reduced intensity conditioning regimens are now routinely used to establish engraftment of donor hematopoietic cells in adults with hematologic malignancies. The success of immunoablative but reduced-intensity regimens suggests that an immunologic barrier rather than a requirement of "hematopoietic space" is a primary factor to ensuring engraftment of donor hematopoietic stem cells. While NMA conditioning regimens have been successfully applied in adults with hematological malignancies, these have been far less successful in hemoglobin disorders. Over a decade ago, Lucarelli et al. described the effects of conditioning regimen dose intensity on overall transplant outcome in HCT for thalassemia. Conditioning regimens containing less than 200 mg/kg of cyclophosphamide (CY) resulted in decreased transplantation-related mortality, with a concomitant increase in graft rejection.[21] For example, in pediatric patients with class III disease, the incidence of graft rejection increased from 10% to 30% after reducing the CY dose to 120-160 mg/kg. Sodani et al. successfully modified this regimen, resulting in a reduced rate of graft rejection from 30% to 8% by introducing a combination of intensive hypertransfusion, hydroxyurea and chelation, to reduce erythropoiesis and expansion of thalassemic clones well before transplantation, and by the addition of fludarabine (Flu) and azathioprine to increase the level of immunosuppression.[22] In another series focused on SCD, Krishnamurti et al reduced the dose of busulfan (Bu) by 50%, substituted Flu for CY and included 500 cGy total lymphoid irradiation and anti-thymocyte globulin[23] in the conditioning regimen. In this series, 6 of 7 patients had stable engraftment after HLA-ID sibling HCT and discontinued immunosuppression with no SCD-related symptoms at 2 to 9 years after HCT. Investigators from Duke University have also demonstrated encouraging results after HCT for SCD using the Bu-Flu backbone in 2 adults, one of whom had end stage renal disease[24]. Shenoy et al substituted the alkylator melphalan for Bu in combination with Flu and alemtuzumab and observed long term stable engraftment in patients with non-malignant disorders including SCD treated by HCT from related or unrelated donors[25]. Hsieh et al demonstrated stable donor

Figure 2. Spectrum of Immunosuppression and Myelosuppression Used in Preparative Regimen of HCT for SCD



engraftment in adult SCD patients following non-myeloablative HCT from HLA-matched sibling donors. Low-dose total-body irradiation (TBI 300 cGy) and alemtuzumab were administered before transplantation, and sirolimus was used for GVHD prophylaxis[26]. However, long-term administration of sirolimus at a median of 30 months post HCT was necessary because patients developed mixed lymphohematopoietic chimerism after transplantation with a perceived risk of late graft rejection[27]. Finally, the application of haplo-identical donor transplantation is in the early stages of development, led by the investigative team at Johns Hopkins. Seventeen children received a non-myeloablative combination of ATG, fludarabine, CY and 200 cGy TBI before transplantation and received high-dose CY after transplant to accomplish in vivo T-cell depletion of alloreactive donor T-cells. While this was safe and effectively prevented severe GVHD, graft rejection occurred in 6 of 14 haplo-identical donor transplants[28]. Thus, while encouraging results have been observed after these non-myeloablative regimens tested in patients with sickle cell disease, the problems of graft rejection and a need for long-term immunosuppressive therapy after transplantation have not been overcome.

Another approach to improve the safety profile of HCT has been to modify the myeloablative Bu/CY backbone of a conventional preparative regimen by substituting fludarabine for cyclophosphamide. This approach has successfully reduced the toxicity of the conditioning regimen but retains very high rates of stable donor engraftment[3,4,29]. Taken together, these studies suggest that modified preparative regimens containing a combination of myeloablative and immunosuppressive drugs can be safely and effectively administered in adults with non-malignant disorders.

1.4.2. Safety and Efficacy of the Conditioning Regimen for HCT in Adults.

Several conditioning regimens aimed at reducing the toxicity of HCT have been developed to support unrelated donor HCT for malignant and nonmalignant diseases (**Table 1**).

Table 1. Summary of outcomes after Bu, Flu, ±Thymoglobulin and Bu (14)/Cy for hematological malignancies and thalassemia. OS- overall survival; DFS-disease free survival; TRM-Transplant related mortality, MRD-matched sibling donor; URD-unrelated donor; GR-graft rejection. TT-Thiotepa; Treo-Treosulfan

Reference	# patients/donor type	Conditioning	Disease/Age range (median)	Outcome
Bernardo et al 2012[30]	20/MRD; 40 URD	Treo (14)/TT (8)/Flu (160) or Treo(14)/TT (8) /Flu(160)/ ATG	Thal/ 1-37 (7 years)	OS 93%/DFS 84%
Russell et al 2008[31]	200/MRD	BU(12.8)/Flu (250)/rATG (4.5)	Hem Malignancies/ 18 – 65 (46 years)	OS 76% / DFS 72%/ TRM 4% OS 64% / DFS 43%/ TRM 6%
Andersson et al 2008[32]	148/MRD& URD	Bu (130 mg/m2 x4d)/Flu(160)	AML/MDS/ 19 – 66 (46 years)	TRM – 12%
La Nasa et al 2007[5]	53/URD	Bu(14)/TT(10)/Flu (160) Bu(14)/TT(10)/ Cy(120-200)	Thal/ 2 – 26 (14 years)	OS 88% / DFS 74% GR 15% /TRM 11%

La Nasa et al[5] demonstrated that a combination of Bu/TT/CY conditioning in the initial series of 32 patients that received unrelated related donor (URD) transplantation had a transplant related mortality (TRM) of 19% and an event-free survival of 69%. The Bu/TT/CY regimen was later replaced with Bu/Flu/TT in the subsequent series, in 17 patients who received a combination of Bu/Flu with thiotepa, the TRM was 0% and thalassemia free survival was 77% after HCT. Bernardo et al substituted busulfan with its dihydroxy derivative treosulfan and demonstrated updated data in 60 patients (40 URD and 20 MRD recipients) indicating an overall survival of 93% and thalassemia free survival of 84%[30]. Together, these data demonstrate incremental improvement in the safety of myeloablative HCT for thalassemia major in adult recipients by modulation of the conditioning therapy and by optimal donor selection. We also interpret these data to suggest that a similar approach to study the safety and efficacy of a trial of HCT following a conditioning regimen with Bu+Flu in patients with SCD is feasible if suitable transplant donors can be identified. As in the thalassemia trials cited above, we would anticipate an event-free survival of at least 80% using this regimen in adult recipients.

The application of non-myeloablative and reduced intensity preparative regimens have been tested in children and adults with severe SCD as a strategy to mitigate the risk of infertility associated with myeloablative BU and to improve the safety profile of conditioning, particularly in adults with co-morbid organ function impairment related to SCD. Two conditioning regimens have emerged with the largest experience. The first of these was updated most recently in 2014.[27] Thirty patients between 16 and 65 years of age received a G-CSF mobilized peripheral blood graft from HLA-identical sibling donors. Patients with severe SCD were prepared with a combination of alemtuzumab and a single fraction of 300 cGy total body irradiation (TBI). Sirolimus was administered for GVHD prophylaxis. Twenty-nine of 30 patients survived with a medial follow-up of 3.4 years and 25 (83%) had full donor-type hemoglobin. A second series of patients prepared for HCT by reduced intensity conditioning was reported in 2015. Forty-three children with SCD and 9 with thalassemia who were between 0.8 and 20.3 years of age were enrolled. They received a reduced intensity combination of alemtuzumab ~3 weeks before transplantation, followed by fludarabine and melphalan. GVHD prophylaxis consisted of a combination of tacrolimus or cyclosporine with methotrexate in most cases. The overall survival was 93% and the event-free survival was 90.7% in the recipients who had SCD. Three patients with SCD died of complications related to GVHD.

Together, these data support the notion that myeloablative and non-myeloablative/reduced intensity conditioning regimens generate similar outcomes after HLA-ID sibling donor HCT for SCD. The potential benefits of administering a modulated regimen include a reduction in the risk of infertility and other toxicities related to the preparative regimen, particularly in older, fragile patients. However, there appears to be a higher risk of graft rejection after reduced intensity/non-myeloablative conditioning for SCD when an alternate or unrelated donor HCT is performed. For this reason, a myeloablative regimen would be preferred if it could be administered with an acceptable safety profile.

1.5. STRIDE Consortium (Sickle cell Transplantation to Prevent Disease Exacerbation in Young Adults – Preliminary Trial)

1.5.1. Preliminary Data From the R34 NIH Planning Grant

A consortium of 23 centers was developed to conduct the STRIDE demonstration study as supported by a R34 planning grant awarded by the NHLBI. Patients between 16-40 years of age were enrolled between October 2012 and June 2015 in 8 of the 23 participating transplant centers. Eligibility criteria included stroke; recurrent episodes of acute chest syndrome (ACS) or sickle pain in the past 2 years; 8 or more RBC transfusions/year; or a tricuspid valve regurgitant jet velocity > 2.7 m/sec. Patients received unmodified bone marrow from a human leukocyte antigen (HLA)-matched sibling or an unrelated donor matched for 8 of 8 HLA loci. Patients were prepared for HCT with Busulfan from day -8 to -5 (13.2 mg/kg), Fludarabine from day -7 to -3 (175 mg/m^2) and Thymoglobulin from day -5 to -2 (6 mg/kg). GVHD prophylaxis consisted of cyclosporine or tacrolimus with methotrexate.

Table 2. Outcomes in Patients Undergoing HCT on Feasibility Study					**GVHD**		**Complications**
% Donor Chimerism T-cell/RBC/Whole Blood/Myeloid					**Acute**	**Chronic**	**Events**
PIN	**Day 28**	**Day 100**	**Day 180**	**1 Year**	**Organ/Grade**		
301R	43/100/100	62/100/96/100	59/100/NA/100/	58 /100/NA/100	None	None	Grade 3 hypercalcemia, Transient elevated ALT
101R	56/100/100/NA	100/100/100/100	100/100/100/100	100/100/100/100	None	None	Bell's Palsy, EBV reactivation
201R	51/100/99/100	68/100/96/100	NA/100/98/NA	87/100/98/100	GII	None	Grade 3 hypertension Gall bladder obstruction
302R	41/100/NA/100	88/100/NA/100	91/100/NA/100	100/100/NA/100	None	Mild	
102R	100/100/NA/100	100/100/NA/100	100/100/NA/100	100/NA/100/100	None	None	Bacteremia, AIHA
901R	66/95/97/NA	72/95/98/NA	68/93/91/ NA	62/80/95/NA	Skin II	Mild	Hyperglycemia Grade 3 itching
303R	54/94/NA/100	66/97/NA/100	66/100/NA/100	77/87/NA/100	None	Skin GR 2	Persistent fever
401R	76/100/98/98	85/100/98/98	91/100/98/NA	98/NA/98/NA	Skin I	None	Pericardial effusion Hemolytic anemia
202R	12/100/95/100	83/100/NA/100	79/100/96/100	79/100/94/98	None	Moderate	
501R	97/94/NA/100	96/97/NA/100	100/97/98/NA	100/91/NA/NA	None	None	Transient inc ALT Hemolytic anemia
402R	27/95/97/99	50/*/96/NA	Not available	Not available	None	None	**Dead** Intracranial hemorrhage
304R	44/100/NA/100	79/100/NA/ 100	100/100/NA/100	100/88/NA/100	None	Liver Gr 2	
403R	78/100/NA/100	10/NA/95/100	11/NA/86/100	12/80/82/100	None	None	Diabetes, Pulmonary edema
503U	84/96/NA/100	35/96/NA/NA	NA/96/NA/99	Not available	Skin I	Lung BOOP	**Dead** VOC, pericardial effusion, BOOP
502R	53/97/NA/100	63/91/NA/98	37/100/NA/NA	51/79/NA/NA	None	None	
305R	75/100/NA/100	81/100/NA/100	75/100/NA/100	96/NA/NA/100	None	None	Pericarditis
504R	78/100/NA/NA	86/100/NA/NA	86/100/NA/100	82/NA/NA/100	None	Skin liver Gr 5	Transient inc ALT
1001R	28/91/NA/100	56/93/NA/100	59/NA/NA/100	82/NA/NA/100	Liver III	None	
701U	NA/90/97/NA	NA/83/97/NA	NA/NA/100/NA	100/NA/100/NA Not available	None	None	
306U	81/NA/NA/100	100/89/NA/100	96/NA/NA/100	100/NA/NA/100	None	None	Seizure, infection
1002U	55/94/NA/100	51/71/NA/100	51/NA/NA/100	75/NA/NA/100	None	None	Transient inc ALT, VOC
307U	20/89/NA/100	0/24/NA/100	0/NA/NA/100	Not available	None	None	Thrombus, pneumonia

Outcomes and Measures: The primary endpoint was 1-year event-free survival with events defined as graft failure, disease recurrence, or death. The Kaplan-Meier probabilities of event-free and overall survival will be determined. Donor chimerism, transplant-related toxicities and clinical and laboratory measures of SCD were secondary endpoints obtained 1 year after HCT.

Results: Twenty-two patients (13 female) who ranged in age from 17-36 (median 22) years were enrolled. Seventeen patients received a sibling and 5 an unrelated donor HCT (Table 2). Enrolled

subjects had stroke (n=2), ACS (n=3), pain (n=14), RBC transfusion ≥8 per year for ≥1 year (n=6) and TRJ velocity ≥2.7 m/sec (n=5); N=8 satisfied eligibility criteria for more than 1 category. N=22 patients are evaluable; 20 of 22 patients are alive with stable engraftment of donor cells at a median 13.6 months after HCT. The overall and event-free survival probabilities are both 90% at 12-months after HCT). Full donor myeloid chimerism was observed after HCT in all patients.

1.5.2. Justification for Proposed Trial Design

Trial design: A randomized clinical trial (RCT) is the ideal trial design when comparing treatment approaches. However there are formidable challenges to conducting an RCT in this setting. The major challenge is limited donor availability; only a third of eligible participants will have a suitably HLA-matched donor. In a randomized design, only participants with a suitably HLA-matched donor could enroll; randomization would then determine whether an HCT were done. Restricting enrollment in this way would mean an accrual time of 5-6 years rather than 2-3 years, even if randomization did not affect patients' willingness to participate. HCT and standard of care are unequal in their intensity, potential toxicity and potential for cure. HCT is an intense treatment with a certain number of early deaths expected from HCT-related complications. On the other hand, it is potentially curative. Supportive care has very low toxicity and early mortality but there is no cure of the underlying disease and the likelihood of death from SCD is high later in life; expected mortality is 4.4 per 100 person-years.[13,33] The decision to undergo HCT is a complex process but once physicians and patients accept the idea of a curative therapy for SCD, despite its risk, they are often unwilling to accept non-curative treatment (standard of care) when a suitable donor is available, posing a barrier to participation. Accepting randomization to a non-curative approach may be a particular problem in a population with demonstrated mistrust of the medical establishment and is likely to result in a serious impediment to timely accrual. Timely completion of a trial is important both scientifically and ethically. It is a key criterion used by Data Safety Monitoring Boards as data generated from a lengthy trial may no longer be scientifically relevant upon the trial's completion, raising ethical issues of asking patients to participate in a trial that cannot answer a question in a timely manner. Therefore, the trial is designed as a biologic assignment trial with the ITT principle.

Justification of primary endpoint: We hypothesize that for participants assigned to the donor arm HCT-related mortality may exert an early impact on survival, but that the rate of mortality should plateau by two years.[34-36] Reports of survival for severe aplastic anemia after related and unrelated donor transplantation suggest early mortality is less than 15% and that this risk plateaus by two years.[34-36] Severe aplastic anemia is the most common non malignant disease indication for transplantation in young adults. Additionally data from the pilot trial mentioned above for young adults with SCD also support 1-year survival of 90%. We hypothesize as well that participants on the no donor arm will not be especially susceptible to early death, but will gradually succumb to the cumulative effects of their disease with a mortality rate higher than in the general population.[13] Published reports for SCD adults receiving standard of care with hydroxyurea suggest this occurs at a rate of 4.4 deaths per 100 person years.[33] Consequently, the survival curves of the 2 groups will eventually cross, with a long-term benefit for HCT if early HCT-related mortality is sufficiently low. For this phase II trial, we will compare survival rates at 2-years, with the goal of establishing that the difference in the proportion surviving is no more than 0.15 lower in the donor

arm. We think that if the early survival disadvantage of HCT is modest, a long-term survival advantage will emerge.

The study design and the acceptability of HCT as a treatment option for adolescents and young adults were discussed with the Sickle Cell Adult Provider Network (SCPAN). There is agreement amongst the SCAPN physicians (~150) that if the 2-year disease-free survival after HCT is 75% they would accept HCT as superior to supportive care in young adults based upon the long-term mortality risks associated with supportive care. Based upon the results in the pilot investigation, there is a strong possibility that clinical practice could change and incorporate HCT as a therapeutic option.

Justification of bone marrow as the graft source: There are several published reports including a phase III randomized trial through the BMT CTN that show higher rates of chronic graft-versus-host disease (GVHD) after transplantation of peripheral blood.[37] Further, studies in severe aplastic anemia, suggest higher mortality after transplantation of peripheral blood.[35,38] Although data are lacking on the use of peripheral blood with the exception of a report from a single institution[27] the protocol team remains concerned about study subjects trading a chronic disease (SCD) for another, chronic GVHD. Chronic GVHD is debilitating and associated with poor quality of life in addition to being at risk for opportunistic infections and death.[39]

Justification for the use of calcineurin inhibitors (CNI): In a cohort of 488 patients (subjects were enrolled on BMT CTN 0401 or transplanted at the Dana Farber Cancer Institute), the use of sirolimus was associated with higher rates of veno-occlusive disease (VOD) in the setting of myeloablative transplantations; 15.8% with sirolimus containing regimens vs. 7.4% with non-sirolimus regimens (tacrolimus + methotrexate). Higher VOD was associated with higher mortality.[40] In another randomized trial that studied the effects of sirolimus in 146 patients, the incidence of VOD was 21% with sirolimus containing regimens compared to 9% with non sirolimus regimens.[41] Since higher rates of VOD and liver complications were also seen in HCT for transfused individuals with thalassemia, for safety reasons we elected not to employ sirolimus in this trial.

Issues in biological assignment: Participants are biologically assigned, based on the presence or absence of a suitable donor, to donor versus no donor arms. Participants in the donor arm are expected to proceed to HCT and those in the no donor arm, to continue with standard of care. However, crossovers may occur, which may lower the statistical power to detect differences between the donor and no donor arms. We have undertaken measures to minimize crossovers. The up-front consultation with the HCT physician should screen out most participants interested in only one or the other treatment option. Consequently, recruitment of highly motivated participants will minimize crossovers and dropouts. In the pilot trial there was only 1 withdrawal after a suitable donor was identified (1 of 23, 4%). Denial of insurance coverage for HCT may prevent some participants assigned to the donor arm from receiving HCT. Based on the pilot trial and the Center for Medicare and Medicaid Services (CMS) guidelines, we anticipate <10% will be denied insurance coverage. Many SCD patients are covered by Medicare and CMS guidelines state the Affordable Care Act (ACA) policy is that if an indication for HCT is in the silent category (such as SCD) and patients are in a federally approved or sponsored clinical trial, Medicare patients are

eligible for HCT coverage. Participants assigned to the donor arm but subsequently unable to proceed to HCT for any reason will remain in the donor arm for the primary analyses. Similarly, there may be participants in the no donor arm who proceed to HCT at a later date with an HLA-mismatched or matched donor. These participants will remain in the no donor arm for primary analyses. A full description of crossovers on both arms will be provided. Another potential problem is that participants with donors may differ from those without donors. Analyses are planned to assess comparability of participants on the 2 treatment arms for demographic and prior sickle related events. Multivariable analysis will be used to adjust for imbalances in characteristics. Although very unlikely, any death occurring prior to identification of a donor would be assigned to the no donor arm.

Enrollment bias: Bias can occur with biologic assignment with differential assignment of higher risk patients to one or the other treatment arm. This occurs when knowledge of the eventual arm assignment differentially influences enrollment of specific types of patients. We will minimize this by deferring initiation of donor search until after enrollment. We will also monitor this by requesting sites to submit a pre-screen log to the DCC. The log will identify potential participants based on their clinical eligibility and confirmation from the site that HLA typing has not been performed. Concurrent with this effort, the Protocol Team will educate site PIs on the importance of refraining from HLA typing potential participants. Participants who have been HLA typed prior to referral are ineligible; however if a participant has had HLA typing with accompanying documentation that relatives were not HLA typed or a search of the unrelated donor registry was not performed the participant will be considered eligible.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

The primary goal of this multicenter study is to determine the safety and efficacy of HCT in young adults with severe SCD compared to a cohort with severe SCD without a suitable donor**.** Study participants are assigned to one of two treatment arms: a donor arm for those with a suitable donor and a no donor arm for those without an available marrow donor. We will compare the difference in the observed proportion of patients surviving at 2 years post biologic assignment between the treatment arms (ITT principle). Secondary outcomes will compare changes in SCD-related events (pulmonary hypertension, cerebrovascular events, renal function, avascular necrosis, leg ulcer), functional outcomes (6MWD, HRQoL), and mean pain intensity assessed by a multidimensional electronic pain diary between the treatment arms.

2.2. Hypothesis and Specific Objectives

2.2.1. Primary Objective

The primary objective of this clinical trial is to compare 2-year OS in young adults with severe SCD who receive HCT compared to standard of care. Participants are selected on clinical eligibility and without knowledge of donor availability when approached for consent. Study participants will be biologically assigned to one of two treatment arms, a donor arm or no donor/standard of care arm, based on the availability of a suitable HLA-matched sibling or 8/8 HLA-matched adult unrelated donor. All participants are initially assigned to the no donor/standard of care arm, and if a suitable donor is identified, patients are re-assigned to the donor arm. The protocol recommends HLA typing of study participant, sibling(s) and/or initiation of search for an unrelated donor to occur as soon as the potential participant is confirmed to be eligible by enrollment or the external eligibility review committee. Subjects assigned to the donor arm are expected to proceed to HCT and those on the no donor arm, to receive standard of care. Regardless of treatment received participants will remain in their assigned arm for analyses (Intent-to-treat principle). The primary endpoint is a comparison of the difference in the observed proportion of patients surviving at 2 years post biologic assignment between the two treatment arms.

We hypothesize that for participants assigned to the donor arm, HCT-related mortality may exert an early impact on survival, but that the rate of mortality will plateau by 2 years. Additionally, we hypothesize that participants on the no donor arm will not be especially susceptible to early death, but will gradually succumb to the cumulative effects of their disease anticipated to be at a rate of 4.4 deaths per 100 person-years.[13,33] Our goal is to establish that the difference in the proportion of participants surviving at 2-years is no more than 0.15 lower in the donor arm compared to the no donor arm. A difference of this magnitude or less at two years is likely to result in a long-term survival advantage.

2.2.2. Secondary Objectives

Secondary objectives will compare changes in SCD-related events including organ function (pulmonary hypertension, cerebrovascular events, renal function, avascular necrosis, leg ulcer) and functional outcomes (6-MWD, HRQoL assessed using the NIH's PROMIS-57 instrument, and mean pain intensity assessed by an electronic pain diary), pulmonary function tests, echocardiogram at baseline and 2-years after assignment to treatment arm. Additionally, HRQoL, 28 day e-pain diary, pulmonary function tests, echocardiogram and the 6MWD test will also be measured at 1 year. Baseline 1 and 2-year assessments will be done at the same sites to minimize variability. Secondary objectives for the donor arm include neutrophil recovery, platelet recovery, graft failure, chimerism, acute and chronic graft-versus-host disease, idiopathic pneumonia syndrome, veno-occlusive disease, and central nervous system toxicity. Additionally, we will ascertain survival status of patients annually, years 3 through 10 and compare survival between the treatment groups.

2.3. Patient Eligibility

2.3.1. Eligibility Criteria for Initial Screening

2.3.1.1. Inclusion Criteria – Initial Screening

1. Age ≥ 15 and < 41
2. Severe sickle cell disease [any clinically significant sickle genotype, for example, Hemoglobin SS (Hb SS), Hemoglobin SC (Hb SC), Hemoglobin SBeta thalassemia (Hb Sβ), or Hemoglobin S-OArab genotype] with at least 1 of the following manifestations (a-f):
    a. Clinically significant neurologic event (stroke) or any neurological deficit lasting > 24 hours;
    b. History of two or more episodes of acute chest syndrome (ACS) in the 2-year period preceding enrollment or referral despite the institution of supportive care measures (i.e. asthma therapy);
    c. An average of three or more pain crises per year in the 2-year period preceding enrollment or referral (required intravenous pain management in the outpatient or inpatient hospital setting)
        i. Clinical documentation of pain management in the outpatient or inpatient setting is required.
    d. Administration of regular RBC transfusion therapy, defined as receiving 8 or more transfusion events per year (in the 12 months before enrollment) to prevent vaso-occlusive clinical complications (i.e. pain, stroke, and acute chest syndrome)
    e. An echocardiographic finding of tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec.

f. Ongoing high impact[1] chronic pain on a majority of days per month for ≥ 6 months as defined as ONE or more of the following:

   i. Chronic pain without contributory SCD complications[2] OR

   ii. Mixed pain type in which chronic pain is occurring at site(s) (arms, back, chest, or abdominal pain) unrelated to any sites associated with Contributory SCD complications[2] (e.g. leg ulcers and/or avascular necrosis).

3. Adequate physical function as measured by all of the following:

   a. Karnofsky/Lansky performance score ≥ 60

   b. Cardiac function: Left ventricular ejection fraction (LVEF) > 40%; **or** LV shortening fraction > 26% by cardiac echocardiogram or by MUGA scan.

   c. Pulmonary function:

      i. Pulse oximetry with a baseline O2 saturation of ≥ 85%

      ii. DLCO > 40% (corrected for hemoglobin)

   d. Renal function: Serum creatinine ≤ 1.5 x the upper limit of normal for age as per local laboratory **and** one of the following:

      i. creatinine clearance >70 mL/min calculated using the Cockcroft-Gault calculator

      ii. creatinine clearance > 70 mL/min by 24 hour urine (preferred)

      iii. GFR > 70 mL/min/1.73 m2 by radionuclide GFR.

   e. Hepatic function:

      i. Serum conjugated (direct) bilirubin ≤ 2x upper limit of normal for age as per local laboratory. Participants are not excluded if the serum conjugated (direct) bilirubin is >2x the upper limit of normal for age as per local laboratory **and**:

         i. There is evidence of a hyperhemolytic reaction after a recent RBC transfusion, OR

         ii. There is evidence of moderate direct hyperbilirubinemia defined as direct serum bilirubin < 5 times ULN and not caused by underlying hepatic disease.

      ii. ALT and AST < 5 times upper limit of normal as per local laboratory.

[1] High impact chronic pain (HICP) is identified as those reporting "severe interference" with life activities OR "usually or always" experiencing a limitation of their life or work activities including household chores. (See guidelines for identifying HICP in the BMT CTN 1503 Manual of Procedures)

[2] Contributory SCD complications are defined as clinical signs (e.g. presence of leg ulcers) or clinical assessments (e.g. imaging confirmation of splenic infarct or avascular necrosis). Chronic pain attributed solely to contributory SCD complications is excluded.

2.3.1.2. Exclusion Criteria – Initial Screening:

1. HLA typing with a donor search prior to referral (consultation with HCT physician).
    a. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time, and also did not have an unrelated donor search, the patient will be considered eligible.
    b. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
    c. If a subject has had HLA typing with no related donor search and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
    d. Subjects with a known HLA-identical sibling or HLA-matched unrelated donor are excluded.
2. Uncontrolled bacterial, viral, or fungal infection in the 6 weeks before enrollment.
3. Seropositivity for HIV
4. Previous HCT or solid organ transplant
5. Participation in a clinical trial in which the patient receives an investigational drug or device must be discontinued prior to date of enrollment
6. A history of substance abuse as defined by version IV of the Diagnostic & Statistical Manual of Mental Disorders (DSM IV).[1]
7. Demonstrated lack of compliance with prior medical care as determined by referring physician.
8. Pregnant or breast feeding females.
9. Inability to receive HCT due to alloimmunization, defined as the inability to receive packed red blood cell (pRBC) transfusion therapy.

2.3.2. Eligibility Criteria for Transplant after Biologic Assignment - Donor Arm Participants

Participants assigned to the Donor Arm at the time of biologic assignment are subject to additional transplant eligibility criteria as specified below. Additionally, repeat clinical assessments prior to transplant should be obtained in accordance with institutional policies and standards of care in the interest of good clinical practice. If participants biologically assigned to the donor arm do not meet the following additional eligibility criteria, they will not be able to proceed with transplant.

[1]American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.* (4th ed.). Washington, DC American Psychiatric Association.

All donor arm participants must meet the following criteria to qualify for transplant:

a. Liver MRI (≤ 90 days prior to initiation of transplant conditioning) to document hepatic iron content is required for participants who are currently receiving ≥8 packed red blood cell transfusions for ≥1 year or have received ≥20 packed red blood cell transfusions (cumulative). Participants who have hepatic iron content ≥ 7 mg Fe/g liver dry weight by liver MRI must have a liver biopsy and histological examination/documentation of the absence of cirrhosis, bridging fibrosis[1], and active hepatitis (≤ 90 days prior to initiation of transplant conditioning).

b. Lack of clinical or radiologic evidence of a recent neurologic event (such as stroke or transient ischemic attack) by Cerebral MRI/MRA within 30 days prior to initiating transplant conditioning. Subjects with clinical or radiologic evidence of a recent neurologic event will be deferred for ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation.

c. Documentation of participant's willingness to use approved contraception method until discontinuation of all immunosuppressive medications is to be documented in the medical record corresponding with the consent conference.

2.4. Trial Design, Screening, and Biological Assignment

In brief, potentially eligible participants are referred to a HCT physician for consultation which includes 1) confirmation of trial specified clinical eligibility; 2) detailed patient education about the trial design including biologic assignment, HCT procedure, and risks and benefits of disparate treatment arms (curative intent versus standard of care); 3) consent for screening tests and HLA typing. Sites will be provided patient-oriented education materials on the design and objectives of the trial for review prior to referral for screening consultation.

Sites participating in this trial will accept referrals from other primary practice/private hematologists/SCD physicians within the community. However, for the purposes of this trial, it is preferred that all visits from time of initial consent through biological assignment be completed at the transplant center. Following biologic assignment, patients assigned to the donor arm should be followed by the transplant center and patients assigned to the no-donor arm may be transferred to the referral site for the remainder of follow up.

Consenting participants are enrolled into the AdvantageEDC^{SM} data collection system with relevant clinical information needed to confirm clinical eligibility without knowledge of donor or health care insurance status. An independent Eligibility Review Committee (ERC) will review clinical eligibility for some participants (see appendix G for additional details). If a participant is not required to be reviewed by the ERC, eligibility will be confirmed upon successful enrollment into AdvantageEDC. If eligibility is not confirmed, that participant will not be followed further.

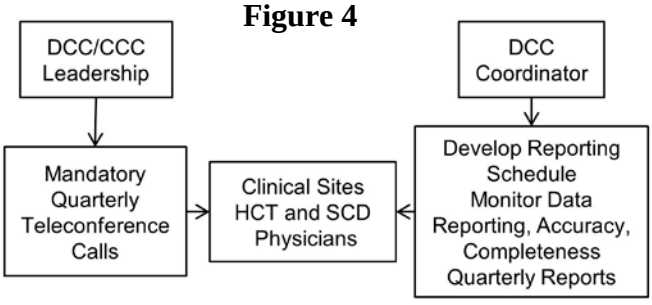
[1]The absence of bridging fibrosis will be determined using the histological grading and staging scale as described by Ishak and colleagues (1995) as described in the Manual of Operating Procedures.

Based on a similar screening program for BMT CTN 0601 and the pilot trial for this protocol, we expect this will happen in <5% of participants. For those with confirmed eligibility, the enrolling site will be informed and the donor search will be initiated. HLA typing and donor search is initiated only after confirmation of eligibility by ERC or AdvantageEDC, as applicable. In the rare instance a potential patient had been HLA typed but without knowledge or documentation of a donor search prior to referral, initiation of donor search can only occur after confirmation of eligibility. Biologic assignment will occur ≤ 180 days after this eligibility confirmation, based on identification of a suitable donor as defined in section 2.5.

For participants assigned to the donor arm, consent is obtained for HCT. If no suitable donor is identified ≤ 180 days after confirmation of eligibility, participants remain in the no donor arm and will continue medical care, trial-related tests, and follow-up for 2 years. The likelihood of a participant dying during the waiting period is highly unlikely given the natural history of SCD.

Follow-up: Follow up for participants on the donor arm is conducted by an HCT physician or designee and for those on the no donor arm, by a SCD physician or designee. Baseline characteristics and monitoring/tests are assessed after confirmation of eligibility, at time of assignment to treatment arm, and every 3 months for 2 years from biologic assignment. For those assigned to the donor arm, additional assessments are performed weekly through day-100 post-transplant. HCT is a very intense treatment requiring inpatient hospital care and careful monitoring of participants. A dedicated DCC coordinator will monitor that data are reported in a timely manner into AdvantageEDC^{SM} for participants on the donor and no donor arms (Figure 4). Our experience suggests compliance is high for BMT CTN trials that employ a similar monitoring strategy with the median percent of forms due for longer than 30 days per patient at 1.2% (range 0.5–3.0% by center).

Figure 4



A Visit Scheduling Calendar, an interactive resource for site coordinators, is available in AdvantageEDC^{SM} to track participant visits. There will be mandatory regularly scheduled teleconferences with the DCC/CCC leadership and all site PIs to discuss accrual, data reporting and compliance. The Protocol Coordinator will develop quarterly reports on site performance metrics for discussion on the teleconference calls. We will foster partnerships between HCT and non-HCT physicians, a strategy that proved effective for follow-up of non-HCT participants in the Scleroderma: Cyclophosphamide or Transplantation trial.[42]

Adopting a similar approach, when HCT and SCD physicians are at the same site (i.e., within the same University), a single contract is issued to that site. When the HCT and SCD physicians are at different sites, separate contracts are issued and "hybrid sites" created where HCT and SCD physicians are paired. For monitoring compliance, each hybrid site is treated as a single site, motivating both physicians to comply with reporting requirements. Sites recruited for this Phase II trial have SCD patient populations >100, are largely academic sites with HCT programs, and

have a track record for participating in national trials. Consequently, there is greater awareness and resources available to fulfill the rigor needed for participant retention and completeness of data reporting.

2.5. Donor Selection Criteria

All donors must meet the criteria below to be considered eligible for donation on this trial based upon the availability of a related or unrelated donor. An adult unrelated donor transplant is recommended only if an HLA-matched sibling is NOT available. **HLA-matched donors that do not meet the donor selection criteria in section 2.5.1 are not suitable donors.**

2.5.1. Criteria Required for Assignment to the Donor Arm

Participants will be assigned to the donor arm if the following criteria are met ≤ 180 days after confirmation of eligibility:

1. Have a suitably matched HLA donor:
    a. Siblings must be at a minimum HLA-6/6 matched to the recipient at HLA –A, -B and –DRB1 at intermediate (or higher) resolution using DNA-based typing. Donors aged <18 years[1] are allowed provided that there is no medically equivalent HLA-matched adult relative who is willing and able to donate

    b. Unrelated adult donors must be at a minimum 8/8 HLA-matched to the recipient at HLA -A, -B, -C and -DRB1 at high resolution using DNA-based typing

2. Donor is willing and able to donate required graft source. Patients with an HLA-identical sibling donor can receive a transplant using one of three regimens: A) Busulfan, Fludarabine, and rabbit ATG using a bone marrow graft *(preferred)*, B) Alemtuzumab/TBI 300 cGy using a peripheral blood graft, **OR** C) Alemtuzumab, fludarabine, melphalan using a bone marrow graft.
    a. In the unlikely event the sole suitable donor is not medically fit to donate bone marrow, a mobilized peripheral blood graft may be permitted subject to review of documentation by the Medical Monitor or Protocol Officer.

3. Absence of anti-donor HLA antibodies. The presence of anti-donor HLA antibodies 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 HLA-A, -B, -C, –DRB1 or –DP with mean fluorescence intensity >1000 by solid phase immunoassay. Anti-donor HLA antibody testing may be performed after confirmation of availability of an HLA-matched sibling or unrelated donor.

Any participant not confirmed to meet the above criteria ≤ 180 days after the date of confirmation of eligibility will remain in the No Donor/SOC arm. If it is known that a potential donor is available

[1]The minimum age of a patient eligible for this trial is 15 years. As the ages of the siblings are with ± 5 years it is unlikely children aged <10 years will serve as donors.

but they will not have been confirmed to meet criteria for assignment to the donor arm within the window, the Protocol Coordinator should be contacted prior to the end of the 180 day window. Expansions to the donor search window will be considered on a case-by-case basis and at the discretion of the Protocol Chairs/Officer.

2.5.2. Criteria Required Prior to Donation

The following must be confirmed prior to BMT for those assigned to the donor arm:

1. All related donors must meet institutional criteria for donation

2. All unrelated donors must fulfill their respective unrelated donor registry criteria for donation.

2.6. Treatment Plan for Patients Assigned to the No Donor Arm

Patients assigned to the no donor arm will continue to receive standard of care treatment per their SCD physician. Co-enrollment on another clinical trial requires the site notify the Protocol Coordinator at EMMES for consultation with Study PIs and Protocol Officer prior to initiating the co-enrollment.

2.7. Treatment Plan for Patients Assigned to the Donor Arm (HCT)

Patients with a matched unrelated donor will receive a bone marrow transplant (unless PBSC graft is pre-approved per section 2.5.1 using a preparative regimen with Busulfan, Fludarabine and rabbit ATG.

Patients with an HLA-identical sibling donor can receive a transplant using one of three regimens:

A. Busulfan, Fludarabine, and rabbit ATG using a bone marrow graft (preferred regimen)

B. Alemtuzumab/TBI 300 cGy using a peripheral blood graft

C. Alemtuzumab, fludarabine, melphalan using a bone marrow graft

Prior to implementation of the version 5.0 protocol, each center will choose one regimen to use for **all** HLA-identical sibling donor transplants on BMT CTN 1503. Centers must register and receive approval for which of the three transplant regimens they will use with the BMT CTN DCC in advance of protocol version 5.0 implementation. If a center wishes to modify their conditioning regimen choice for HLA-identical sibling donor transplants, they must contact the BMT CTN DCC and obtain approval prior to administration of a new regimen.

A summary of the conditioning regimen options is summarized in Table 2.7. Details on each conditioning regimen is available in section 2.7.2.

Table 2.7: Transplant Regimens for Related and Unrelated Donor Transplants	
Matched Unrelated Donor	Matched Related Donor (i.e. Sibling)
Busulfan, Fludarabine, and rabbit ATG using a bone marrow graft	A. Busulfan, Fludarabine, and rabbit ATG using a bone marrow graft
	B. Alemtuzumab/TBI 300 cGy using a peripheral blood graft
	C. Alemtuzumab, fludarabine, melphalan using a bone marrow graft

2.7.1. Pre-Transplant Procedures

2.7.1.1. Hemoglobin S Level

Hb S level must be ≤ 30% within 30 days prior to initiation of conditioning regimen for HCT. This may be achieved by exchange or simple transfusion according to local institutional practice. If doing an exchange transfusion, it is recommended that a hematocrit level of 30% is targeted, while not exceeding 36%.

2.7.1.2. Hydroxyurea and Iron Chelation Therapy

Hydroxyurea must be discontinued at least 1 week before initiation of conditioning regimen for HCT. Iron chelation therapy must be discontinued no later than 48 hours prior to commencement of the conditioning therapy. Iron chelation therapy or a program of phlebotomy may be resumed after neutrophil and red cell engraftment at the discretion of the transplanting center.

2.7.2. Preparative Regimen

Patients who have a matched unrelated donor will receive the preparative regimen as shown in **Table 3.** Patients who have an HLA-identical sibling donor will receive either the regimen in Table 3 (Regimen A) or the alternative non-myeloablative regimen in Table 4 (Regimen B) or the reduced intensity regimen in Table 5 (Regimen C). Centers must register and receive approval for which of the three HLA-identical donor transplant regimens they will use per section 2.7. All patients with an HLA-identical matched sibling will receive a transplant with the same, single, pre-approved regimen for the center.

2.7.2.1. Unrelated Donor HCT and HLA-Identical Sibling HCT Regimen A:

Table 3. SCHEMA OF CONDITIONING REGIMEN	
Day	Treatment
–8	BU 3.2 mg/ kg/dose IV
–7	BU 3.2 mg/kg/dose IV, Fludarabine 35mg/m2 IV
–6	BU 3.2 mg/kg/dose IV, Fludarabine 35mg/m^2 IV, rabbit ATG 0.5mg/kg IV

Table 3. SCHEMA OF CONDITIONING REGIMEN	
–5	BU 3.2 mg/kg/dose IV, Fludarabine 35mg/m^2 IV, rabbit ATG 1 mg/kg IV
–4	Fludarabine 35mg/m^2 IV, rabbit ATG 1.5mg/kg IV
–3	Fludarabine 35mg/m^2 IV, rabbit ATG 1.5mg/kg IV
–2	rabbit ATG 1.5mg/kg IV
–1	Rest
0	Stem cell infusion

Busulfan (Bu) and fludarabine dosing will be based on adjusted body weight (AjBW) in patients weighing >125% Ideal Body Weight (IBW). The following are dose adjustment formulas:

IBW in kg is estimated as follows:

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

AjBW = adjusted body weight is estimated as follows:

AjBW = IBW + 0.25(Actual Body Weight - IBW)

Initial busulfan dosing should be followed by pharmacokinetic dosing to ensure targeted exposure

2.7.2.2. Fludarabine

Fludarabine 35 mg/m^2/day will be administered on Day –7 to Day –3 (for a total of 175 mg/m^2 over 5 consecutive days) and administered IV over a minimum of 30 minutes. The IV infusion may take longer per institutional guidelines. Preparation, administration, and monitoring will be according to institutional standard practice. Fludarabine will be adjusted to adjusted body weight (AjBW) in patients weighing > 125% IBW.

2.7.2.3. Busulfan

Busulfan 3.2 mg/kg as a daily single dose will be given IV on Days –8 to -5 (4 days) before transplantation. Busulfan injection (6 mg/mL) should be diluted with 0.9% sodium chloride or 5% dextrose injection to a quantity 10 times the volume of the injection (e.g. 5 mL of busulfan injection should be diluted in 50 mL of NS or D5W) prior to the infusion. Busulfan should be infused over 3 hours. The line should be completely flushed with D5W or NS at the end of the infusion to ensure administration of the complete dose. Blood will be collected for busulfan pharmacokinetics (2 mL of blood in green top vacutainer). The collection time-points will be per institutional standards. The following schedule is recommended but not required: at the end of the infusion (+15 min), 4, 5, 6 and 8 hours after the start of the first infusion on day -8 of the preparative regimen.

Busulfan dose will be targeted to achieve a concentration at steady state (Css) of 600-900 ng/mL (target 750 ng/mL) or a daily area under the plasma concentration curve (AUC) of 3507–5261 µM•min (target 4384 µM•min) on the subsequent day. The total regimen AUC will be in the range of 14,000 – 21,000 µM•min. (Appendix D).
Supportive care management during busulfan administration will follow institutional guidelines.

2.7.2.4. Rabbit ATG

Rabbit ATG (r-ATG) will be administered on day -6 at 0.5 mg/kg, day -5 at 1 mg/kg and days -4, -3, and -2 at 1.5 mg/kg for a total dose 6 mg/kg. Each vial of r-ATG lyophilized powder is reconstituted with 5 mL of soluble water for injection and transferred into the bag of infusion solution (saline or dextrose). It is recommended to use 50 mL of infusion solution for each vial of thymoglobulin. Total volume is usually between 50 to 500 mL. It is infused through a 0.22-micrometer filter into a high-flow vein over a minimum of 6 hours for the first dose and over at least 4 hours for subsequent doses. Premedication with corticosteroids, acetaminophen, and diphenhydramine 1 hour prior to the infusion is recommended to reduce the incidence and intensity of side effects during and after the infusion. Other sources of ATG are contra-indicated. Please notify Protocol Coordinator if patient is unable to tolerate r-ATG.

2.7.3. Infusion of Bone Marrow

Target total nucleated cell count (TNC): $\geq 3.5\ 10^8$/kg (actual recipient body weight). Institutional procedures should be followed for requesting and receiving marrow units for infusion. Under no circumstances are the marrow cells to be irradiated. No in-line leukocyte filter should be used and no medications or fluids should be given through the catheter lumen that is used for infusion of stem cells during the infusion of bone marrow. Monitoring immediately prior to, during infusion of bone marrow cells, and thereafter will be according to institutional guidelines. Pre-medication prior to infusion of bone marrow will be according to institutional guidelines.

2.7.3.1. HLA-Identical Sibling HCT Preparative Regimen B:

Table 4. SCHEMA OF CONDITIONING REGIMEN B for HLA-ID SIB TRANSPLANTS

Day	Treatment
–7	Alemtuzumab 0.03 mg/kg IV
–6	Alemtuzumab 0.1 mg/kg IV
–4	Alemtuzumab 0.3 mg/kg IV
–4	Alemtuzumab 0.3 mg/kg IV
–3	Alemtuzumab 0.3 mg/kg IV
–2	TBI 300 cGy

Table 4. SCHEMA OF CONDITIONING REGIMEN B for HLA-ID SIB TRANSPLANTS	
–1	Rest
–0	Stem cell infusion

2.7.3.2. Alemtuzumab

Alemtuzumab will be administered on day -7 (0.03 mg/kg), day -6 (0.1 mg/kg) and day -5, -4, and -3 (0.3 mg/kg).

Pre-medication should be commenced 30 minutes prior to each infusion of alemtuzumab and should be continued for at least 48 hours after the last dose of alemtuzumab.

Recommended pre-medication include the following combination of medications:
Diphenhydramine: 25 – 50 mg IV or PO q 8 hours (maximum 50 mg/dose)
Acetaminophen: 650 mg PO q 6 hours (maximum 4 grams qd)
Hydrocortisone: 50 mg IV q 6 hours
Meperidine: 50 - 75 mg IV q 4-6 hours as needed for rigors

Alemtuzumab will be administered in-patient and the initial dose must be administered over 2 hours and subsequent doses not less than 24 hours apart. If the patient has a severe or life threatening adverse reaction to alemtuzumab (e.g., severe hypotension, severe bronchospasm) the adverse event meets expedited reporting requirements (within 24 hours) through the expedited AE reporting system via AdvantageEDC^{SM}. A study chair(s) may also be consulted regarding further doses at the discretion of treating physician.

Alemtuzumab will be diluted in 100cc of 0.9% normal saline (NS) and infused intravenously over a minimum of 6 hours each day for 5 consecutive days. Since serious infusion reactions are not uncommon during alemtuzumab infusion, it is strongly recommended that vital signs should be recorded q 15-30 minutes during each infusion of alemtuzumab.

Total Body Irradiation (TBI) 300 cGy on day -2 in a single dose, with testicular shielding. TBI may be delivered from either linear accelerator or Cobalt sources per institutional practice.

Rest on Day -1

Day 0 is the day of transplant; G-CSF mobilized peripheral blood stem cells is the preferred source of donor hematopoietic cells

Testicular/Gonadal Shielding during TBI

Testicular shielding will be administered to all male patients.

The testis is one of the most radiosensitive tissues, and even low doses of radiation can cause impairment of function. In adult men, doses as low as 10 cGy can cause damage to spermatogonia50. At single fraction doses of 200 to 300 cGy there is overt damage to spermatocytes in adult men and return to pre-irradiation sperm concentrations and germinal cell numbers may take up to 30 months51. Fractionated doses are more toxic to spermatogenesis, and

complete sterilization may occur if the fractionated dose exceeds 100 – 200 cGy. However, in the pre-pubertal state, the impact of radiotherapy is mitigated. In one study of 12 pre-pubertal boys who received 2400 cGy testicular irradiation to treat ALL, it was observed that testosterone levels were normal in all 12 and basal LH was normal in 9 and elevated in 352. Nonetheless, to preserve fertility and Leydig cell function in post-pubertal males, we propose to administer testicular shielding to all males during the single fraction of TBI. This shielding will have no impact on the immunosuppressive effect of the radiotherapy.
There will be no gonadal shielding in female patients.
The effects of radiotherapy on ovarian function and fertility are dose- and age-dependent. However, ovarian doses of less than 400 cGy do not result in permanent ovarian dysfunction and the calculated LD50 of the human oocyte dose is approximately 400 cGy53 54 55. Thus, ovarian shielding to preserve ovarian function will not be necessary for the dose of TBI administered in this investigation; moreover, shielding in this setting could reduce the immunosuppressive effects of TBI if intra-abdominal lymph nodes were inadvertently shielded.

Infusion of fresh mobilized donor peripheral blood stem cells (PBSC)
Target total nucleated cell count (TNC): $\geq 3.5\ 10^8$/kg (actual recipient body weight) and $>3 \times 10^6$ CD34+ cells/kg recipient weight. Institutional procedures should be followed for mobilizing PBSC and collecting via apheresis. Under no circumstances are the PBSC to be irradiated. No in-line leukocyte filter should be used and no medications or fluids should be given through the catheter lumen that is used for infusion of stem cells during the infusion of PBSC. Monitoring immediately prior to, during infusion of PBSC, and thereafter will be according to institutional guidelines. Pre-medication prior to infusion of PBSC will be according to institutional guidelines.

2.7.3.3. HLA-identical Sibling HCT Preparative Regimen C:

TABLE 5: SCHEMA OF CONDITIONING REGIMEN C FOR HLA-ID SIB TRANSPLANTS

Day	Treatment
24 hours prior to 1st dose of Alemtuzumab	Alemtuzumab test dose 3 mg IV once
–22 –21 –20 –19 –18	Alemtuzumab 10 mg IV[1] Alemtuzumab 15 mg IV[1] Alemtuzumab 20 mg IV[1]
–8	Fludarabine 30mg/m^2 IV
–7	Fludarabine 30mg/m^2 IV
–6	Fludarabine 30mg/m^2 IV
–5	Fludarabine 30mg/m^2 IV
–4	Fludarabine 30mg/m^2 IV
–3	Melphalan 140 mg/m^2 IV
–2	Rest
–1	Rest
0	Stem cell infusion
+7	G-CSF 5 µg/kg/day continue until neutrophil engraftment

[1]Alemtuzumab doses may be administered between Days–22 and –18 but are required to be on three consecutive days.

The cytoreductive medications fludarabine and melphalan will be adjusted to the ideal body weight (IBW) in patients weighing > 125% IBW, as above.

Pre-medication

Pre-medication should be commenced 30 minutes prior to each infusion of alemtuzumab and including the test dose and should be continued for at least 48 hours after the last dose of alemtuzumab.

Recommended pre-medication include the following combination of medications:

Diphenhydramine: 1 mg/kg IV or PO q 8 hours (maximum 50 mg/dose)

Acetaminophen: 10-15mg/kg PO q 6 hours (maximum 4 grams qd)

Hydrocortisone: 1-2 mg/kg IV q 6 hours

Meperidine: 0.5 mg/kg IV q 4-6 hours may be used as needed for rigors

Test dose and administration

Alemtuzumab 10 – 15- 20 mg may be administered between Days –22 and –18 but are required to be on three consecutive days. Alemtuzumab will be administered in-patient and the patient may be discharged the day after completion of Alemtuzumab infusions. The test dose of alemtuzumab (3 mg IV) must be administered over 2 hours and not less than 24 hours prior to administration of the first dose. It is recommended that the test dose be administered Monday through Thursday, in the morning, to allow for time for notification of the Study Chair in the case of a severe adverse reaction.

<u>If the test dose is not tolerated:</u>

If the patient has a severe or life threatening adverse reaction to alemtuzumab (e.g., severe hypotension, severe bronchospasm) the adverse event meets expedited reporting requirements (within 24 hours) through the expedited AE reporting system via AdvantageEDC^{SM}. The study chair(s) may also be consulted regarding further doses at the discretion of treating physician.

<u>If the test dose is tolerated:</u>

Alemtuzumab will be diluted in 100cc of 0.9% normal saline (NS) and infused intravenously over a minimum of 6 hours each day for three consecutive days beginning between Days –22 and –18.

Since serious infusion reactions are not uncommon during alemtuzumab infusion, it is strongly recommended that vital signs should be recorded q 15-30 minutes during each infusion of alemtuzumab.

Fludarabine

Fludarabine 30mg/m^2 will be administered IV, on Day –8 to Day –4 (for a total of 5 days) given over a minimum of 30 minutes daily. The infusion can take longer per institutional guidelines.

Preparation, administration, and monitoring will be according to institutional standard practice.

Fludarabine will be adjusted to the ideal body weight (IBW) in children weighing > 125% IBW.

Melphalan

Melphalan 140 mg/m^2 will be given IV on Day –3 given over a minimum of 30 minutes. The infusion can take longer per institutional guidelines.

Melphalan will be adjusted to the ideal body weight (IBW) in children weighing > 125% IBW.

Infusion of Bone Marrow

Under no circumstances is the bone marrow stem cell product to be irradiated. Vital signs should be monitored before beginning the infusion and periodically during administration. Pre-medications and hydration prior to stem cell infusion will be administered per institutional procedure. Diphenhydramine, epinephrine, and hydrocortisone should be available at the bedside for emergency use if infusion reactions occur. Oxygen with nasal prongs for standby use should be present in the room.

2.7.4. GVHD Prophylaxis

GVHD prophylaxis should be given in accordance with the preparative regimen received by the patient.

A. Patients who received a matched unrelated donor transplant or who received an HLA-identical sibling transplant using regimen A (BU/Flu/r-ATG) will receive the GVHD prophylaxis regimen described in Table 2.7.4A. Therapeutic levels of tacrolimus must be maintained at all times (per institutional standard). Those unable to tolerate tacrolimus may receive cyclosporine with therapeutic levels maintained per institutional standard.
B. Patients who received an HLA-identical sibling transplant using regimen B (Alemtuzumab/TBI 300 cGy) will receive the GVHD prophylaxis regimen described in Table 2.7.4.B.
C. Patients who received an HLA-identical sibling transplant using regimen C (Alemtuzumab/Flu/Mel) will receive the GVHD prophylaxis regimen described in Table 2.7.4.C.

Additional details on each GVHD prophylaxis medication is below.

Table 2.7.4.A GVHD prophylaxis	
Day	GVHD Regimen
-3	Tacrolimus at therapeutic doses through day 180, then taper per institutional practice
0	Stem cell infusion
+1	Methotrexate 15 mg/m^2 IV
+3	Methotrexate 10 mg/m^2 IV
+6	Methotrexate 10 mg/m^2 IV
+11	Methotrexate 10 mg/m^2 IV

Table 2.7.4.B GVHD Prophylaxis for Regimen B (HLA-ID Sibling transplantation)	
Day	GVHD Regimen
-1	Sirolimus at therapeutic doses through day 180, then taper per institutional guidelines if donor CD3+ >50%

Table 2.7.4.C GVHD Prophylaxis for Regimen C (HLA-ID sibling transplantation)	
Day	GVHD Regimen
-3	Tacrolimus at therapeutic doses through day 180, then taper per institutional practice
0	Infusion of bone marrow
+1	IV methotrexate 7.5 mg/m^2
+3	IV methotrexate 7.5 mg/m^2
+6	IV methotrexate 7.5 mg/m^2

2.7.4.1. Calcineurin Inhibitor

Tacrolimus will be administered beginning on Day –3 and doses will be adjusted to maintain appropriate levels according to institutional guidelines. Tacrolimus can be administered by continuous or intermittent infusion per institutional guidelines. Dose adjustments will be made based on toxicity and blood levels. Tacrolimus will be converted to an oral form, preferably microemulsion, at 2-3x the IV dose when oral medications are tolerated. Tacrolimus dosing will be monitored and altered as clinically appropriate (per institutional standard). Patients will receive tacrolimus until day +180 and tapered thereafter in the absence of GVHD. A suggested taper in the absence of GVHD is 10% per week. In case of unstable mixed donor chimerism or GVHD, the duration of tacrolimus alone or in combination with additional immunosuppressive agents may be modified at investigator's discretion/institutional guidelines as dictated by patient's condition. A similar schedule will apply for those receiving cyclosporine. Please see section 3.3.7.1 about PRES prevention. If PRES occurs in a study subject, administration of the calcineurin inhibitor

should be suspended until there is clinical stabilization. In addition, if an episode of PRES occurs beyond the typical risk period for VOD/SOS, the calcineurin inhibitor may be replaced by sirolimus. Administering sirolimus and tacrolimus together is not recommended.

2.7.4.2. Methotrexate

Methotrexate will be given IV at a dosage of 15mg/m^2 on day +1 and 10mg/m^2 on days +3, +6, and +11. The day +1 dose of methotrexate will not be administered until 24 hours following completion of the marrow infusion. Mucositis is treated symptomatically. Methotrexate doses used in the setting of marrow transplantation are not sufficient to cause liver disease. In the absence of renal impairment, third space fluid collection (ascites, pleural effusion, etc.), or severe mucositis, all planned doses of methotrexate should be administered. The attending transplant physician should assess patient prior to delivery of each dose and decide if any methotrexate dose adjustments are necessary. Guidelines for methotrexate dose adjustments are provided in Appendix E.

2.7.4.3. Sirolimus:

Sirolimus for participants ≥18.00 years old: A one-time sirolimus loading dose, 6 mg PO, is given on Day -1. Sirolimus is then continued at a maintenance dose (start 2 mg PO QD) with dose adjustments to maintain a trough of 10-15 ng/mL for the first 3-4 months and ~10 ng/ml for the remainder of year 1. Sirolimus may be tapered at end of year 1 if donor T cell chimerism is >50% in the absence of GVHD.

Sirolimus for participants <18.00 years old: Sirolimus dosing is based on actual body weight; however, an adjusted body weight may be used if the actual weight is > 50% greater than IBW. A one-time sirolimus loading dose, 3 mg/m2 PO with the dose not to exceed 6 mg, is given on Day -1. Sirolimus is then continued at a maintenance dose (start 1 mg/m2 PO QD maximum 2 mg QD) with dose adjustments to maintain a trough of 10-15 ng/mL for the first 3-4 months and ~10 ng/ml for the remainder of year 1. Sirolimus may be tapered at end of year 1 if donor T cell chimerism is >50% in the absence of GVHD.

2.7.5. Supportive Care

Institutional practice guidelines should be followed after transplantation for nutritional support, treatment of infections, blood products, and treatment for acute or chronic GVHD. Institutional practice guidelines should be followed regarding determination of caregiver status during and after transplantation.

Additional supportive care guidelines are recommended below. The treating investigator or appropriate research team designee may contact the Emmes protocol coordinator with questions (i.e. treatment plans for mixed chimerism).

Treatment of a transplant-related complication such as GVHD, interstitial pneumonitis, veno-occlusive disease, or a complication that is NOT an endpoint for the trial is at the discretion of the treating physician or institutional standard.

Any consideration of enrollment on a clinical trial for non-treatment related purposes (i.e. addition of an immunosuppressive agent for GVHD prophylaxis or to facilitate engraftment) requires approval from the Protocol Chairs/Protocol Officer. Please contact Emmes protocol coordinator with any inquiries.

2.7.5.1. Venous Access

Recipients will have appropriate long-term central venous access placed, per institutional standard practice, prior to beginning the conditioning regimen. The placement of a double lumen tunneled catheter is recommended.

2.7.5.2. Blood Products

The hemoglobin level must be maintained between 9.0 and 11.0 g/dL and platelet count > 50,000/mL after transplantation to minimize the risk of neurological adverse events. Irradiated blood products should be administered universally, and cytomegalovirus (CMV) negative or leuko-filtered blood products are recommended for CMV sero-negative recipients. In those patients who do not receive chronic RBC transfusions or who have a Hgb S fraction > 30%, a partial exchange transfusion will be performed to reduce the hemoglobin (Hgb) S to ≤ 30% before commencing the conditioning regimen. The Hgb and % Hgb S should be re-checked 4 hours after the exchange transfusion.

2.7.5.3. Hypertension

Hypertension should be strictly controlled to prevent central nervous system (CNS) toxicity. Blood pressure should be monitored closely and both systolic and diastolic hypertension should be treated promptly to maintain blood pressure at the patient's pre-transplant baseline. Explicit orders must be written to intervene if systolic or diastolic blood pressure exceeds 10% over baseline. Refer to section 3.3.7 for additional information.

2.7.5.4. Treatment of Fever/Infections

Patients should be monitored closely for clinical manifestations of infection and treated per institutional guidelines with broad-spectrum antibacterial, antiviral, and antifungal agents. Early and severe immunosuppression of the patient necessitates prompt and adequate treatment of infections to prevent systemic spread. Patients are especially susceptible to bacterial and viral infections in the early post-transplant period.

2.7.5.5. Infection Surveillance and Prophylaxis

Please use institutional guidelines for infection surveillance and prophylaxis. Where institutional guidelines do not exist, the following **guidelines** are recommended.

Antiviral Prophylaxis
Acyclovir prophylaxis is recommended after transplantation until immune reconstitution in patients who are sero-positive for Herpes Simplex or Varicella Zoster Virus. If unable to tolerate oral medications, IV therapy will be necessary.

Pneumocystis Prophylaxis
Trimethoprim-sulfamethoxazole or an equivalent drug should be administered beginning after neutrophil recovery and continued until there is full immune reconstitution.

Fungal Prophylaxis
Due to the level of immune suppression, anti-fungal prophylaxis for candida and invasive mold infection is recommended with agents such as itraconazole, voriconazole, or posaconazole until Day 180. Frequent monitoring of tacrolimus levels will be necessary during azole therapy to avoid toxic drug levels.

Bacterial Prophylaxis
Prophylaxis against bacterial infections is generally not recommended. However, antibiotic prophylaxis according to institutional guidelines is acceptable.

Cytomegalovirus (CMV)
It is recommended that recipients be tested weekly using the polymerase chain reaction (PCR) method beginning a week after commencing conditioning regimen and until Day 100. Antiviral therapy for CMV reactivation should commence preemptively if CMV testing reveals a high or rising viral load. Treatment of CMV should be undertaken per institutional guidelines. If CMV reactivation occurs at or before engraftment, foscarnet may be considered as an alternative to ganciclovir mitigate marrow suppression.

Adenovirus
It is recommended that testing for adenovirus infection in the blood by PCR method is recommended in the event of symptoms suspicious for infection such as diarrhea, hepatic dysfunction, or respiratory symptoms. If an active systemic infection is diagnosed, therapy should be instituted with cidofovir or other active agents per institution guidelines.

Epstein-Barr Virus (EBV)
It is recommended that Patients will have EBV DNA quantitative PCR testing on peripheral blood every two weeks from Day 14 to Day 100. In the event of persistent EBV virema or signs/symptoms consistent with EBV-related Post-transplant lymphoproliferative disease (PTLD, adenopathy, fever, etc.) therapy with rituximab is recommended.

2.7.5.6. Intravenous Immune Globulin

Intravenous immune globulin may be administered according to institutional practice guidelines.

2.8. Graft Failure

Graft failure may occur following HCT in patients with sickle cell disease and is usually associated with autologous reconstitution of the bone marrow with host hematopoiesis. Both in related and unrelated donor settings the data suggest most patients experience autologous reconstitution of the bone marrow with host hematopoiesis. It is associated with a steady decline in donor chimerism, increasing representation of hemoglobin S (in the absence of ongoing RBC transfusion therapy), and clinical manifestations of sickle cell disease. The management of graft failure is at the

discretion of the treating physician / transplant center. Autologous bone marrow harvest is not recommended. Most SCD patients experience autologous reconstitution, and second transplantation from a haplo-identical relative has been reported as an acceptable treatment.

Please contact the protocol chairs with any questions on the management of patients with declining donor chimerism.

2.9. Toxicities of Hematopoietic Stem Cell Transplantation

2.9.1. Toxicities Related to the Preparative Regimen

2.9.1.1. Pancytopenia

The administration of fludarabine and busulfan is expected to produce pancytopenia with absolute neutrophil count (ANC) < 500/μL, hemoglobin < 7-8 g/dL and platelet < 50,000/μL for as long as several weeks in most patients. Thus, these patients will require RBC and platelet transfusions until hematological recovery after BMT. In addition, many patients will develop fever and approximately 30% will develop a documented infection during the period of neutropenia. Complications related to pancytopenia may be life threatening or fatal.

2.9.1.2. Chemotherapy-Specific Toxicities

The clinical management of chemotherapy-specific toxicities will be at the discretion of the treating physician and institutional guideline/protocols.

Busulfan
Administration can cause decreased blood counts, nausea, vomiting, diarrhea, oral ulcers, decreased immunity, sterility, interstitial pneumonitis, lung fibrosis, allergic reactions, and rarely seizures (with very high doses). We recommend counseling patients for infertility including gamete cryopreservation in accordance with institutional practice.

Fludarabine
Administration can cause hemolytic anemia, neutropenia or thrombocytopenia, low blood counts secondary to bone marrow suppression, nausea, vomiting, diarrhea, stomatitis, skin rash, pneumonitis, edema, fever, chills, fatigue, blurred vision, peripheral neuropathy, confusion, coma, decreased immunity and rarely encephalopathy.

Rabbit Anti-Thymocyte Globulin
Thymoglobulin (r-ATG) is a purified, pasteurized, gamma immune globulin obtained by immunization of rabbits with human thymocytes, and thus contains cytotoxic antibodies directed against antigens expressed on human T-lymphocytes. Infusion toxicities include leukopenia, malaise, and post-transplant lymphoproliferative disease (PTLD). Chills and fever commonly occur in patients receiving ATG. Minor toxicities can usually be managed by symptomatic treatment and temporary slowing of the infusion. Pruritus and erythema occasionally develop. These symptoms are generally controlled with diphenhydramine. Respiratory distress and hypotension may be signs of anaphylaxis. In such cases, the infusion should be discontinued. If reaction persists, diphenhydramine, epinephrine, or hydrocortisone or a combination should be

administered. Serum sickness syndrome may present with fever, arthralgias, and rash. Symptoms usually occur with some delay after initial ATG administration. Treatment is with steroids. Other toxicities include pain in chest, flank, or back which may be a sign of anaphylaxis or hemolysis. Infusion should be discontinued if anaphylaxis is suspected.

Alemtuzumab
Alemtuzumab side effects include:

- Cardiovascular: dysrythmias (most commonly tachycardia), hypotension, hypertension, cardiomyopathy, congestive heart failure
- Dermatologic: rash, itching
- Endocrine: Thyroid disorders
- Gastrointestinal: anorexia, nausea, vomiting, abdominal pain, diarrhea, acute acalculous cholecystitis
- Hematologic: anemia, thrombocytopenia, leukopenia
- Musculoskeletal: myalgia, arthralgia muscle weakness, muscle spasms
- Neurologic: headache, dizziness, insomnia, anxiety, tremor, progressive multifocal leukoencephalopathy
- Miscellaneous: infection, infusion reaction, allergic reaction, cough, sweating, lower extremity swelling

Melphalan
Melphalan side effects include:

- Cardiac and vascular: edema, heart failure, vasculitis
- Gastrointestinal: mucositis, nausea, vomiting, diarrhea General: fatigue
- Hematologic: anemia, thrombocytopenia, neutropenia
- Hepatic: abnormal liver function tests, hepatitis
- Pulmonary: shortness of breath, pulmonary fibrosis
- Renal: renal impairment
- Miscellaneous: allergic reaction including anaphylaxis, secondary malignancy

Total Body Irradiation
Total body irradiation will be administered (300 cGy) in Regimen B. This dose is a fraction of the irradiation delivered in a myeloablative conditioning regimen, thus modulated toxicity is anticipated. Nonetheless, irradiation can cause short-term and long-term toxicities, particularly in children. The long-term toxicities include a risk of malignancy secondary to the exposure and a risk of infertility.

Low dose (less than 400cGy) Total Body Irradiation side effects include:

- Cutaneous: erythema, hyperpigmentation, alopecia
- Gastrointestinal: nausea, vomiting, diarrhea, parotitis, mucositis, abdominal cramping
- General: fever, fatigue
- Genitourinary: gonadal impairment
- Hepatic: hepatic sinusoidal obstruction syndrome

- Hematologic: myelosuppression, anemia, thrombocytopenia
- Pulmonary: interstitial pneumonitis
- Renal: nephropathy
- Miscellaneous: infection, short stature, vertebral deformities, cataracts, secondary malignancy, hormonal impairment

2.9.2. Toxicities Related to Hematopoietic Stem Cell Infusion

Infusion of allogeneic BM cells can result in shortness of breath, fever, hemolysis with renal dysfunction and back pain, or anaphylaxis. To reduce the risk of reactions to product infusion, patients will be hydrated before and after administration of allogeneic BM, and will be monitored closely before, during, and after infusion.

2.9.3. Toxicities Related to GVHD Prophylaxis

2.9.3.1. Tacrolimus

Tacrolimus (or cyclosporine) may cause nephrotoxicity, seizures, hypertension, hirsutism, thrombotic microangiopathy, electrolyte imbalances, paresthesias/neuropathy, gingival hyperplasia, transient-blindness, and hepatic dysfunction.

2.9.3.2. Methotrexate

Myelosuppression and stomatitis are the most common dose-limiting side effects. At the dosage used in this study, no other significant side effects are anticipated.

2.9.3.3. Sirolimis

Sirolimus side effects include:

- Cardiovascular: hypertension, tachycardia, venous thromboembolism (which can cause pulmonary embolism or deep vein thrombosis)
- Cutaneous: itching, rash, acne, exfoliative dermatitis, impaired wound healing
- Endocrine and metabolic: hyperglycemia, hypokalemia, hypertriglyceridemia, hypercholesterolemia
- Gastrointestinal: constipation, diarrhea, nausea, abdominal pain, mouth sores
- Hematologic: anemia, thrombocytopenia, leukopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, transplant associated thrombotic microangiopathy
- Musculoskeletal: bone necrosis, myalgia, arthralgia
- Neurologic: headache dizziness
- Pulmonary: interstitial lung disease
- Renal: proteinuria, increased creatinine, edema
- Miscellaneous: infection, allergic reaction, epistaxis, secondary malignancy

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is to compare the difference in the observed proportion of patients surviving at 2 years post-biologic assignment between the donor and the no donor arms.

3.2. Secondary Endpoints

In addition to comparing the observed proportion of patients surviving at 2 years post-biologic assignment using the ITT approach, we will also compare the difference in the observed proportion of patients surviving at 2 years post-biologic assignment between groups by treatment received (i.e., as treated). The "as treated" approach will compare OS between patients who received a transplant to patients who received standard of care. Secondary endpoints will examine record-based assessment of sickle-related events using the system identified by Elmariah and colleagues (pulmonary hypertension, cerebrovascular events, renal function, avascular necrosis of hip/shoulder, and leg ulcers)[19]; cardiac function, pulmonary function, functional assessment by administration of 6MWD test, HRQoL and mean pain intensity over a 28-day period. Additionally, HRQoL, 28-day e-pain diary, and the 6MWD test will also be measured at 1-year. We will examine changes between baseline, at 1-year and at 2-years between participants on the donor and no donor arms. Additionally, changes within assigned group will also be reported. Extended follow up for survival status is planned years 3 through 10 from biologic assignment.

3.2.1. Occurrence of Sickle-Related Events

Elmariah and colleagues have created a severity score on five parameters.[19] We will track occurrence of these events over two years and compare the proportion of patients experiencing each component within two years. The events are pulmonary (pulmonary hypertension as measured by TRV or O_2 saturation < 92%); cerebrovascular (stroke, transient ischemic attack, or seizure); renal (proteinuria or creatinine >1); avascular necrosis of the hip or shoulder; and leg ulcers. The prevalence of these events will be extracted from the histories of subjects at study entry, noting that these events can constitute eligibility criteria for the study. We will also examine and describe the occurrence of these events on study (i.e., for the period between biologic assignment and 2-years).

3.2.2. HRQoL

We will assess health related quality of life using the PROMIS-57 instrument and the stiffness impact short form from ASCQ-Me for all participants. The PROMIS-57 and ASCQ-Me Stiffness Scale are available in Spanish and English. Participants who do not speak Spanish or English will not complete the HRQoL surveys.

We will focus on changes from baseline, assuming, on average, no change in the no donor group and improvement in the donor group. The results on these instruments are scaled to a mean of 50 and a standard deviation of 10, with the directionality of the interpretation reflecting the wording of the domain (high scores indicate worse sleep disturbance, but better physical function). We have assumed no correlation to maximize the variability of the estimate of change. PROMIS-57 and ASCQ-Me Stiffness Scale will be administered within the last 3 weeks of the electronic pain diary as PROMIS-57 and ASCQ-Me Stiffness Scale capture data for the last 7 days prior to administration. This will permit a direct comparison of these two approaches to assessing pain. While our primary endpoint is the change between the baseline and two-year assessments, we will also examine HRQoL at one year in order to better understand the trajectory of changes, should they occur, during the two-year follow up period.

3.2.3. Mean Pain Intensity

Based on estimates of daily pain in adults with SCD[43], we anticipate that patients in the no donor arm will report pain with a mean pain intensity of 3.9 on a scale of 10 at baseline. We expect that this will be unchanged at follow-up. We anticipate that baseline pain assessments will be similar in the donor cohort but that these patients will demonstrate a clinically significant decline in mean pain intensity to a level of 1.3 units on a scale of 10 two-years later. While our primary endpoint is the change between the baseline and two-year assessments, we will also examine pain at one year, in order to better understand the trajectory of changes during the two year follow up period.

Pain data will be recorded over time using the pain diary. The pain diary will be utilized in assessing and determining the burden of pain pre-transplant, post-transplant and with standard of care. The diary will be administered at baseline, 1 year and 2 years for 28 days at each time point. The pain diary enables real time data capture which allows us to capture pain metrics in real time and in the participant's natural environment. Additionally, we will be able to compare diary data to NIH-PROMIS measures of pain.

The pain diary electronic application is only available for English speaking participants. Non-English speaking participants will not complete the pain diary. Additionally, the pain diary is only available in electronic format. Participants who do not have access to an internet enabled device will not complete the pain diary. Please contact the BMT CTN 1503 Pain Diary Coordinator in the event a study participant will not be completing the pain diary.

3.2.4. Exercise Capacity

We will use the 6MWD, testing under standardized procedures, to assess exercise capacity (see guidelines as outlined in the BMT CTN 1503 Manual of Procedures). This endpoint will measure absolute change from baseline with increased distance identified as positive change. We anticipate an improvement of at least 50 m for subjects in the donor arm on average, compared to subjects in the no donor arm, in whom we anticipate no improvement. While our primary endpoint is the change between the baseline and two-year assessments, we will also examine 6MWD test at one year in order to better understand the trajectory of changes during the two-year follow up period.

3.2.5. Cardiac Function

Tricuspid regurgitant velocity (TRJV) is a marker for the severity and progression of SCD. While our primary endpoint is the change between the baseline and two-year assessments, we will also examine TRJV at one year in order to better understand the trajectory of changes during the two-year follow up period. All cardiac function evaluations obtained and/or reported for study purposes must include adequate documentation of TRJV. It is recommended that cardiac evaluations are obtained at the same institution to minimize variability.

3.2.6. Pulmonary Function

There is a growing body of evidence to indicate that the pulmonary toxicity of SCD is progressive.[44,45] We anticipate changes in Forced Expiratory Volume 1 second (FEV1) of 49 cc/year[45] for participants on the no donor arm, compared to half that rate in the donor arm, based on Field's observation of a general population decrease of 20 to 26 cc/year.[44,45] We will also assess the proportion of participants on the treatment arms in whom we find evidence of restrictive lung disease, defined as total lung capacity (TLC) below the 5th percentile adjusted for age, gender, race, and height. The complete pulmonary function test will include FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation. It is recommended that pulmonary evaluations are obtained at the same institution to minimize variability.

3.2.7. Renal Function

Guasch reported that 61% of SCD subjects between 18 to 30 years of age had either micro- or macroalbuminuria based on a single measurement.[46] We will assess renal function through measurements of albuminuria (urine-albumin creatinine ratio) and serum creatinine.

3.3. Secondary Endpoints for Patients Assigned to the Donor Arm

3.3.1. Neutrophil and Platelet Recovery

Absolute Neutrophil Count (ANC) recovery: defined as the first day of 3 measurements on different days when the patient has an absolute neutrophil count of ≥ 500/μL after conditioning.

Platelet Recovery: defined as the first day of a minimum of 3 measurements on different days that the patient has achieved a platelet count > 50,000/μL AND did not receive a platelet transfusion in the previous 7 days. Platelet data will be collected via the CIBMTR.

Primary Graft Failure: defined as never achieving ANC ≥ 500/μL or never achieving ≥ 5% donor whole blood or myeloid chimerism (myeloid is preferable) assessed by bone marrow or peripheral blood chimerism assays by day +42 post-transplant. Second infusion of hematopoietic cells is also considered indicative of primary graft failure by day +42 post-transplant.

Secondary Graft Failure: defined as < 5% donor whole blood or myeloid chimerism (myeloid is preferable) in peripheral blood or bone marrow beyond day +42 post-transplant in patients with prior documentation of hematopoietic recovery with ≥ 5% donor cells by day +42 post-transplant.

Second infusion of hematopoietic cells is also considered indicative of secondary graft failure.

3.3.2. Lineage Specific Chimerism

Chimerism studies are recommended on whole blood, CD3 sorted mononuclear cells as well CD15, or CD33 sorted mononuclear cells as per institutional practice. Erythroid chimerism assays will be performed at the Blood Center of Wisconsin (See BMT CTN 1503 MOP for more info). The assay involves reverse transcription of total RNA followed by digital droplet PCR with fluorescently-labeled hydrolysis probes specific for the HBB gene HbA and HbS transcripts. The percent chimerism is calculated taking into account the genotype of the donor (AA or AS). The results of these assays will not be used for clinical care.

3.3.3. Grade II-IV and Grade III-IV Acute GVHD

Acute GVHD will be graded according to the BMT CTN Manual of Operating Procedures (MOP). The time of onset of acute GVHD grades II-IV and III-IV will be recorded as well as the maximum grade achieved (including the date of maximum grade).

3.3.4. Chronic GVHD

Data will be collected according to the recommendations of the NIH Consensus Conference. Eight organs will be scored on a 0-3 scale to reflect degree of chronic GVHD involvement. Liver and pulmonary function test results and use of systemic therapy for treatment of chronic GVHD will also be recorded. These data will allow calculation of the NIH global severity scores of mild, moderate, and severe chronic GVHD, which has been associated with transplant related mortality and overall survival.

3.3.5. Idiopathic Pneumonia Syndrome (IPS)

Evidence of widespread alveolar injury in the absence of documented active lower respiratory tract infection:

a. Radiographic evidence of bilateral, multi-lobar infiltrates (by chest x-ray or CT scan), AND

b. Evidence for abnormal respiratory physiology, based upon oxygen saturation (SpO2) < 93% on room air, or the need for supplemental oxygen to maintain oxygen saturation ≥ 93%.

3.3.6. Veno-Occlusive Disease (VOD)

Veno-occlusive disease (VOD) is diagnosed by the presence of two or more of the following with no other identifiable cause for liver disease:

a. Jaundice (direct bilirubin > 2 mg/dL or > 34 μmol/L)

b. Hepatomegaly with right upper quadrant pain

c. Ascites and/or weight gain (> 5% over baseline)

3.3.7. Central Nervous System (CNS) Toxicity

CNS toxicity will be defined as seizures, CNS hemorrhage, or posterior reversible leukoencephalopathy syndrome (PRES), which is defined as an increased diffusion coefficient in areas of T2 hyper intensities on diffusion-weighted imaging in the context of clinical symptoms or physical findings including headache, seizures, visual disturbances, and/or altered level of consciousness. PRES results from endothelial injury related to abrupt blood pressure changes or direct effects of cytokines on the endothelium, which leads to the breakdown of the blood–brain barrier and subsequent brain edema. With early diagnosis and appropriate management, PRES is reversible, both radiographically and clinically, and generally has a favorable prognosis. PRES commonly occurs in the first month following HCT although patients remain at risk during the course of immune suppression therapy.

Measures for prevention of PRES include extended duration of anticonvulsant prophylaxis, intensified antihypertensive management (including mean arterial pressure if indicated), and aggressive platelet support. Blood pressure values must be compared against published normal values appropriate for age and race (African Americans have normal blood pressure adjusted for age compared to Caucasians). Blood pressure values in SCD patients are lower compared to population norms adjusted for age and race.

3.3.7.1. Prevention of Posterior Reversible Leukoencepaholpathy Syndrome (PRES): Recommended Guidelines

In addition to the recommended guidelines below, refer to Appendix G for additional guidelines regarding the prevention and/or management of PRES.

- **Control of Blood Pressure**

  Blood pressure in patients with SCD has been reported to be lower than published standards for age, sex, and race-matched controls. Pressures above the 90th percentile for HbSS may overlap levels considered normal in non-SCD patients. Blood pressure (BP) may be elevated with fluid infusions or use of medications such as corticosteroids or CNIs. Supportive care orders must indicate the importance of keeping BP within 10% above the median for age for HbSS patients as described by Pegelow et al (Table 5)[47] or the baseline BP for the patient, whichever is lower. Mean arterial pressure (MAP) should be maintained at < 70mmHg. Close monitoring and aggressive management with anti-hypertensive agents will be required to prevent PRES.

Table 5. Median and 90th percentiles of systolic (SYS BP) and diastolic (DIA BP) blood pressure for sickle cell anemia subjects by age (years) in the Cooperative Study of Sickle Cell Disease

Age		2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17	18-24	25-34	35-44
Female N		257	97	72	68	57	71	89	81	227	199	66
SYS BP	Median	90	95	96	104	106	110	110	110	110	110	110
	90th	100	110	110	110	110	118	120	122	122	125	130

Age		2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17	18-24	25-34	35-44
DIA BP	Median	52	60	60	60	60	62	70	70	64	68	70
	90th	62	70	70	70	74	74	80	78	80	80	84
Male N		276	111	78	66	75	61	75	53	179	166	41
SYS BP	Median	90	95	100	100	100	110	108	112	112	114	110
	90th	104	110	108	116	112	120	120	128	130	130	132
DIA BP	Median	54	60	60	60	60	64	64	70	68	70	70
	90th	66	68	68	70	70	72	78	80	80	80	84

- **Maintenance of Adequate Platelet Count**

  Thrombocytopenia and coagulopathy may be associated with increased risk of PRES-related intra-cranial hemorrhage. It is therefore recommended to keep platelet count > 50,000.

- **Maintenance of Euvolemic State**

  Large fluid shifts should be avoided. Close attention must be paid to fluid balance since fluid overload with weight gain associated with increased blood pressure and consequently, increased risk of PRES.

- **Maintenance of Adequate Level of Serum Magnesium**

  The association between hypomagnesemia and cyclosporine toxicity was first observed during the initial clinical trials of the drug for GVHD prophylaxis.[48,49] Magnesium sulphate is considered the drug of choice in the treatment of PRES associated with eclampsia. It is therefore recommended that patients receive magnesium supplementation in order maintain magnesium level at 1.8mg/dL Maintenance of mild hypermagnesemia with serum magnesium 2-3mg/dL may be advisable, but may be difficult to achieve.

- **Seizure Prophylaxis**

  Seizure prophylaxis should be commenced prior to conditioning therapy (therapeutic level prior to initiation of conditioning) and continued at least until immunosuppression is withdrawn.

- **Platelets**

  Platelet counts should be monitored frequently after starting conditioning therapy, and platelet transfusions should be administered to keep counts $\geq 50 \times 10^9$/L

3.3.7.2. Infection

Significant infections will be recorded including but not limited to bacterial or fungal sepsis, CMV reactivation with/without clinical disease, adenovirus infection, EBV PTLD, other significant viral reactivations or community-acquired viral infections, and invasive mold infections. The incidence

of definite and probable viral, fungal, and bacterial infections will be tabulated for each intervention arm. The cumulative incidence of CMV reactivation in the first 100 days post HSCT will be described. All Grade 2 and 3 infections will be reported according to the BMT CTN MOP.

3.3.7.3. Long-Term Follow Up

Survival status of all participants will be collected annually, years 3 through 10. The probability of survival annually beginning year 3 will be calculated for each treatment arm.

CHAPTER 4

4. PATIENT REGISTRATION, ENROLLMENT AND EVALUATIONS

4.1. Screening and Enrollment Procedures

Participants are identified and recruited by the site investigator, an SCD physician. If initial consultation with the potential participant confirms interest in the proposed phase II trial, the patient is referred to a HCT physician for further consultation. This consultation includes a detailed review of the trial design including the concept of biologic assignment to treatment arms based on donor availability, the anticipated benefits and complications of both treatment arms, importance of adherence to assigned treatment arm, and compliance including availability at 1- and 2-years later for trial assessments. The order of events for patient enrollment is as follows:

1. Interested participants will sign a study informed consent form which will include consent for screening assessments, HLA typing, and all non-transplant related follow up. Following local assessment of eligibility criteria, the potential participant will be enrolled into Segment 0 in AdvantageEDC, a web-based data collection system. The time period from initial consent for eligibility screening to biological assignment is defined as Segment 0 of the protocol.

2. Following Segment 0 enrollment, as applicable, the Eligibility Review Committee (ERC) will independently review the clinical eligibility data regarding disease severity to confirm or deny eligibility according to procedures outlined in Appendix G. All participants enrolled under the neurologic deficit SCD severity criteria will be reviewed. For participants who do not require ERC review, confirmation of eligibility will be confirmed upon enrollment into Segment 0. If the participant is not confirmed to be clinically eligible then he/she is off-study and no further follow up is required. Criteria for clinical eligibility are described in Section 2.3.1.

3. If clinical eligibility is confirmed, the site is notified and will proceed with HLA typing and donor search. All patients will be assigned to the no donor arm upon confirmation of eligibility. HLA typing is performed on the participant and full siblings (if applicable) to determine donor status. While it is acceptable to wait to initiate the search for an adult unrelated donor after establishing an HLA-matched sibling is not available, it is recommended that the related and unrelated donor searches occur simultaneously to avoid delays in identifying a suitable donor. Any participant for whom a suitable sibling or unrelated donor as defined in section 2.5.1 is not confirmed $\leq$ 180 days from confirmation of eligibility will remain in the no donor/standard of care arm.

4. Following a donor search, biologic assignment is determined $\leq$ 180 days from the date of confirmation of eligibility; those with an HLA-matched donor meeting requirements in section 2.5.1 are assigned to the donor arm, and those without a donor are assigned to the no donor/standard of care arm.

a. For donor arm patients, the date of biologic assignment is the date a suitable donor (defined as meeting all criteria outlined in section 2.5.1 of the protocol) is confirmed. Donor arm participants should be approached with the transplant consent as soon as possible after identification of a suitable donor. Initiation of transplant conditioning for those assigned to the donor arm should occur ≤ 30 days after signature on the transplant consent. Workup is a continuum rather than an interrupted process.
b. For no donor arm patients, the date of biologic assignment is the date the site becomes aware that the patient does not have a suitable related or unrelated donor.

5. Once the participant has been biologically assigned, they will be enrolled into Segment A in AdvantageEDC. The time period from biological assignment to the end of the study is defined as Segment A of the protocol. It is recommended that enrollment in Segment A occur ≤ 30 days after biologic assignment. For donor arm patients, consent for transplant should be obtained prior to Segment A enrollment.

4.2. Patient Follow up and Study Assessments

4.2.1. Follow-up Schedule

The Follow-up Schedule for scheduled 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 Data Management Handbook and User's Guide.

TABLE 4.2.1: FOLLOW-UP SCHEDULE

Study Visit	Target Day
Pre-Enrollment	
Pre-Enrollment*	≤ 1 year prior to Segment 0 Enrollment
	≤ 3 months prior to Segment 0 Enrollment
	≤ 30 days prior to Segment 0 Enrollment
Screening Segment	
PBA	≤ 30 days following confirmation of Eligibility; prior to biologic assignment
Pre-Transplant Visits for Donor Arm Participants Only	
Pre-conditioning**	≤ 90 days prior to initiation of transplant conditioning
Pre-conditioning	≤ 30 days prior to initiation of transplant conditioning
Pre-conditioning	Within 7-14 days prior to initiation of transplant conditioning

Post-Transplant Visits for Donor Arm Participants Only	
Week 1	7 ± 3 days
Week 2	14 ± 3 days
Week 3	21 ± 3 days
Week 4	28 ± 3 days
Week 5	35 ± 3 days
Week 6	42 ± 3 days
Week 7	49 ± 3 days
Week 8	56 ± 3 days
Week 9	63 ± 3 days
Week 10	70 ± 3 days
Week 11	77 ± 3 days
Week 12	84 ± 3 days
Week 13	91 ± 3 days
Day 100	100 ± 3 days
Day 180	180 ± 14 days
Day 365	365 ± 14 days
Day 730	730 ± 14 days
Post-Biologic Assignment Visits	
Day 0 post-BA	0 ± 14 days
Day 100 post-BA	100 ± 14days
Day 180 post-BA	180 ± 14 days
Day 270 post-BA	270 ± 14 days
Day 365 post-BA	365 ± 14 days
Day 450 post-BA	450 ± 14 days
Day 540 post-BA	540 ± 14 days
Day 630 post-BA	630 ± 14 days
Day 730 post-BA	730 ± 14 days

* Refer to section 4.2.2 for the required timing of each pre-enrollment assessment
**Pre-conditioning visit ≤ 90 days prior to initiation of transplant conditioning only required in the event a liver biopsy is needed (see section 4.2.5.1 for additional information)

4.2.2. Required Assessments PRIOR to enrollment in Segment 0:

Prior to enrollment in Segment 0, patients must meet the clinical eligibility for referral to an HCT physician as described in section 2.3.1. Screening assessments should be completed after obtaining consent for eligibility screening with the exception of the cardiac and pulmonary assessments which can be a historical assessment performed ≤ 1-year prior to enrollment. These assessments are summarized below and in Table 6.

The following assessments must be completed for all participants ≤ 1-year prior to enrollment into Segment 0:

- Cardiac: LVEF or LV shortening fraction by echocardiogram or by MUGA, evaluation must include documentation of tricuspid valve jet velocity (TRJV). Refer to Section 3.2.5.
- Pulmonary: The complete pulmonary function test will include FVC, FEV1, FEV1/FVC, DLCO, and oxygen saturation.

The following assessments must be completed for all participants ≤ 3 months prior to enrollment into Segment 0 unless otherwise noted below:

- History and physical examination, height and weight. The baseline history should reference participant's sickle cell genotype and all relevant past medical history in relation to his/her severe SCD.
- Karnofsky/Lansky performance score
- Renal: serum creatinine and one of the following:
    - creatinine clearance calculated using the Cockcroft-Gault calculator,
    - creatinine clearance by 24 hour urine (preferred), OR
    - Radionuclide GFR including assessment for albumin
- Hepatic: direct bilirubin, alkaline phosphatase, ALT, and AST
- CBC with differential
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Infectious disease testing per institutional standards. Infectious disease testing must include HIV.
- Pregnancy test per institutional practices (serum or urine) for females of child-bearing potential (required ≤ 30 days prior to enrollment in Segment 0).
- Sickle Cell Disease Genotyping: Assessment of SCD genotype can be done at any time but must be known *prior* to enrollment in segment 0.

4.2.3. Eligibility Review Committee Approval & Initiation of HLA Typing

As detailed in Section 4.1, potential BMT CTN 1503 participants may be screened and approved for protocol eligibility by a three-member review panel comprised of experts in sickle cell disease and transplantation (Appendix G) following Segment 0 enrollment into AdvantageEDC. All participants enrolled under the neurologic deficit SCD severity criteria will be reviewed, and participants enrolled under the other SCD severity criteria will be reviewed as necessary. For participants who do not undergo ERC review, confirmation of eligibility will be confirmed upon enrollment into Segment 0. Potential participants are reviewed by the ERC after signing of the study informed consent and completion of screetning eligibility evaluations as defined in section 4.2.2, and *prior* to initiation of HLA typing and subsequent biologic assignment. The ERC's adjudication decision is based on data contained in the patient registration (Segment 0) form as well as uploaded source documentation establishing protocol eligibility as defined in Section 2.3.1. Additional details regarding the 1503 ERC adjudication process are available in Appendix G.

Initiation of HLA typing and donor search is permitted only after the confirmation of eligibility and notification is received from the DCC in writing. Refer to section 2.5 for further details

regarding HLA typing standards and donor selection criteria. The Protocol Officer or his/her designee will review and confirm all HLA typing for donor-recipient pairs assigned to the Donor Arm of the study.

Additional screening tests prior to transplant for participants on the donor arm are described in section 2.3.2. These tests are not subject to review/adjudication by the ERC.

4.2.4. Required Assessments Prior to Biologic Assignment for ALL Participants

The following assessments are required for all participants after confirmation of eligibility and prior to date of biologic assignment:

- 6 minute walk distance test (6MWD)
- HRQoL: PROMIS-57 and ASCQ-ME Stiffness Scale
- Review and documentation of SCD Events of Special Interest (SCD-EOSI) at baseline. Refer to section 4.3.4.2. for additional details on SCD EOSI and defining a single occurrence of any given SCD-EOSI.
- Review and documentation of compliance with medical treatment
- 28 day pain diary (begins following initiation of donor search and continues for 28 days)
    - Please contact the BMT CTN 1503 Pain Diary Coordinator in the event a study participant will not be completing the pain diary for the duration of the study.
- Assessment for toxicities

4.2.5. Required Assessments Following Biologic Assignment for ALL Participants

The following assessments are required for all participants following biologic assignment. These are also summarized in Table 7.

- History and Physical Examination
- Karnofsky/Lansky performance score
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Renal[1]: serum creatinine and 24 hour urine creatinine clearance; or Radionuclide GFR including assessment for albumin
- Hepatic Function Tests: direct bilirubin, alkaline phosphatase, ALT, and AST
- CBC with differential, electrolytes, and serum creatinine
- Pulmonary function tests[1] FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation.
- Echocardiogram[1] with documentation of TRJV

[1] Any renal, pulmonary, and cardiac assessments that have been performed ≤ 180 days prior to biologic assignment as part of screening do not need be repeated after biologic assignment.

- **OPTIONAL** Research samples to be sent to the CHOA Biorepository[1]:
    - Peripheral Blood collection (31.5mL) (see BMT CTN 1503 MOP for details)
    - Urine Sample (50mL) (see BMT CTN 1503 MOP for details)
- Assessment for toxicities

4.2.5.1. Additional Required Assessments Following Biologic Assignment for Patients Assigned to the Donor Arm:

The following assessments are required for Donor Arm participants following signature of the Transplant consent:

- Cerebral MRA/MRI (≤ 30 days prior to initiation of transplant conditioning). Cerebral MRI images will be uploaded for central MRI review. Refer to the BMT CTN 1503 MOP for details.
    - If there is clinical or radiologic evidence of a recent neurologic event (such as stroke or transient ischemic attack), subjects will be deferred ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation. Please notify DCC when deferring HCT for this or any reason.
- Liver MRI (≤ 90 days prior to initiation of transplant conditioning)[2] for estimation of hepatic iron content for participants who are currently receiving ≥8 packed red blood cell transfusions for ≥1 year or have received ≥20 packed red blood cell transfusions (lifetime cumulative)
    - If hepatic iron content ≥ 7 mg Fe/g, a liver biopsy is required to document absence of absence of cirrhosis, bridging fibrosis[3], and active hepatitis (≤ 90 days prior to initiation of transplant conditioning).
- Pregnancy test (7 - 14 days prior to initiation of transplant conditioning)

4.2.6. Required Assessments for patients assigned to the No-Donor Arm after Segment A enrollment

The follow up assessments noted below are required for all participants assigned to the no-donor arm as outlined below following enrollment in Segment A. Date of biologic assignment is Day 0. The mandatory follow up assessments are also summarized in Table 7.

The following assessments are required at **every 3 months post biological assignment starting at Day 100 and continuing through Day 730:**

- Survival status, history, and physical examination

[1] Collected ≤ 14 days after biologic assignment and prior to the initiation of study arm-specific therapies
[2]May use prior [liver] MRI if done within 6 months prior to initiation of conditioning; otherwise this imaging is required within 90 days prior to initiation of transplant conditioning
[3]The absence of bridging fibrosis will be determined using the histological grading and staging scale as described by Ishak and colleagues (1995) as described in the Manual of Operating Procedures.

- Review and documentation of all interim occurrences of SCD-EOSI. Refer to section 4.3.4.2 for details on SCD EOSI and defining a single occurrence of any given SCD-EOSI.
- Review and documentation of compliance with medical treatment
- Assessment for toxicities

The following additional assessments are required at **Day 100 AND Day 180 post biologic assignment:**

- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.

The following additional assessments are required at **Day 365 post biologic assignment:**

- 6MWD test
- HRQoL: PROMIS-57 and ASCQ-ME Stiffness Scale
- Pain diary over a 28 day period (Year 1: day 337 to 365)
- Pulmonary function tests: FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Echocardiogram with documentation of TRJV.

The following additional assessments are required at **Day 730 post biologic assignment:**

- Karnofsky/Lansky performance score
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Renal: serum creatinine and 24 hour urine creatinine clearance; or Radionuclide GFR including assessment for albumin
- Liver Function Tests: direct bilirubin, alkaline phosphatase, ALT, and AST
- CBC with differential, electrolytes, and serum creatinine
- 6MWD test
- HRQoL: PROMIS-57 and ASCQ-ME Stiffness Scale
- Pain diary over a 28 day period (Year 2: day 702 to 730)
- Pulmonary function tests: FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation
- Echocardiogram with documentation of TRJV
- 6MWD test
- **OPTIONAL** Research samples to be sent to the CHOA Biorepository:
    - Peripheral Blood collection (31.5mL) (see BMT CTN 1503 MOP for details)
    - Urine Sample (50mL) (see BMT CTN 1503 MOP for details)

4.2.7. Required Assessments for patients assigned to the Donor Arm

The follow up assessments noted below are required for all participants assigned to the donor arm following enrollment in Segment A. Assessments are either tied to date of transplant or date of biologic assignment as outlined below. These mandatory follow up assessments are also summarized in Table 7.

4.2.7.1. Required Assessments Post Transplant

The follow up assessments noted below are required for all participants assigned to the donor arm following enrollment in Segment A. Date of transplant is Day 0. These mandatory follow up assessments are also summarized in Table 7.

- Physical examination and appropriate lab evaluations to assess GVHD and other morbidity weekly starting at day 7 post-transplant through Day 100 post-transplant in accordance with the BMT CTN MOP.
- Chimerism analysis (peripheral blood or bone marrow) at Days 28, Day 42[1], and 100 post-transplant.
- Whole Blood (10mL) OR Marrow (3-5mL) Research Sample for Erythroid Chimerism Testing at Day 100 and Day 730 post-transplant to be sent to Blood Center of Wisconsin (see BMT CTN 1503 MOP for details)

4.2.7.2. Required Assessments Post Biologic Assignment

The follow up assessments noted below are required for all participants assigned to the donor arm following enrollment in Segment A. Date of biologic assignment is Day 0. These mandatory follow up assessments are also summarized in Table 7.

The following assessments are required at **every 3 months post biological assignment starting at Day 100 and continuing through Day 730:**

- Survival status, physical examination and appropriate lab evaluations to assess GVHD and other morbidity in accordance with the BMT CTN MOP.
- Review and documentation of all interim occurrences of SCD-EOSI. Refer to section 4.3.4.2. for additional details on SCD EOSI and defining a single occurrence of any given SCD-EOSI.
- Review and documentation of compliance with medical treatment
- Assessment for toxicities

The following additional assessments are required at **Day 100 and Day 180 post biologic assignment:**

- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.

[1]In the event that the chimerism assessment at day 28 reflects >5% donor hematopoietic cells by whole blood or myeloid chimerism (myeloid is preferable) in peripheral blood or bone marrow, the day 42 chimerism does not need to be done.

The following additional assessments are required at **Day 365 post biologic assignment:**

- 6MWD test
- HRQoL: PROMIS-57 and ASCQ-ME Stiffness Scale
- Pain diary over a 28 day period (Year 1: day 337 to 365)
- Pulmonary function tests: FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Echocardiogram with documentation of TRJV.
- Chimerism analysis (peripheral blood or bone marrow)

The following additional assessments are required at **Day 730 post biologic assignment:**

- Karnofsky/Lansky performance score
- Assessment of Hemoglobin S percent per institutional methods with documentation of the date of last packed red blood cell transfusion is required.
- Renal: serum creatinine and one of the following:
    - creatinine clearance calculated using the Cockcroft-Gault calculator,
    - creatinine clearance by 24 hour urine (preferred), OR
    - Radionuclide GFR including assessment for albumin
- Hepatic: direct bilirubin, alkaline phosphatase, ALT, and AST
- CBC with differential, electrolytes, and serum creatinine 6 MWD test
- HRQoL: PROMIS-57 and ASCQ-ME Stiffness Scale
- Pain diary over a 28 day period (Year 2: day 702 to 730)
- Pulmonary function tests: FVC, FEV1, FEV1/FVC, VC, TLC, RV, ERV, IC, FRC, DLCO, and oxygen saturation
- Echocardiogram with documentation of TRJV
- 6MWD test
- Chimerism analysis (peripheral blood or bone marrow) at Days 28 and 100 post-transplant.
- Cerebral MRA/MRI (Cerebral MRI images will be uploaded for central MRI review . Refer to the BMT CTN 1503 MOP for details.)
- **OPTIONAL** Research samples to be sent to the CHOA Biorepository:
    - Peripheral Blood collection (31.5mL) (see BMT CTN 1503 MOP for details)
    - Urine Sample (50mL) (see BMT CTN 1503 MOP for details)

4.2.8. Follow Up for Patients who are not Biologically Assigned

Patients who are found to be ineligible following enrollment will be considered off-study and will not be followed for any study related assessments. The DCC will track the number of cases enrolled and number of ineligible and eligible cases as determined by the ERC (required for

CONSORT diagram upon study completion). All eligible patients will be followed for the primary endpoint.

Should a patient withdraw consent prior to biologic assignment, no further follow up is permitted. The site is expected to submit written documentation of the patient's withdrawal of consent to the DCC. The numbers of patients withdrawing consent will be tracked by the DCC (CONSORT diagram).

In the event HLA typing/donor search does not occur after enrollment, the physician/site is expected to provide written documentation to the DCC for review by the Protocol team.

4.2.9. Follow Up for Patients who are Biologically Assigned

All eligible patients will be followed for at least 2 years from biologic assignment for survival status (the primary endpoint) unless the patient withdraws consent (documentation submitted to DCC). In the event a patient has only a single suitable donor for assignment to the donor arm (meeting all criteria in section 2.5.1) who is subsequently deemed ineligible to donate (does not meet all criteria in section 2.5.2), that patient will remain assigned to the donor arm and be counted as a crossover. Patients who have a suitable donor and are assigned to the donor arm may decline to proceed with transplantation. Such patients will be followed on the donor arm for at least 2 years for survival and will complete all assessments (except the transplant-specific assessments). Similarly, a patient assigned to the no donor arm may opt for HLA-mismatched related or HLA-mismatched unrelated donor transplantation. As noted above, these patients will remain in the no donor arm of the study, report survival status for at least 2 years and complete other no donor/SOC arm assessments as specified in the protocol. With continued education, we hope to minimize crossovers and withdrawal of consent. Any participant that receives a fully matched transplant using the BMT CTN 1503 conditioning regimen with or without the protocol specified GVHD prophylaxis will follow the Donor Arm Follow up Schedule in sections 4.2.5.1, 4.2.7, and Table 8.

The protocol team has taken steps to minimize crossovers in the 2 years after biologic assignment as follows: 1) instituting the screening visit with an HCT physician who is expected to discuss the rationale for the study design (i.e., we do not know if HCT will result in a survival advantage long-term) and 2) describing the burden of morbidity and mortality associated with transplantation especially the up front risks. Further, we believe only committed providers and patients will subject themselves to a trial that biologically assigns subjects to a treatment option. Providers and patients who favor one treatment approach over another are unlikely to participate in a trial such as this. During the course of the trial we will monitor for crossovers (overall and by site) and maintain a log. As this is a relatively modest sized phase II trial, should a patient crossover from the assigned treatment arm, the DCC will enter into discussions with the site to ascertain the cause for the crossover. The trial has met criteria for "coverage with evidence" (CED) as determined by the Centers for Medicare and Medicaid Services, an incentive for trial participation.

Should a patient withdraw consent after to biologic assignment, no further follow up is permitted. The site is expected to submit written documentation of the patient's withdrawal of consent to the

DCC. The numbers of patients withdrawing consent will be tracked by the DCC (CONSORT diagram).

Table 6: Study Assessments from prior to Segment 0 Enrollment through HLA typing and donor search initiation for ALL PARTICIPANTS

Study Assessments/Testing	After Screening Consent	After eligibility confirmation
History, physical examination[1]	X	
Karnofsky/Lansky performance score[1]	X	
Renal and Hepatic Function Assessment[1] (*per section 4.2.2)*	X	
Cardiac and Pulmonary Function Assessment[2] (*per section 4.2.2)*	X	
CBC with differential[1]	X	
Hemoglobin S Level and date of last packed red blood cell transfusion is required[1]	X	
Infectious disease markers[1]	X	
Pregnancy test[3]	X	
Sickle Cell Disease Genotyping[4]	X	
HLA Typing and Donor Search		X[5]

[1] Must be done within 3 months prior to enrollment into Segment 0
[2] Must be done within 1-year prior to enrollment into Segment 0
[3] Must be done within 30 days prior to enrollment into Segment 0
[4] Can be done any time prior to enrollment in Segment 0
[5] If a subject has had HLA typing with accompanying documentation that relatives were not HLA typed and that a search of the unrelated donor registry was not performed the subject will be considered eligible. Documentation will be reviewed and adjudicated by the Protocol Officer or his/her designee. (See guidelines as outlined in BMT CTN 1503 Manual of Procedures.)

Table 7: Study Assessments after initiating HLA typing for No-Donor Arm Participants

Study Assessments/Testing	Prior to Biologic Assignment[1]	After Biologic Assignment[2]	Days Post Biologic Assignment							
			100	180	270	365	450	540	630	730
History, physical examination[3]		X	X	X	X	X	X	X	X	X
Karnofsky/Lansky performance score[3]		X								X
Renal and Hepatic Function Assessment		X[4]								X
Pulmonary Function Assessment		X[4]				X				X
CBC with differential, electrolytes, and serum creatinine		X								X
Hemoglobin S Level and date of last packed red blood cell transfusion is required		X	X	X		X				X
Echocardiogram with documentation of TRJV		X[4]				X				X
6MWD Test	X					X				X
HRQoL[5]	X					X				X
28-day Pain Diary	X					X[6]				X[6]
Review and Documentation of compliance with medical treatment	X		X	X	X	X	X	X	X	X
Review and Documentation of SCD Events of Special Interest *(per section 4.3.4.2)*	X		X	X	X	X	X	X	X	X
Assessment for reportable adverse events and toxicities	X	X	X	X	X	X	X	X	X	X
Optional Research Samples		X[7]								X[8]

[1]Must be performed after eligibility confirmation and prior to Biologic Assignment
[2]Must be performed after biologic assignment and prior to initiating any study-arm specific therapies
[3]The performance score and History/Physical examination at Biologic Assignment should be obtained on at the same visit.
[4]Any renal, pulmonary, and cardiac assessments that have been performed ≤ 180 days prior to biologic assignment as part of screening do not need be repeated after biologic assignment.
[5]Must be conducted at a single visit from ≥7 days and ≤ 28 days from initiating the pain diary
[6]Must be conducted during 28 days leading up to the patient's yearly visit.
[7]Samples should be collected ≤ 14 days after Biologic Assignment and prior to the initiation of study-arm specific therapies
[8]Samples should be collected on Day 730 ± 30 days

Table 8: Study Assessments after initiating HLA typing for Donor Arm Participants

Study Assessments/Testing	Prior to Biologic Assignment[1]	After Biologic Assignment[2]	Days Post Transplant					Days Post Biologic Assignment							
			Weekly from Day 7- Day 100	28	42	100[9]	730	100[9]	180	270	365	450	540	630	730
History, physical examination[3]		X	X	X		X		X	X	X	X	X	X	X	X
Karnofsky/Lansky performance score[3]		X													X
Renal and Hepatic Function Assessment		X[4]													X
Pulmonary Function Assessment		X[4]									X				X
CBC with differential, electrolytes, and serum creatinine		X													X
Hemoglobin S Level and date of last packed red blood cell transfusion is required		X						X	X		X				X
Echocardiogram with documentation of TRJV		X									X				X
GVHD Assessment			X												
Chimerism Analysis				X	X[5]	X					X				X
6MWD Test	X										X				X
HRQoL[6]	X										X				X
28-day Pain Diary	X										X[7]				X[7]
Cerebral MRA/MRI[8]		X													X
Pregnancy Test		X													
Liver MRI[10]		X													
Liver biopsy[11]		X													
Review and Documentation of compliance with medical treatment	X							X	X	X	X	X	X	X	X
Review and Documentation of SCD Events of Special Interest *(per section 4.3.4.2)*	X							X	X	X	X	X	X	X	X
Assessment for reportable adverse events and toxicities	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Required Research Sample for Erythroid Chimerism Testing						X	X[13]								
Optional Research Samples		X[12]													X[13]

[1]Must be performed after eligibility confirmation and prior to Biologic Assignment
[2]Must be performed after biologic assignment and prior to initiating any study-arm specific therapies
[3]The performance score and History/Physical examination at Biologic Assignment should be obtained on at the same visit.
[4]Any renal, pulmonary, and cardiac assessments that have been performed ≤ 180 days prior to biologic assignment as part of screening do not need be repeated after biologic assignment.
[5] If the chimerism assessment at day 28 reflects >5% donor hematopoietic cells in peripheral blood or bone marrow, the day 42 chimerism does not need to be done
[6]Must be conducted at a single visit from ≥7 days and ≤ 28 days from initiating the pain diary
[7]Must be conducted during the 28 days leading up to the patient's yearly visit.
[8]If there is clinical or radiologic evidence of a recent neurologic event (such as stroke or transient ischemic attack), subjects will be deferred ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation. Please notify DCC when deferring HCT for this or any reason.
[9]If Day 100 post-transplant and Day 100 post-biologic assignment visits are within 14 days of one another, they can be conducted at the same visit.
[10]For participants who are currently receiving ≥8 packed red blood cell transfusions for ≥1 year or have received ≥20 packed red blood cell transfusions (lifetime cumulative)
[11]If hepatic iron content ≥ 7 mg Fe/g, a liver biopsy is required to document absence of absence of cirrhosis, bridging fibrosis, and active hepatitis (≤ 90 days prior to initiation of transplant conditioning).
[12]Samples should be collected ≤ 30 days after Biologic Assignment and prior to the initiation of study-arm specific therapies
[13]Samples should be collected on Day 730 $\pm$ 30 days

4.3. Data Reporting

4.3.1. Criteria for Forms Submission

Forms that are not entered into AdvantageEDC[SM] within 30 days of the calculated target date will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC[SM] and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File.

4.3.2. CIBMTR Data Reporting (Patients Assigned to the Donor Arm and Receive HCT)

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 #1503 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.

4.3.3. Follow Up Beyond 2 Years

The informed consent will include consent from all patients for extended follow-up annually to determine survival status (years 3 through 10). For patients on the donor arm, survival status will be obtained through the CIBMTR. The CIBMTR tracks HCT recipients until death or loss to follow up and has several publications that report late mortality after HCT.[50] For patients on the no donor arm and for those assigned to the donor arm but did not proceed to HCT, the sites will be contacted annually for survival status. If patients are lost to follow up (either treatment arm) the participating site is requested to search the National Death Index (NDI), a centralized database of death record information in state vital statistics offices. The NDI assists in determining whether a person is dead and, if so, will provide the name of the state in which the death occurred, the date, and the corresponding death certificate numbers. The team (through the participating site) will contact the appropriate state office to review the death certificate for cause of death. Alternatively, the cause of death is available through the NDI with about a 12-month lag period. Adopting these strategies, we plan to compare 5-year and 10-year survival of patients enrolled on both treatment arms. We will also explore differences in pattern of survival by donor type for those patients enrolled on the donor arm. Operationally, the clinical trial dataset (at the end of the trial funding period – 5 years) will be transferred to the Medical College of Wisconsin for maintenance and extended follow up of patients assigned to the donor and no donor treatment arms. The CIBMTR will assume responsibility for long-term follow up of patients enrolled on the donor and no-donor arms of the trial.

4.3.4. Adverse Event (AE) Reporting

Adverse event reporting requirements as detailed in this section become effective at the time of the participant's biologic assignment. Events occurring prior to biologic assignment do not require expedited reporting as detailed in this section. Participant death occurring prior to biologic assignment requires prompt completion of the event driven Death form only. Refer to the 1503 Forms Guide for further details.

4.3.4.1. Required Adverse Event Reporting

Adverse event reporting will be consistent with BMT CTN procedures (BMT CTN Administrative Manual of Procedures, Chapter 6). Unexpected, serious adverse events (SAEs) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, life-threatening and fatal (grade 4-5) 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 as a single event 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 (e.g., the Re-Admission, Infection, GVHD and Toxicity Forms). Any expected life-threatening SAE not collected on another study form must be reported through the expedited AE reporting system via AdvantageEDC.

Expectedness of AEs should be determined based on treatment received rather than treatment assignment. For participants that receive standard of care, the expectedness of AEs will be determined by the institutional PI based upon the toxicity profile of the treatment received and those listed in section 4.3.4.3. Any participant that receives a fully matched transplant using the BMT CTN 1503 conditioning regimens with or without the protocol specified GVHD prophylaxis will report expectedness of AEs relative to the Donor Arm, regardless of biologic assignment. AEs will not be collected on participants that receive a transplant with an alternative graft source or other experimental therapy. AE reporting on patients that receive a transplant with an alternative graft source or other experimental therapy will continue until the date of transplant or start date of experimental therapy.

In addition to the standard BMT CTN Unexpected SAE reporting, all deaths, diagnosis of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS), and/or events requiring advanced care interventions or admission/transfer to an intensive care unit (ICU) for an indication below are required to be reported via the expedited AE reporting system in AdvantageEDC. All event reporting is to be expedited. Grade 4-5 events should be reported within 24 hours of knowledge of the event. All other events should be reported within three business days of the event.

For the purposes of this protocol, examples of "intensive care unit (ICU)" or "advanced care intervention" requiring expedited AE reporting are one or more of the following:

- The patient is transferred to an advanced care unit *or* the ICU* (see footnote below)
- Continuous Renal Replacement Therapy (CRRT) by dialysis (CAVHD) or filtration (CAVH)

- Non-invasive positive pressure ventilation: continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP), intermittent positive pressure ventilation (IPPV)
- Endotracheal intubation with mechanical ventilation
- Pressor support
- Organ failure – acute renal failure, acute liver failure, acute respiratory distress syndrome, respiratory failure, or multi-organ failure.

*** Elective transfer to an advanced care/ICU unit for a scheduled intervention does not need to be reported via the Adverse Event forms in AdvantageEDC.**

4.3.4.2. Sickle Cell Disease Related Events of Special Interest Reporting

The following sickle cell disease related events of special interest (SCD-EOSI) are expected events for all participants, regardless of biologic assignment:

- pulmonary hypertension[1]
- significant cerebrovascular events, including:
  - stroke
  - transient ischemic attack
  - seizure
- renal function compromise[1], including:
  - proteinuria
  - increased creatinine grades ≥2 per CTCAE version 4.0
- avascular necrosis of the hip or shoulder[1]
- leg ulcers[1]
- acute chest syndrome (ACS) requiring hospitalization
- vaso-occlusive pain crisis (VOC) requiring hospitalization or administration of parenteral opioid drugs in an outpatient setting. Self-reported events without clinical documentation should not be included.

While these events may not require expedited reporting via completion of the Adverse Events forms, each occurrence of any SCD-EOSI must be reported on the SCD-EOSI Targeted Toxicities form at each regularly scheduled follow up interval. A single event occurrence is defined as a new onset of any of the above listed SCD-EOSIs after screening evaluations are completed. A single occurrence resolves once the SCD-EOSI returns to the participant's baseline. Therefore, multiple occurrences of the same or several SCD-EOSIs may be reported in one reporting interval. The completion of the SCD-EOSI Targeted Toxicities form is required for all participants regardless of biological assignment.

4.3.4.3. No-Donor Arm Expected Event Reporting

For participants assigned to the no-donor arm, there are expected toxicities associated with the standard of care. These expected toxicities do not require expedited reporting on the Adverse Event Forms. These toxicities may include but are not limited to:

[1] Each new onset event

- Transfusions
    - Transfusion reaction, including but not limited to: fever, rash, hives, itching, allergic reaction, bronchospasm, hypotension, hypoxia, anaphylaxis, hematuria, hemolysis, renal impairment
    - Infection
    - Iron overload
    - Development of allo-antibodies
- Hydroxyurea
    - Decreased blood cell counts, which can lead to infection or bleeding
    - Nausea
    - Diarrhea
    - Constipation
    - Hyperpigmentation of skin under nails
    - Thinning hair
    - Reduced sperm production

Expedited AE reporting requirements for the no donor arm are described in section 4.3.4.1.

4.4. Subject Payment

Patients on both treatment arms will be paid $25 at baseline, 1 year and two years (total of $75) for their time to complete the HRQoL assessment. Payments are made only upon completion of required HRQoL forms.

Patients will be paid $1.00 for each electronic pain diary entry. This compensation will be the same for all three of the 28-day reporting periods. The potential compensation for completing the pain diary at all of these time points is $168.

The total possible compensation is $243.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

This study is designed as a phase II, multi-center trial of hematopoietic transplantation (HCT) versus standard of care for sickle cell disease. Eligible participants will be biologically assigned to HCT or standard of care based on the availability of an HLA-matched related or unrelated donor by day 180 after confirmation of clinical eligibility. Insurance coverage and donor availability are not known at referral or consultation. Availability of HLA typing prior to referral makes the potential subject ineligible for the trial. However, if a subject has had HLA typing with accompanying documentation that full siblings were not HLA typed and a search of the unrelated donor registry was not performed, the subject will be considered eligible. Documentation will be reviewed and adjudicated by the Protocol Officer or his/her designee.

5.2. Accrual

It is estimated that 36 months of accrual will be necessary to enroll approximately 200 patients. The sample size for the donor arm is fixed at 60 based on donor availability for ~30% of participants. The sample size for the no donor arm is anticipated to be approximately 140 but may vary according to true availability rate. Accrual will be reported by gender and age.

5.3. Biological Assignment

Participants are biologically assigned, based on the presence or absence of a suitable donor, to donor versus no donor arms.[51,52] Participants in the donor arm are expected to proceed to HCT and those in the no donor arm, to continue with standard of care. However, crossovers may occur, which may lower the statistical power to detect differences between the donor and no donor arms. There may be participants in the no donor arm who proceed to HCT at a later date with an HLA-mismatched or matched donor. These participants will remain in the no donor arm for primary analyses. There may be participants on the donor arm with a suitable donor who may decline HCT. However, we anticipate such crossovers to be <5% based on our planned intensive counseling by a SCD physician prior to referral and an HCT physician at referral but prior to enrollment in AdvantageEDC for confirmation of clinical eligibility. At all steps of enrollment as shown in Figure 4, the protocol coordinator will keep a tally of potential participants who did not proceed as indicated in figure 4. Additionally, a full description of crossovers on both arms will be provided. The DSMB will be provided with data describing the crossovers at the regularly scheduled meetings. The DCC will consult the DSMB if the crossover rate exceeds 5% for consideration of the necessity of increasing accrual due this level of failure to adhere to protocol assignment. Another potential problem is that participants with donors may differ from those without donors, although this is not anticipated. Analyses are planned to assess comparability of participants on the 2 treatment arms for demographic and sickle-related events at baseline. Multivariable analysis will be used to adjust for imbalances in characteristics. Although very

unlikely, any death occurring prior to identification of a donor would be assigned to the no donor arm.

5.4. Primary Endpoint

The primary endpoint is the estimate of overall survival at two years after biologic assignment. Participants on the donor arm are expected to receive HCT and those on the no donor arm, standard of care. Regardless of treatment received, subjects will remain in their assigned treatment arm for analysis of survival (ITT principle.).[51,52] As donor availability is not known at enrollment, all patients are assigned to the "no donor arm". Upon donor search, those with a suitable donor will be re-assigned to the "donor arm". All participants will remain in their assigned treatment arm regardless of treatment received. Participants who withdraw consent prior to the site's determination of whether or not there is a suitable donor found will not be considered on study if the site provides documentation that the donor search and eligibility qualification process were stopped before determining whether a suitable donor was available; these participants will also not be part of the statistical analysis.

A consort diagram (number of eligible patients who consented for the study, their biologic assignment and treatment received) will be maintained. Patients will not be treated as failures in the unlikely event they do not receive treatment per their biologic assignment.

5.5. Primary Hypothesis

We hypothesize that for participants assigned to the donor arm HCT-related mortality may exert an early impact on survival, but that the rate of mortality should plateau by two years.[34-36] Mortality after HCT for severe aplastic anemia is less than 15% at 2 years and thereafter, plateaus.[34-36] For young adults with SCD, the available data suggest mortality after HCT is about 10%. We hypothesize as well that participants on the no donor arm will not be especially susceptible to early death, but will gradually succumb to the cumulative effects of their disease with a mortality rate higher than in the general population.[23] Published reports suggest this occurs at a rate of 4.4 deaths per 100 person years. Consequently, the survival curves of the 2 groups will eventually cross, with a long-term benefit for HCT if early HCT-related mortality is sufficiently low. For this phase II trial, we will compare survival rates at 2-years, with the goal of establishing that the difference in the proportion surviving is no more than 0.15 lower in the donor arm. We think that if the early survival disadvantage of HCT is modest, a long-term survival advantage will emerge. We therefore propose the following approach: P_D is the probability of overall survival at 2-years on the donor arm and P_{ND} is the probability of overall survival on the no donor arm. We can write the hypothesis as follows:

$$H_0: P_{ND} - P_D \leq 0.15; H_1\ P_{ND} - P_D > 0.15.$$

5.6. Sample Size and Power Considerations

For our calculations, we assume 60 participants on the donor arm and 140 on the no donor arm and that at 2 years 0.95 participants on the no donor arm and 0.80 participants on the donor arm will remain alive. We will test at the 0.10 one-sided significance level which means that we will

define a rejection region that is 1.282 standard deviations beyond the null. Our test will yield more than 80% power to reject an alternative difference of 0.30. We chose an expanded one-sided significance level of 0.10 to control the size of the rejection region. Under our assumptions, the standard error estimate of the difference is 0.0548; this leads us to reject the null hypothesis if the observed difference in two-year survival between the groups is 0.22 or higher. That is, we will reject the null hypothesis of no more than a 0.15 difference if the observed difference is significantly larger than 0.15, and the point at which the difference is considered significantly larger is 0.22. We postulate that to be able to demonstrate a survival advantage long-term, the difference in survival between the groups of participants cannot exceed 22% at 2-years. There is a potential for bias resulting from biologic assignment, and we will compare the two groups to identify factors that may differ. If such factors are identified, we will extend our comparison of survival between the donor and no donor arms to adjust for such factors, using a multivariable Cox model. Our survival estimate of 80% for the donor arm is based on two-year overall survival of 80% in young adults after HLA-matched related and unrelated HCT for severe aplastic anemia[34,35] and 93% for thalassemia after related and unrelated HLA-matched HCT in children and young adults.[30] Our survival estimate for the no donor arm is based on a mortality rate of 4.4 deaths per 100 person-years in SCD patients receiving supportive care.[33] In a long-term study of patients with severe aplastic anemia who underwent HCT, the risk of death after 2 years was only modestly higher than, and by the 6th year after HCT did not differ significantly from, an age- and sex-matched general population.[36] With a mortality rate of 4.4 deaths per 100 person-years in SCD patients receiving supportive care we expect the survival curves to cross beyond year 6.

5.7. Interim Analysis and Stopping Guidelines

5.7.1. Interim Analysis for Efficacy

There will be no interim analyses for efficacy.

5.7.2. Guidelines for Safety Monitoring

Monitoring of key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified so that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as triggers for consultation with the DSMB for additional review. Guidelines have been prepared using a sequential probability ratio test (SPRT) for day-100 mortality for participants on the donor arm; 1-year mortality and day 100 graft rejection will be monitored separately for participants transplanted from HLA-matched related and unrelated donors.

5.7.2.1. Overall Mortality by Day 100

For the donor arm, overall mortality in this trial is projected to be less than 20% at day 100 post-transplant. The stopping rule for overall mortality will be triggered if there is significant evidence that the 100 day overall mortality rate exceed 15% based on the truncated sequential probability ratio test (SPRT). The truncated SPRT is based on contrasting 15% versus 30% 100 day mortality, with nominal type I and type II error rates of 10% and 20%, respectively. The common slope of the parallel lines is 0.219 and the intercept for the upper boundary is 2.344. The stopping rule is summarized in the following table.

Table 10. Stopping Rules for Overall Mortality by Day 100 for Participants on the Donor Arm

Number of evaluable patients enrolled*	Stop if death occurs in:
3	3
4-7	4
8-12	5
13-16	6
17-21	7
22-25	8
26-30	9
31-34	10
35-39	11
40-44	12
45-48	13
49-53	14
54-57	15
58-60	16

*An evaluable patient is one who starts the conditioning regimen

5.7.2.2. Overall Mortality at 1-Year

For the donor arm, the stopping rule for overall mortality at 1 year post transplant will be triggered if there is significant evidence that the 1-year overall mortality rate exceeds 15% for participants with matched related donors and 15% for participants with matched unrelated donors based on the truncated SPRT. The truncated SPRT is based on contrasting 15% versus 30% 1-year mortality with nominal type I and type II error rates of 15% and 20%. The common slope of the parallel lines is 0.219 and the intercept for the upper boundary is 1.887. The stopping rule is summarized in the following table. We anticipate that 40% of participants on the donor arm will have matched related donors.

Table 11. Stopping Rules for Overall Mortality at 1-Year for Participants on the Donor Arm

A. Participants with matched related donors (N=24)	
Number of evaluable patients enrolled*	Stop if death occurs in:
3-5	3
6-9	4
10-14	5
15-18	6
19-24	7

*an evaluable patient is one who starts the conditioning regimen

B. Participants with matched unrelated donors (N=36)	
Number of evaluable patients enrolled*	Stop if death occurs in:
3-5	3
6-9	4
10-14	5
15-18	6
19-23	7
24-27	8

B. Participants with matched unrelated donors (N=36)	
28-32	9
33-36	10

*An evaluable patient is one who starts the conditioning regimen

5.7.2.3. Graft Rejection by Day-100

For participants with matched related donors (N=24 expected), failure to engraft donor cells (defined as having primary or secondary graft failure per section 3.3.1) by day-100 post-transplant should occur in <10% of patients. The stopping rule for graft rejection by day-100 will be triggered if there is significant evidence that the day-100 graft rejection rate exceed 10% based on truncated SPRT. The truncated SPRT is based on contrasting 10% versus 20% 100-day graft rejection, with nominal type I and type II error rates of 15% and 20%. The common slope of the parallel lines is 0.14524 and the intercept for the upper boundary is 2.06427 for late rejection. The stopping rule is summarized in Table 12. For the participants with matched unrelated donors (N=36 expected), failure to engraft donor cells (defined as having primary or secondary graft failure) by day-100 should occur in < 15% of participants. The stopping rule for graft rejection by day-100 will be triggered if there is significant evidence that the day-100 graft rejection rate exceed 15% based on the truncated SPRT. The truncated SPRT is based on contrasting 15% versus 30% 100-day graft rejection, with nominal type I and type II error rates of 15% and 20%. The common slope of the parallel lines is 0.219 and the intercept for the upper boundary is 1.8866 for late rejection. The stopping rule is summarized in Table 12.

Table 12: Stopping Rules for Graft Rejection by Day-100 for Participants on the Donor Arm

A) Participants with matched related donors (N=24)	
Number of evaluable patients enrolled	Stop if graft rejection occurs in:
3-6	3
7-13	4
14-20	5
21-24	6

*An evaluable patient is one who starts the conditioning regimen

B) Participants with matched unrelated donors (N=36)	
Number of evaluable patients enrolled	Stop if graft rejection occurs in:
3-5	3
6-9	4
10-14	5
15-18	6
19-23	7
24-27	8
28-32	9
33-37	10

*An evaluable patient is one who starts the conditioning regimen

5.8. Analysis of Primary Endpoint

The primary outcome will be assessed in a final analysis to be performed after the last enrolled patient has been followed for two years post-biological assignment. The two-year overall survival

probability and confidence interval will be calculated. The event is death from any cause. Patients alive at the time of the last observation are censored at the time of the last observation; however, all patients are expected to have survival status reported at or beyond 2 years. Overall survival will be compared between treatment arms using a point-wise comparison at 2-years, and the survival curves will be estimated using the Kaplan Meier product limit estimator.

In addition to comparing the difference in the observed proportion of patients surviving at 2 years post-biologic assignment using the ITT approach, we will also compare the difference in the observed proportion of patients surviving at 2 years post-biologic assignment between groups by treatment received (i.e., as treated). The "as treated" approach will compare OS between patients who received a transplant to patients who received standard of care. The 2-year OS probability and confidence interval will be calculated. OS will be compared between treatment arms using a point-wise comparison at 2-years and the survival curves will be estimated using the Kaplan-Meier product limit estimator.

Exploratory analysis comparing the difference in the observed proportion of patients surviving at 2 years post-biologic assignment among recipients of HLA-matched sibling and HLA-matched unrelated donor transplantations will be performed. We will focus on descriptive analyses, as the statistical power will be lacking for alternatives of interest. We will explore both the point estimate of overall survival at two years, and the full survival curves estimated using the method of Kaplan and Meier, as the tempo of deaths with different donor types may differ even if the two-year estimates do not. We will also report patient and disease characteristics on the two donor arms, and, if the data support it, fit models to explore the impact donor source and other features on the overall survival of transplanted patients. Because our hypothesis is that the survival curves will ultimately cross, we will continue our assessment of overall survival in the donor and no donor arms, using data submitted to the CIBMTR augmented by information obtained from the National Death Index, at 3, 4, 5, and 10 years of follow up.

Additionally, we will describe outcomes separately for any matched related donor conditioning regimen used for 5 or more patients. Similarly, we will describe outcomes separately for patients for whom peripheral blood is the stem cell source, should there be 5 or more such patients.

There is a potential for bias resulting from biologic assignment, and we will compare the two groups to identify factors that may differ. If such factors are identified, we will extend our comparison of survival between the donor and no donor arms to adjust for such factors, using a multivariable Cox model.[53]

5.9. Secondary Endpoints

The secondary endpoints will examine changes in record-based assessment of sickle-related events using the system developed by Elmariah and colleagues[19]; cardiac function, pulmonary function, and functional assessments by administering the 6MWD test, HRQoL, and a 28-day electronic pain diary to capture mean pain intensity. The secondary endpoints will examine changes between baseline and 2-years between participants on the donor and no donor arms. Additionally, HRQoL, 28-day e-pain diary, and the 6MWD test will be measured at 1-year; therefore changes between

baseline, 1- and 2-years will be examined. Additional endpoints for patients undergoing HCT will be analyzed.

5.9.1. Occurrence of Sickle-Related Events

We will examine the occurrence of the sickle-related events identified by El Mariah on study.[19] Exact logistic regression will be used to estimate an odds ratio of each of these events between treatment groups, assuming that at least one event occurs on study in each of the treatment groups, controlling for other patient related characteristics and individual history of the event of interest.

5.9.2. HRQoL

We will measure HRQoL using the PROMIS-57 and the stiffness impact short form from ASCQ-Me. We will focus on changes from baseline, and assume on average no change in the no donor group and improvement in the donor group. We have assumed no correlation to maximize the variability of the estimate of change. Using a two-sample t-test, we will have power of 0.98 to identify a 10-point difference in changes within a domain between donor and no donor, testing at the two-sided 0.05 significance level. This calculation is based on 45 participants on the donor arm and 113 on the no donor arm completing the two-year assessment; power to identify as statistically significant an even smaller difference will be increased if adherence to the two-year measurements is higher than we have assumed. We will also analyze the trajectory of change using baseline, year 1, and year 2 measurements, using either a generalized linear model or generalized estimating equations, as appropriate, and adjusting the assessment of the trajectory, in addition of the primary question of donor/no donor, by incorporating additional demographic factors as well as adjusting for whether the assigned treatment was delivered. More complex models may be required if the changes over time are strongly nonlinear.

5.9.3. Mean Pain Intensity

The electronic pain diary is administered twice daily for 28 consecutive days. As the pain diary is administered twice/day, an average value will be computed for each day on which the diary shows two entries. Should the diary reflect only a single entry for a day that value will be used and if a patient did not enter a value on a given day, that non-adherence will be tallied separately. The mean pain intensity from the diary will be the sum of the reported daily pain intensities averaged over the number of days on which at least one pain intensity was reported.

The PROMIS-57 HRQoL instrument asks the patient to rate his/her pain intensity over the past 7 days. The PROMIS-57 will be administered at least 7 days into the daily electronic pain diary so that reporting periods overlap and the two measures can be compared. The ASCQ-Me instrument should be administered on the same day as the PROMIS-57 instrument.

Based on estimates of daily pain in adults with SCD[43], we anticipate that all patients will report pain with a mean pain intensity of 3.9 on a scale of 10 at baseline. We expect that this will be unchanged at follow-up for patients in the no donor arm. We anticipate however that patients in the donor arm will demonstrate a clinically significant decline in mean pain intensity to a level of 1.3 units on a scale of 10 at two years. Assuming a correlation of 0.95 within patient, we will have

94% power to detect this difference, testing at the one-sided 0.05 significance level. We will also analyze the trajectory of change using baseline, year 1 and year 2 measurements, using either a generalized linear model or generalized estimating equations, as appropriate, and adjusting the assessment of the trajectory, in addition of the primary donor/no donor question, by incorporating additional demographic factors as well as whether the assigned treatment was delivered. More complex models may be required if changes in pair do not occur early making changes over time strongly nonlinear.

5.9.4. Exercise Capacity

We will use the 6MWD, testing under standardized procedures, to assess exercise capacity. The ATS guidelines indicate sensitivity of this test to a number of subject characteristics, but we will be focusing on the change between two time points, and this orientation will permit us to make a more straightforward comparison. This endpoint will measure absolute change from baseline, with increased distance identified as positive change. We anticipate an improvement of at least 50 m in the subjects in the donor arm on average, compared to subjects in the no donor arm, in whom we anticipate at best no improvement. However, we have not identified an estimate of variability of the change in for 6MWD over a one- or two-year period. We will use the two-sample t-test to examine the changes in distance walked between the groups of subjects, and will also examine linear mixed models to understand how other factors, in addition to transplant/control, may affect those changes. Finally, we will interrogate the impact of baseline distance on the magnitude of change at one- and two-years; this may lead to a parallel analysis based on the percentage change from baseline.

5.9.5. Cardiac Function

Tricuspid regurgitant velocity (TRV) is an important marker for the severity and progression of SCD. In a series of 148 adults with SCD followed over 9 years, patients with a progressive increase in TRV during follow-up had increased mortality[54] In another series of 54 adults with SCD a linear mixed effects model indicated an overall rate of increase in the TRV of 0·02 m/s per year.[55,56] Desai and colleagues[55] found that, using a linear mixed model, the estimated average increase per year in TRV was 0.02 m/s, and that 56% of the subjects experienced an increase in TRV over time (with 4.5 years median follow up). They also report, using the same model, that administration of hydroxyurea was responsible for an estimated reduction in change in TRV of -0.20 m/s. Again, using the model, they report that among the subjects whose TRV increased, the estimated average increase per year was 0.07 m/s. We note that the subjects in that study were older than those in the present study. Increase in TRV over time was not associated with whether the TRV was above 2.5 at baseline. We will measure changes in TRV jet velocity (TRJV) over time (at 1-year and 2-years) using a two sample t-test as well as on a linear mixed model for the rate of change in TRJV while incorporating both transplant status and baseline value. We will also use a linear mixed model incorporating time and transplant/control status to estimate the rate of change in TRV. We will use the model for obtaining estimates for the group as a whole, with an estimate of the impact of transplant on change in TRV. We will also examine the proportion of patients with increases in TRV as a planned subset analysis, in the context of the same model. Finally, we will examine the relationship of increases in TRV as a function of whether the baseline TRV was ≤ 2.7 m/s or > 2.7 m/s, using the Fisher exact test.

5.9.6. Pulmonary Function

There is a growing body of evidence to indicate that the pulmonary toxicity of SCD is progressive.[44,45] In a series from the Cooperative Study of Sickle Cell disease, only 10% of adults had normal pulmonary function test (PFT) results.[6] The rate of progression of pulmonary function abnormalities is not certain, but in 1 series of children and adolescents tested over 42 +/- 23 months, 56% had normal PFTs at the baseline, and only 29% stayed normal at the second testing, with obstructive patterns being observed more frequently than restrictive.[57] In another series of 413 children with SCD who had pulmonary function testing results analyzed by a linear mixed effects model, showed significant serial decline in the percent predicted values for FEV1, forced vital capacity (FVC), and forced expiratory flow (FEF25-75) across age.[58] Thus, these data strongly suggest that the negative impact of sickle vasculopathy on pulmonary function is progressive. This type of pulmonary injury appears to be halted by successful HCT.[1] We anticipate changes in FEV1 of 49 cc/year[45] for participants on the no donor arm, compared to half that rate in the donor arm, based on Field's observation of a general population decrease of 20 to 26 cc/year.[44,45] We will also assess the proportion of participants on the treatment arms in whom we find evidence of restrictive lung disease, defined as total lung capacity below the 5th percentile adjusted for age, gender, race, and height, as is also reported by Field et al.[45] used generalized estimating equation models on the serial PFT measurements for 92 subjects with SCD, and reported that the average loss in FEV1 was 49 cc/year. This paper also cites a general population drop with age of 20 to 26 cc/year. Based on this we would also use a generalized linear mixed model as we will have only two time points, and feel that we will be able to assess the variance/covariance structure, rather than the Generalized Estimating Equation (GEE) which Field used with 2 to 4 time points per subject. We will also assess the proportion of subjects in both arms in which we find evidence of restrictive lung disease, defined as TLC below the 5th percentile adjusted for age, gender, race, and height, as is also reported in the Field paper.

5.9.7. Renal Function

Guasch et al.[46] report that 61% of SCD subjects aged 18 to 30 had either micro- or macroalbuminuria; for subjects aged 30 to 40, this percentage was 66%, based on a single measurement. We will examine changes in albuminuria at the two time points separately for the transplanted and control subjects using the McNemar test, and we will compare the proportions of subjects at the each measurement time using the Fisher exact test.

5.10. Secondary Endpoints for Participants who Undergo HCT

For participants assigned to the donor arm (expected to undergo HCT) the following outcomes will be monitored and described:

1. Cumulative Incidence of neutrophil and platelet recovery will be reported
2. Cumulative Incidence of primary graft failure will be reported
3. Cumulative Incidence of secondary graft failure will be reported
4. Lineage specific chimerism will be described taking into account the genotype of the donor (AA or AS).
5. The cumulative incidence of grade II-IV and III-IV aGVHD at day-100 will be reported.

6. The cumulative incidence of chronic GVHD and the severity of chronic GVHD at 1- and 2-years will be reported.
7. The occurrence of other HCT-related complications will be described.
8. IPS, VOD, CNS toxicity including hemorrhage and PRES, significant infections (bacterial, viral, fungal including mold infections), CMV reactivation and EBV-PTLD will be reported.
9. The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for separately for HLA-matched related and unrelated transplants. The cumulative incidence of CMV reactivation in the first 100 days post HSCT will be described. All Grade 2 and 3 infections will be reported according to the BMT CTN MOP.

5.11. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status and other baseline characteristics. Between group comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test.

5.12. Handling of Missing Data

Two-year measurements can only be obtained on surviving subjects who return for testing at two years. **We will not impute values for subjects with missing data.** We recognize the challenges in retaining control subjects in whom no intervention beyond enrollment and measurement is performed, and therefore assume that 15 % of surviving control subjects will not be evaluable at both time points.

5.13. Extended Follow Up

The probability of survival of patients in both treatment groups will be calculated annually years 3 through 10 using the Kaplan-Meier estimator and the 95% confidence interval generated using the Greenwood formula. Comparative p-values will be generated at time-points 3 through 10 years using point-wise estimator rather than the log rank test as we except the survival curves will over time cross. We anticipate crossing hazards as most deaths in the donor group will occur within the first 2 years; however, most deaths in the no-donor group will occur beyond 2-years.

APPENDIX A

HUMAN SUBJECTS PROTECTION

APPENDIX A

HUMAN SUBJECTS PROTECTION

Risks to Subjects

Subjects Involvement and Characteristics: 200 patients with severe SCD will be recruited; we anticipate 60 will be enrolled on the donor arm based on ~30% having a HLA-matched related or unrelated donor and 140, on the no donor arm.

Recruitment of Women and Minorities as Research Subjects: Equal number of women and men are likely to be recruited. Majority of the patients will be of minority ethnic origin because of the demographics of distribution of SCD. The racial, gender and ethnic characteristics of the proposed subject population reflects the demographics of the study sites. We shall attempt to recruit subjects in respective proportion to these demographics. No exclusion shall be based on race, ethnicity, or gender.

Inclusion of Children as Research Subjects: Previous studies have demonstrated the benefit of HCT for children from matched sibling donor in children up to age 16 years. There is currently an ongoing study of HCT for children up to age 16 years from unrelated donors. We therefore propose a study for children above age 15 years and for adults up to age 40 years. This study attempts to further reduce toxicity in patients, age 15-40 years, receiving HCT for SCD. The risk involved in the participation of the study is greater than minimal, but has the potential for direct benefit to the individual. The risk is justified by the extent of potential benefit to the involved children and the relation of the risk to the potential benefit is at least as favorable to the subject as that presented by alternative approaches. As such this study fulfills criterion 2 of 45CFR 46 .405.

Expertise of the Investigative Team in Dealing with Patients of the Specific Age Ranges: Investigators are Board Certified in Pediatric or Adult Hematology/Oncology/HCT with experience in taking care of SCD patients and HCT patients. PIs of the study have previously conducted IRB approved multicenter trials of HCT for SCD.

Adequacy of Facilities to Accommodate Patients of Specified Age Ranges: All the participating sites have dedicated inpatient oncology units, Blood and Marrow Transplant (BMT) rooms and outpatient clinics equipped with high efficiency air and water purification systems, seamless floors and drywall ceilings. These units accommodate patients in the acute phase of HCT and offer intensive care for returning patients with serious complications related to HCT. The units are equipped with state-of-the-art air handling capabilities and are staffed by clinical nurses with a primary interest in blood and marrow HCT, HCT research nurses as well as staff physicians with experience in HCT.

Potential Risks: HCT is the only modality that can cure severe hemoglobinopathy. If HCT is successful, it is anticipated that patients will not have symptoms related to the disease, have no requirement of transfusion and have stabilization of organ damage. The risk of mortality is low in

patients <16 years of age receiving HCT from matched siblings (4-5%) [59]. Risks are higher among older patients and those receiving HCT from an unrelated donor. Preliminary data suggest that this protocol is well tolerated in recipients of HCT from an unrelated donor. However, serious viral or bacterial infections and acute and chronic graft versus host disease pose significant risks of morbidity and mortality even in patients receiving HCT following a non-myeloablative conditioning regimen. While there is no information available on the effect of busulfan alone on fertility, the use of high doses of another alkylator, cyclophosphamide alone in HCT conditioning regimens is associated with recovery of ovarian function in all patients under the age of 26 years and in 61% of patients over the age of 26 years[60,61]. At least half of the patients with aplastic anemia who received high doses of cyclophosphamide for HCT and survived ≥2 years preserved or regained the ability to become pregnant or father children[62]. With the regimen used in this trial, there is a small risk (<5%) for a malignancy, and the potential for other late toxicities including infertility.

Discussion of Alternatives to Participation in the Study: Patients will be clearly apprised of alternatives to participation on the study, which is continuation of standard of care (chronic transfusion, hydroxyurea, pain management).

Adequacy of Protection Against Risks: Subjects for this study will be recruited from among patients followed at or referred to the clinical sites. The study will be discussed with the patient or family members by one of the investigators and informed consent obtained. All potential subjects will sign informed consent according to guidelines of the local Institutional Review Boards. Patients will be evaluated and, if eligible for the trial, consent will be obtained for enrollment. Enrollment prompts ad hoc review of clinical eligibility by an Eligibility Review Committee (ERC). If eligibility is confirmed by successful enrollment into AdvatageEDC or review by the ERC, patients undergo HLA typing and donor search is initiated. Patients with a suitably HLA-matched donor are assigned to the donor arm for transplantation. Those without a donor are assigned to the no donor arm.

Protection Against Risk: This protocol will be reviewed and approved by the IRB of record for each site, as defined by FDA regulations (21CFR Part 56) and DHHS regulations (45 CFR part 46). Sites may choose to use the NMDP IRB of record or institutional IRB for this study. Reporting of unanticipated events, protocol deviations, protocol amendments, and other information to the IRB of record should follow institutional or NMDP IRB practice. Reporting of events to the DSMB and federal agencies by the BMT CTN will follow the BMT CTN MOP.

External Data Safety and Monitoring Board: An external Data safety monitoring board will be constituted by NHLBI. The External DSMB will convene via an in-person meeting or teleconference at a minimum of twice a year to assess progress on patients enrolled on the study. Administrative reports from these meetings will be available to site staff.

Risk Management Procedures: Procedures for minimizing specific risks associated with study procedures are outlined above. Patients assigned to the donor arm will be admitted to the HCT beds and will receive standard care. Once engraftment has been demonstrated the patients will be followed closely in the outpatient clinic. In addition, the protocol chairs and protocol officer are to

address trial-related concerns from physicians. Patents assigned to the no donor arm will continue to receive standard of care administered by their hematologist. At individual institutions, a physician or designee is available 24/7 for patient-related queries; these will follow institutional guidelines. Confidentiality will be maintained throughout the study. Subjects will be identified by research study numbers, which will be the only identifying information to appear on data and documents used for evaluation or statistical analysis. No verbal or written information concerning any subject will be released without the written consent of the subject. Records will be maintained only in anonymous research files, kept in locked quarters and made available only to qualified research personnel.

Potential Benefits of the Proposed Research to the Subjects and Others: Potential benefits to patients include cure of the severe SCD and alleviation of chronic morbidity and possibly reversal of organ damage.

Importance of the knowledge to be gained: It is anticipated that a safe and effective reduced toxicity approach to HCT for severe SCD in young adults will greatly enhance the applicability of this modality of treatment to this group of patients. By comparing with a group of similarly affected patients we will compare overall survival and sickle-related events 2-years after enrollment.

Donor Human Subject Protection

In the interest of safeguarding the safety of the clinical procedure of bone marrow donation by minor donors, and in keeping with the American Academy of Pediatrics Guidelines for minors as hematopoietic stem cell donors (Pediatrics Vol. 125 No. 2 February 1, 2010 pp. 392 -404), informed consent for a marrow harvest in minors who meet donor eligibility is sought only when all 5 criteria below are satisfied:

1. There is no medically equivalent histocompatible adult relative who is willing and able to donate
2. There is a strong personal and emotionally positive relationship between the donor and recipient
3. There is a reasonable likelihood that the recipient will benefit
4. The clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient; a child mental health professional as well as donor advocate will be involved to help clarify the child's concerns
5. Parental permission and, when appropriate, child assent are obtained.

Additionally, the work-up and consenting of all minor donors are subject to the laws in the state in which they reside including but not limited to the designation of an independent advocate.

All donors will be evaluated for eligibility by an independent physician separate from the research team. Related donor eligibility (minors and adults) is subject to established clinical practice at

participating sites and compliant with state and federal laws. Adult unrelated donors are identified through the NMDP and subject to NMDP's policy and procedures.

All donors will undergo screening procedures including blood tests (approximately 10-15ml); a urinalysis, pregnancy test (for female donors of child bearing potential), and any tests clinically indicated for the safety of the donor during general anesthesia. The risks involved in the screening procedures include discomfort from phlebotomy. Since the bone marrow donation occurs under general anesthesia, there is some risk associated with anesthesia. The most common side effects related to the collection of bone marrow are: pain in the hip bones, back stiffness and bruising and bleeding in the skin where the needles were placed. Rare complications include infections in the skin and bone or major bleeding problem. It is possible that a blood transfusion will be necessary so that the donor is not too anemic after the bone marrow collection. In some cases, it will be possible to collect blood in advance from the donor and store it so that it can be given after the bone marrow collection. There is also a potential for psychological distress to the donor in case of serious HCT related complications to the recipient.

Measures that will be taken to minimize the risks of procedures to the donors:

- **a.** Every effort will be made to use aseptic technique as well as measures to minimize the discomfort from phlebotomy, including the use of topical analgesia.
- **b.** Pregnancy tests will be done prior to any radiological procedure.
- **c.** Adequate pre, intra, and post-operative analgesia will be ensured in order to minimize the risk of pain. Appropriate aseptic technique will be used to minimize the risk of infections. Appropriate anesthetic technique and monitoring will be ensured to minimize the risk from anesthesia.
- **d.** Where the patient is eligible for autologous blood donation (e.g., children>16 years of age, weighs > 50 kg), we would recommend that this be done so as to limit the possibility of requiring transfusion from an Allogeneic donor.
- **e.** Blood will be placed on hold with the Blood Bank should the patient become anemic and require a transfusion.
- **f.** A psychologist will be available to see the donor prior to donation and will be available subsequently to address any behavioral and/or psychological consequences of bone marrow donation.

Donation of bone marrow has no prospect of direct benefit to individual subjects, but represents an opportunity to understand, prevent, and alleviate sickle cell disease, which is a serious problem that affects the health and welfare of those with sickle cell disease. There is no research conducted on donors; only donor demographic data (gender and age), donor's relationship to subject (sibling/unrelated) and donor HLA typing will be collected.

Protected health information will be obtained for subjects enrolled on the study research purposes. This study involves reviewing patients' medical records. The consent form will be reviewed with the subject prior to accessing the potential subject's information. We will require that the subject sign these forms prior to enrollment.

Each prospective subject will be told during the consent process that he or she can withdraw at any time from the study. The investigator will inform each potential subject that participation is voluntary and declining to participate in the study will not affect the medical care they receive at the institution.

In the event a subject also received care at another institution, the subject will be asked to sign a Release of Information form. Written consent and release of information forms will be reviewed with participants during the consent process. Prospective participants will be given the contact information of the principal investigator if further questions arise. Prior to review of the medical records the PI will require that the subject has returned and signed a copy of this consent and that each participant has received a copy of the written consent and release of information form.

Protected Health Information:

Protected health information will be obtained for research purposes. This study involves reviewing patients' medical records. We will review the written consent with the subject prior to accessing the potential subject's information. We will require that the patient sign these forms before enrolling them in this study and will be encouraged to ask questions. Prospective participants will not have to enroll immediately after they are approached.

Each prospective subject will be told during the consent process that he or she can withdraw at any time from the study. The investigator will inform each potential subject that participation is voluntary. In the event a subject also received care at another institution, the subject will be asked to sign a Release of Information form. Written consent and release of information forms will be reviewed with participants during the consent process. Prior to review of the medical records the PI will require that the subject has returned and signed a copy of this consent and that each participant has received a copy of the written consent and release of information form.

APPENDIX B-1

INFORMED CONSENT AND ASSENT FORMS TO PARTICIPATE IN RESEARCH

Informed Consent to Participate in Research

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR AN ADULT TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

This is a clinical trial, which is a research study to answer specific medical questions.
The information from this study may also help future patients. The Study doctor (the person in charge of the research) will explain the study to you. This research study will include only people who choose to take part in the study. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

1. Introduction

You are being invited to be part of a research study at [Insert institution]. The people who take part in research studies are called "participants". This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. Before you decide if you would like to participate, we want you to know why we are doing this study. Being in this study is voluntary. You do not have to take part in this study. You have a choice between a standard treatment for sickle cell disease and this clinical trial. Do not join this study unless all of your questions are answered.

After reading and discussing the important information in this consent form you should know:

- Why this research study is being done
- What will happen during the study
- Any possible benefits to you
- The possible risks to you
- How your personal health information will be treated during the study and after the study is over
- Whether being in this study could involve any costs to you
- What to do if you have problems or questions about this study

Please read, or have read to you, this consent form carefully. After you finish, talk with the study doctor and ask questions. You may also want to talk to family, friends, your primary care doctor, or other health care provider about joining this study. If you decide that you would like to take part in the study, you will be asked to sign this form. You will be given a copy of the signed form to keep.

Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to read and discuss with family or friends before making your decision. There are also names and telephone numbers of people you can call to get answers to any questions you may have now or at any time during or after the study. You may change your mind about staying in the study at any time. However, due to the nature of the treatment provided during this study, it might not be safe for you to immediately stop being in the study. If you have any questions about your staying in the study, please talk with the study doctor or study team.

This research study is sponsored by National Heart, Lung, and Blood Institute of the National Institutes of Health (the "Sponsor"). [Insert institution] is being paid by the Sponsor to conduct this study.

If you choose to take part in this study, it is important that you give a true and complete medical history. You must be honest about your past and present use of medications. Information that is untrue or incomplete could have very serious effects on your health and safety during the study.

2. Background

As you know, SCD is an inherited blood disorder. It is caused by a change in the hemoglobin protein that helps red blood cells (RBC) carry oxygen in the body. This change in hemoglobin leads to blockage of blood flow in small blood vessels that can cause severe pain. It also damages body organs, such as the lungs, brain, spleen, and kidneys. The treatment known as hematopoietic cell or bone marrow transplant (HCT/BMT) can replace the defective blood cells with blood cells from a healthy donor who could be a sibling or an unrelated donor with a tissue-type match that is similar to yours. Unrelated adult volunteer donors are persons who list themselves with a donor registry for the purpose of donating their blood or bone marrow cells to patients who may benefit from HCT/BMT but do not have a sibling who is a tissue-type match to the patient and able to donate blood or bone marrow. This treatment (HCT/BMT) may stop the disease and its health problems. HCT/BMT for SCD is successful in children but has not yet been tested in very many adults.

We are conducting this trial to study if adolescents and young adults who are treated with HCT/BMT live longer than those who are not treated with HCT/BMT. The clinical trial is designed to have two groups. In one group are patients who have a donor and expected to be treated with HCT/BMT (donor arm) and in the other group (no donor arm), patients without a donor who will receive standard of care (this is the same treatment you now receive for your SCD).

Neither you or your doctors know whether you have a donor until your doctors confirm you are eligible for the clinical trial. After you have heard about the trial and are interested, your doctor will submit test results and other documents to confirm you are eligible for the trial. Then your blood will be sent for tissue typing along with blood from any available full siblings (brother or sister, from same set of parents) that agree to be typed. If your brother or sister is not a tissue match or if you do not have a brother or sister, your doctor will search the unrelated donor registry for a donor who is tissue matched to you.

- If the tests confirm you have a suitable donor (no longer than 6 months from when you were confirmed eligible), you will be moved to the “donor arm” of the trial.
- If you do not have a donor (no longer than 6 months from when you were confirmed eligible), you will remain in the “no donor arm” for 2 years.

The study will recruit 200 subjects with severe SCD from approximately 40 hospitals in the United States. Approximately a third of subjects (60 subjects) are likely to have a tissue matched donor. These subjects will be assigned to the donor arm and are eligible for transplant (HCT/BMT). The remaining 140 subjects will be assigned to the ‘no donor arm’ and will continue to receive ongoing standard of care treatment for SCD.

This study is open to males and females between 15 - 40 years old with SCD and have one or more serious problems that include:

- stroke or another serious brain complication
- 2 or more episodes of acute chest syndrome in the last 2 years even though treatment such as hydroxyurea to stop acute chest syndrome was given to you

- 6 or more episodes of severe vaso-occlusive pain (pain crises) in the last 2 years
- Receiving regular RBC transfusions (receiving 8 or more blood transfusions per year to prevent sickle related health problems)
- An echocardiographic finding of tricuspid value regurgitant (TRJ) velocity ≥ 2.7 m/sec
- Chronic Pain on a majority of days per month for ≥ 6 months

You cannot be in this study if you:

- Have cirrhosis of the liver (a very serious condition of liver failure)
- Have now or have had a very serious bacterial, viral or fungal infection in the past six weeks
- Have human immunodeficiency virus (HIV) infection
- Have already received a HCT/BMT
- Are currently pregnant or breast feeding

In order for you to qualify to participate in this research study, your medical history and the results of your screening evaluation will be checked to see if the sickle cell disease (SCD) complications that you have had and the results of your screening evaluation make you eligible to take part in this trial. If you are eligible for this trial, we need to first find out if we can identify an individual who can serve as a blood or bone marrow donor for your transplant. This is done by determining your HLA type.

Human Leukocyte Antigen (HLA) typing is done to learn your tissue type. Your immune system uses the HLA genes to tell the difference between your own tissues, which are not attacked, and germs and other foreign cells, which should be attacked. A transplant is most likely to be successful when the donor and recipient share the same HLA type. The person most likely to be HLA matched is a brother or sister from the same parents. It is also possible to search for a volunteer donor who by chance has the same HLA genes as you. In order to receive a HCT/BMT, a suitable HLA-matched donor must be identified and be willing to donate blood or bone marrow.

If you have previously undergone HLA typing and your doctor found a donor, you will not be able to take part in this study. We are informing you of all the risks and benefits of participating in this study if you do not have a donor at this time. If you do have a donor, you will be given a second consent form explaining the risks and benefits of HCT/BMT so that you can make a decision as to whether you will be willing to undergo a transplant.

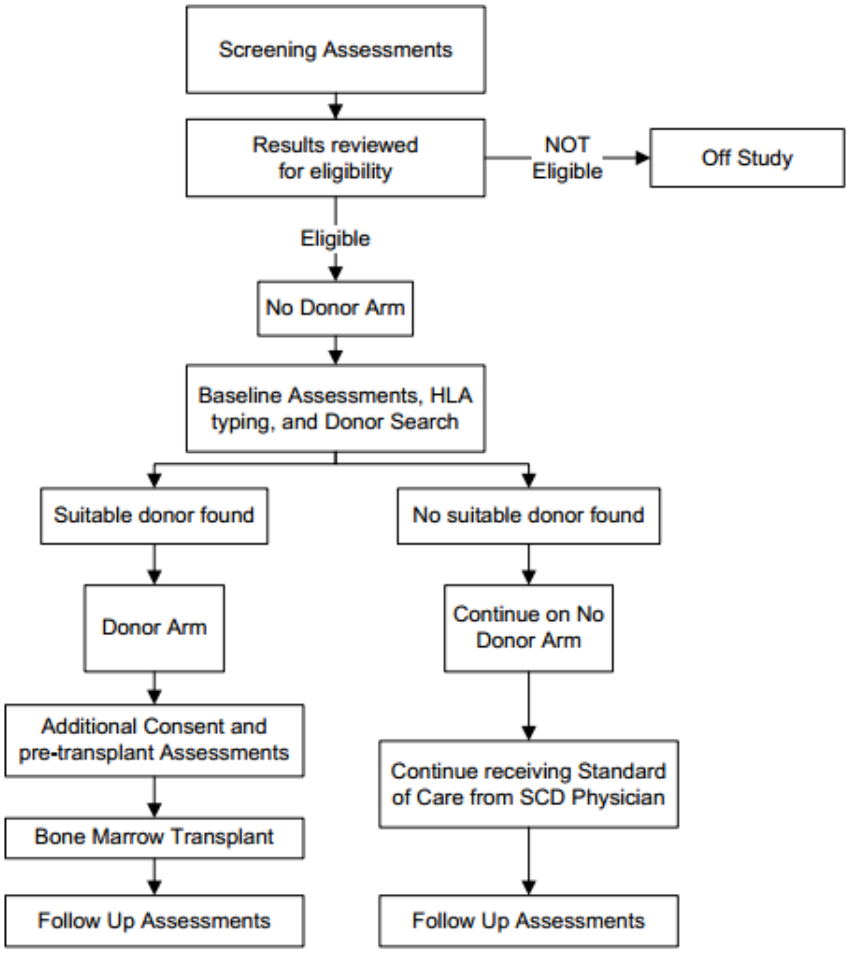
3. Purpose

The purpose of this research study is to compare transplant (HCT/BMT) to standard of care treatment in young adults with SCD.

We recommend that you participate in this study only if you have decided that you wish to take part in a study whose results will help us better understand the best treatment option for severe SCD. This means that if you have a donor, you will be assigned to the donor treatment group and will receive HCT/BMT. If you don't have a donor, you will remain in the no donor

treatment group and will continue to receive the care you are currently receiving. Both treatment groups will be followed for 2 years. There are scheduled tests now and for 2 years after we determine if you have a donor so we can compare how both groups are doing. This comparison allows physicians to compare the two treatment approaches. It is very important that you carefully consider whether assignment to one of two treatment groups is acceptable to you and that you are willing to be followed by 2 years. Between years 3 and 10 from enrollment, we will ask your doctor annually whether you are alive or dead and the date of last contact with your doctor. If you are not alive, we will ask for the date of death and the cause of death. If you doctor has lost contact with you, we will search the National Death Index, maintained by the government to record all deaths that occur in the U.S. Through the National Death Index, we will obtain the date of death and the cause of death.

4. Study Treatments and Tests



When you first enroll in the study:

- During this consultation, the BMT physician will review and confirm that you meet the eligibility criteria for the study which is based on your disease (SCD).
- If the BMT physician confirms you meet the eligibility criteria based on your disease and you agree to participate in this study, a series of screening evaluations will be conducted

to determine if your body can tolerate the treatment called transplant (BMT). These **screening assessments** include:

- History, Physical exam, height and weight
- Assessment of your performance status (how well you are able to do your normal activities)
- Urinalysis to check for protein and/or infection in your urine
- Blood Samples (about 3 teaspoons, or 1 tablespoon) will be drawn from one of the veins to conduct routine laboratory blood tests of your …
  - Blood counts (number of each type of blood cell),
  - Blood chemistries (elements and minerals in your blood, as well as elements that show kidney and liver health and check your blood clotting).
  - Hemoglobin S percent (a measure of the different kinds of hemoglobin in the blood such as transfused hemoglobin and sickle hemoglobin)
  - Blood drawn for HLA typing (about 1 tablespoon and tested only when eligibility is confirmed)
- If you are a female who can bear children, a pregnancy test will be performed using a sample of your blood or urine
- Echocardiogram (a test that takes numerous pictures of your heart to make sure the heart is functioning properly)
- Pulmonary function test (a test that measures how well the lungs work)
- 24-hour urine collection (a test to measure the amount of water and chemicals present in the urine) and/or a Radionuclide GFR (a blood test to measure kidney function)

- After you complete your screening assessments, your clinical information and SCD history will be verified to determine whether you are eligible for the study.
  - In the unlikely event you are not eligible for the study, you will not be enrolled on study and you will no longer be asked to provide follow up.
  - If you are confirmed eligible for the study, we will perform tissue typing and search for a donor.
- If you are confirmed eligible, HLA typing (tissue-typing) will be done to determine if you have a suitably matched donor (related or unrelated) who can donate blood or bone marrow cells for HCT/ BMT. If you have full siblings (i.e., from the same parents), we will contact them, and if interested, HLA type them to determine whether you are tissue matched to any of your siblings. If you do not have any full siblings, we will search among unrelated donors to determine if someone is matched to you. We will search for a donor for 180 days. If we are not able to find a donor within 180 days, you will be on the no donor arm for the remainder of the study.
- While we are searching for a donor, we will perform **baseline assessments** so we can have a better idea of your organ function and quality of life. Some of these baseline assessments are done <u>before</u> we know if you have a donor or not. These include:
  - 6 minute walk distance test: a test to measure how far you can walk in 6 minutes
  - Questionnaires about your health and quality of life: surveys to measure health outcomes from the patient perspective. Your doctor and/or the research team will provide the instructions and materials you will need to complete the survey at

each time point it is due Whenever possible, this questionnaire will be completed electronically during your study visits.
    - Pain diary: You will document your pain twice daily for 28 days via an electronic application. Your doctor and/or research team will provide the instructions you will need to complete the pain diary.
- The rest of the baseline assessments are done <u>after</u> we know if you have a donor or not. These include:
    - History, Physical exam, height and weight
    - Assessment of your performance status (how well you are able to do your normal activities)
    - Urinalysis to check for protein and/or infection in your urine
    - 24-hour urine collection (a test to measure the amount of water and chemicals present in the urine) and/or a Radionuclide GFR (a blood test to measure kidney function)
    - Blood Samples (about 3 teaspoons, or 1 tablespoon) will be drawn from one of the veins to conduct routine laboratory blood tests of your …
        - Blood counts (number of each type of blood cell),
        - Blood chemistries (elements and minerals in your blood, as well as elements that show kidney and liver health and check your blood clotting).
        - Hemoglobin S percent (a measure of the different kinds of hemoglobin in the blood such as transfused hemoglobin and sickle hemoglobin)
    - A blood and urine sample for future genetic testing (optional)
    - Echocardiogram (if it was not already done within the last 60 days)
    - Pulmonary function test (if it was not already done within the last 60 days)

If you have a donor:

- If the HLA typing shows that you have a suitably matched donor who is available**,** you will be re-assigned to the donor arm treatment group.
- You will be asked to sign a second consent form explaining the risks and procedures related to HCT/BMT. The detailed information about the risks and benefits of HCT/BMT will be explained by a doctor who performs the HCT/BMT.
- You will undergo **additional assessments in preparation for HCT/BMT** and for monitoring your health after HCT/BMT.
- You will receive chemotherapy drugs to prepare your body to receive stem cells from your donor.
- You will have a HCT/BMT
- We will study the side effects of transplant (HCT/BMT) including those that are expected and unexpected with additional follow up assessments. You will be followed weekly for the first 100 days after your transplant, and every 3 months thereafter

If you do <u>not</u> have a donor:

- You will remain in the no donor arm
- You will receive standard of care for your SCD (same treatment as you are receiving, or your sickle cell doctor may change that treatment depending on whether there are new medications available)

- You will be followed every 3 months for 2 years after it is determined you do not have a suitable donor

Follow up for all participants:

- You will be asked to come in for a study visit every 3 months for 2 years after we determine if you have a donor or not. We will measure the health of your body organs (lungs, brain, and kidneys) and functional outcomes. These tests will be done at baseline, one, and two years to compare the results between patients who receive standard of care treatment and patients who receive transplant. The following assessments will be performed regardless of whether you have a donor or not:

  Day 100, 180, and 270 Follow up Assessments:
  - History and Physical Exam
  - Review of any SCD events that have occurred since your last visit
  - [only at day 100 and day 180] Blood test to measure your hemoglobin S percent (a measure of the different kinds of hemoglobin in the blood such as transfused hemoglobin and sickle hemoglobin)

  Follow up Assessments at 1 year (Day 365):
  - 6 minute walk distance test: a test to measure how far you can walk in 6 minutes
  - Questionnaires about your health and quality of life: surveys to measure health outcomes from the patient perspective. Your doctor and/or the research team will provide the instructions and materials you will need to complete the survey at each time point it is due Whenever possible, this questionnaire will be completed electronically during your study visits.
  - Pain diary: You will document your pain twice daily for 28 days via an electronic application. Your doctor and/or research team will provide the instructions you will need to complete the pain diary.
  - Echocardiogram
  - Pulmonary function test and oxygen saturation by pulse oximetry

  Day 450, 540, and 630 Follow up Assessments:
  - History and Physical Exam
  - Review of any SCD events that have occurred since your last visit

  Follow up Assessments at 2 years (Day 730):
  - History and Physical Exam
  - Blood Samples (about 3 teaspoons, or 1 tablespoon) will be drawn from one of the veins to conduct routine laboratory blood tests of your …
    - blood counts (number of each type of blood cell),
    - blood chemistries (elements and minerals in your blood, as well as elements that show kidney and liver health and check your blood clotting).
    - Hemoglobin S percent (a measure of the different kinds of hemoglobin in the blood such as transfused hemoglobin and sickle hemoglobin)
  - Pulmonary function test and oxygen saturation by pulse oximetry
  - 6 minute walk distance test: a test to measure how far you can walk in 6 minutes
  - Urine test for protein (albumin) in your urine
  - Echocardiogram

  - Questionnaires about your health and quality of life: surveys to measure health outcomes from the patient perspective. Your doctor and/or the research team will provide the instructions and materials you will need to complete the survey at each time point it is due. Whenever possible, this questionnaire will be completed electronically during your study visits.
  - Pain diary: You will document your pain twice daily for 28 days via an electronic application. Your doctor and/or research team will provide the instructions you will need to complete the pain diary.
- Between years 3 and 10 from enrollment we will ask your doctor annually whether you are alive and the date you last talked with your doctor. If you are not alive, we will ask for the date of death and the cause of death. If you doctor has lost contact with you, we will search the National Death Index, maintained by the government to record all deaths that occur in the U.S. Through the National Death Index, we will obtain the date of death and the cause of death.

5. Risks and Discomforts

All participants will be asked to come in for a study visit every 3 months for 2 years after we determine if you have a donor or not. We will collect information including blood and other tests at follow up visits for 2 years. These tests are associated with no more than minimal risk although you may experience minor discomfort with blood draw. Participating in the health survey will not cause any physical discomfort but you may find some of the questions or topics on the survey upsetting. If this is the case, your doctor will refer you to a psychologist for counseling.

HCT/BMT and Standard of Care (SOC) are not the same in their chance of causing serious health problems, chance of early death, or chance of curing your sickle cell disease. The Standard of Care (SOC) treatment you receive for supportive care of your sickle cell disease has very low chance of causing health problems, and the chance of early death from your sickle cell disease is very low, but does increase as you get older. The Standard of Care (SOC) treatment you are receiving for your sickle cell disease will not cure the disorder. HCT/BMT is a procedure that has a higher risk of causing serious health problems and early death. However, HCT/BMT may cure your disease.

If you do not have a donor, there are no treatments that are research. Your condition may not get better or may get worse during the course of the study. Your doctor will treat you as before or may offer other treatment options. If your condition gets worse, your doctor will determine the best treatment for care.

All the procedures and potential risks associated with HCT/BMT will be outlined in a separate consent form that will be given to you if you have a donor and are assigned to the donor arm. If you have questions about the procedures, risks, and benefits associated with HCT/BMT you should ask your doctor now.

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate. If new

information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. Possible Benefits

You may or may not receive medical benefit from taking part in this study. If you are assigned to the transplant arm and the transplant is successful, you may benefit by not having further symptoms and complications of severe sickle cell disease.

Allowing us to collect SCD-related information at enrollment and 2 years later would allow us to directly compare the health outcomes for patients who receive HCT/ BMT to those patients who receive standard of care (regular/routine care). This is very important as this is the first time that SCD physicians will be able to do a direct comparison of patients with severe SCD to determine whether HCT/BMT is a better or worse treatment than routine care for severe SCD. In other words, even though you may not benefit directly, you will contribute towards helping treat future patients with severe SCD.

7. Optional Research Samples

This section of the Consent Form is about collection of optional blood and urine research samples from patients who are taking part in the trial. These research samples will be used for future research studies on patients with SCD.

You can choose to give blood and urine samples if you want to. You can still be a part of the main study even if you say "no" to giving optional blood and urine samples for these studies. You and/or your insurance will not have to pay for these samples to be collected or for any of the important research tests to be performed on these samples. Please mark your choice at the end of this section.

We would like to collect two (2) blood and urine samples over the course of the primary study for future research. If you agree, these samples will be collected at two different times during the primary study.

1. Within a few days after your specific primary study therapy is determined, we would collect about 6 teaspoons (31.5 mL) of blood and 10 teaspoons of urine (50 mL). Usually the blood can be drawn from a vein in your arm at the same time as other blood collections.

2. And about 2 years after your primary study therapy was determined, we would once again collect about 6 teaspoons (31.5 mL) of blood and 10 teaspoons of urine (50 mL).

The blood and urine samples collected for future research purposes will be sent to the Children's Healthcare of Atlanta (CHOA) Biorepository. The samples will be labeled with unique codes that do not contain information that could identify you. 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 biorepository where your samples are being stored does not have a link to this code. Your de-identified research samples may also be given

to investigators outside of Emory University for approved research studies. However, these laboratory investigators will not be able to trace the sample back to you.

Your research samples will continue to be stored at the (CHOA) Biorepository until they are used up for research. They will be kept unless you happen to change your mind and request to have your samples destroyed by withdrawing from the study or the Sponsor requests use of stored samples to be discontinued. If you stop being in the primary study before it is finished, upon your written request to [Insert site investigator] any remaining research samples you have given will be discarded when you tell us that you want to stop being in the study. Results we get before you stop being in the study will be kept.

Genetic Studies
DNA from your stored blood samples might be used in future genetic studies. We would like to test your DNA (or genes) to learn if some genes predict who will have serious complications of sickle cell disease. DNA is inherited information like a blueprint about the structure and functions of human body traits that make up the color of our hair and eyes and may affect the way our bodies respond to things that happen outside the body such as smoking, an illness, or infections. Based on genetic studies of patients with sickle cell disease that have been done already, we believe that common differences in genes that control inflammation (entry of white blood cells into tissue) are important reasons for differences in sickle cell disease symptoms. Thus, we are interested in the possibility that there are genes besides the sickle hemoglobin mutation that also contribute to problems with blood flow in your arteries and veins that cause pain and other sickle cell symptoms. In the course of these studies we may find new genes that are inherited and predict the development of other sickle cell disease symptoms.

Risks of Genetic Testing
In the course of these studies we may find new genes that are inherited and predict the development of sickle cell disease related illnesses. Once we have obtained your DNA (or genes) from the white blood cells, we will put the DNA in tubes. These tubes will be labeled with a code, and will have no markings to link the tube with you specifically. If we learn anything of importance to our research from this testing, we may publish the results in a medical journal. However, you will not be identified in the article as the patient who provided the blood sample for our testing.

In rare instances, it is possible that we could find out information about a specific gene that could affect you or other members of your family in terms of insurability, employability or paternity. We will do everything possible to ensure that your identity and confidentiality will not be breached. As previously mentioned, the code linking your identifying information to the sample will be kept secure by the BMT CTN DCC staff in a password protected file on a secure location.

Genome-Wide Association Studies
DNA from your stored blood samples 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 researcher is required to add your test results and sample information into a shared, 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, although the results of genetic studies could theoretically include identifying information about you.

Benefits of Genetic Testing
There will be no direct benefit to you for providing this additional blood sample for genetic testing. We hope that the information learned from the study treatment trial and these genetic research tests will help us understand what genes are important. This may further our understanding of the possible treatments to patients with sickle cell disease.

You will be given an additional choice to indicate whether or not your research samples can be used in these important genetic studies. You may choose not to participate in the genetic testing study and still have your blood and urine samples used for other important research. Once again, your decision does not affect your care and participation in the primary study.

Things to Think About:
The choice to let us have blood and urine 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 and urine can be kept for future research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

In the future, people who do research on these blood and urine 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, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your blood and urine will be used only for research and will not be sold. The research done with your blood and urine may help to develop new products in the future.

Benefits:
The benefits of research using blood and urine include learning more about how your body's immune system recovers after a transplant, as well as to gain knowledge that may help people in the future and make transplants even more successful.

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

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

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 [Insert institution].

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

Statement of Consent
The purpose of storing blood and urine 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 use of my blood and urine for research. 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 blood and urine samples may be collected and that my blood, urine and related health information can be stored indefinitely by the Children's Healthcare of Atlanta (CHOA) Biorepository and used for transplant-related and sickle cell disease research.

- ☐ I do agree to give optional blood samples for future research **which may include DNA genetic studies**.
- ☐ I do not agree to give optional blood samples for future research **which may include DNA genetic studies**.
- ☐ I do agree to give optional urine samples for future research.
- ☐ I do not agree to give optional urine samples for future research.

____ ____________
Signature Date

♦ ♦

8. Other Treatments

You do not have to participate in this study. Your participation is ***voluntary***. If you choose not to participate in the study, you will not be missing out on any standard therapy for sickle cell disease. You will receive the same excellent care from the doctors and nurses whether or not you decide to take part in this study. In addition, other types of transplants are currently available to you. You may also choose to receive a transplant that uses a different combination of medications or a higher or lower dosage of the same medications. The different transplant treatment plans each will have different risks and benefits. Your doctors can discuss each type of transplant with you in greater detail. If you do not have a suitably matched related or unrelated donor and want to still consider HCT/BMT as an option, you may be eligible for other clinical trials that utilize mismatched related or unrelated donors.

9. Costs and Reimbursements

Most of the care given in this study is standard care; it will be billed to you or your insurer in the usual way. This study is also approved by Centers for Medicare and Medicaid Services (CMS) for reimbursement. Standard costs include those of your hospitalization, doctor's visits, standard laboratory tests, medications, and the cost of the donor's blood or bone marrow. There will be no charge for research tests.

The study will pay for the research-related items or services that are provided only because you are in the study as outlined above. If you get a bill you think is wrong, call the researchers.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan or if you think your health plan may not cover these costs during the study, please talk to the research team or call your health plan's medical reviewer.

If you receive a bill, or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or [Insert institution] Patient Billing Services.

You and/or your health insurance will be charged, in the standard manner, for services and procedures provided for your routine care. Any deductibles, co-insurances or co-payments that are a part of your insurance coverage will apply.

10. Compensation of Payment

You will be paid $25 for completing the health related quality of life questionnaires. You will be asked to complete these questionnaires when you first enroll and at 1 and 2 years later. You can earn up to a total of $75 for completing the health related quality of life questionnaire.

You will receive $1.00 for each electronic pain diary entry. If you complete the pain diary twice daily, you will receive $2.00/day. This compensation will be the same for all three of the 28-day reporting periods. The potential compensation for completing the pain diary at all of these time points is $168.

The total amount of money you can earn for being in this trial is $243.

11. Physical Injury as a Result of Participation

[Insert institution] researchers and their associates who provide services at the [Insert institution] recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

If you believe that you are injured as a result of the research procedures being performed, please contact [Insert site PI name] immediately. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals [Insert institution]. The study sponsor, the National Heart, Lung, and Blood Institute, does not offer financial compensation or payment if you are injured as a result in participating in this research study. However, you are not giving up any legal rights by signing this form.

It is possible that [Insert institution] may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below.

12. Rights as a Participant

Your participation in this research study, including the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for your participation in this research study will have no effect on your current or future relationship with the [Insert institution]. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a [Insert institution] hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your physician is involved as an investigator in this research study. As both your physician and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with

this research study. You are not under any obligation to participate in any research study offered by your doctor.

If you have questions about your rights as a research participant or if you have questions, concerns or complaints about the research, you may contact the [Insert institution] Institutional Review Board (IRB) at the toll free number [Insert IRB Number].

13. Ending Your Participation

You may withdraw your consent, at any time, for your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for your participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form. Your decision to withdraw your consent for your participation in this research study will have no effect on your current or future medical care at [Insert institution] hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you are thinking about withdrawing from this study, talk with one of the research team members and your regular doctor first so they can help you decide what may be best for your medical care once you are off study. If you leave the study before the planned final visit, the study doctor may ask to have some of the end of study procedures done for your safety and well-being.

Your study doctor or NHLBI may decide to take you out of the study if:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in this study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

14. Privacy, Confidentiality, and Use of Information

By signing this consent form, you are giving the researchers your permission to obtain, use, and share information about you for this study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care. This may include information about hospital admissions or visits during this study, so that we know about any possible problems or side effects. If health information is needed from your doctors or hospitals from other institutions, you will be asked to give permission for these records to be sent to the researchers.

Any information about you obtained from this research will be kept as confidential (private) as possible. Federal Privacy Regulations protect your privacy, restrict who is allowed to look at your records, and require security to protect your records. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a unique study ID number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Information gathered during this study and your medical records may be inspected and verified by staff of the study sponsor (the National Heart, Lung, and Blood Institute/National Institutes of Health), Office for Human Research Protections, [Insert institution], or the Institutional Review Board (IRB). Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records shared outside of [Insert institution]. For records shared outside of [Insert institution], you will be given a study ID number. The list that can match you to the study ID number will be kept in a locked file cabinet in [Insert location].

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

> Authorized representatives of the sponsor of this research study, the National Institutes of Health, or the Office for Human Research Protections or the Blood and Marrow Transplant Clinical Trials Network will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.
>
> In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law.
>
> While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the [Insert institution] cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.
>
> Authorized representatives of the [Insert institution] or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for

the purpose of: (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e., quality assurance).

Data Warehouse Consultants (DWC) which is an agent of Emory University that will manage the pain diary. DWC will have access to your phone number, email address, IP Address and data that is entered in the pain diary application.

At the end of the study, the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI) will be given data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. The data and/or materials may be shared with other scientists who meet NHLBI requirements. These requirements include treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties.

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for ten years from enrollment on to study. Beyond the finding period (5-years), the dataset will be transferred to the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin for extended follow up. Data regarding your clinical situation, including follow-up after 2 years, may be obtained from the CIBMTR, which captures information on all US transplants.

Extended follow up: Between years 3 and 10 from enrollment, we will ask your doctor annually whether you are alive or dead and the date of last contact with your doctor. If you are not alive, we will ask for the date of death and the cause of death. If you doctor has lost contact with you, we will search the National Death Index annually using your Social Security number. The National Death Index is maintained by the government to record all deaths that occur in the U.S. Through the National Death Index, we will obtain the date of death and the cause of death. This follow up will apply to all subjects regardless of assigned treatment arm.

In accordance with the [Insert institution] Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

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.

15. Health Insurance Portability and Accountability Act (HIPAA)

HIPAA authorization to use and disclose individual health information for research purposes:

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *Bone Marrow Transplantation for Adolescents and Young Adults with Severe Sickle Cell.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results). The identities of individuals such as names and addresses will not be shared or de-identified to make sure information cannot be linked to you.

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain 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:

Members of the BMT CTN Data and Coordinating Center and BMT CTN #1503 Protocol Team

National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors

The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research

The Blood Center of Wisconsin (BCW), which is a central lab that will do specialized testing on blood samples required during the study

Data Warehouse Consultants (DWC) which is an agent of Emory University that will manage the pain diary. DWC will have access to your phone number, email address, IP Address and data that is entered in the pain diary application.

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

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 research-related treatment that is provided through the study. However, 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 the 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 or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date. However, you can elect at any time to withdraw your authorization to participate in the study.

16. For More Information

If you'd like more information about this study, or if you have any problems while you're participating in this study, you can contact the study doctor or staff. They may be contacted at the telephone numbers listed here:

[Insert name and contact details]

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.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, [Insert institution and number] to discuss problems, concerns, and answer any questions I have about my rights as a research participant, to obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Signature of Participant	Participant's Printed Name	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date

Assent to Participate in Research

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR A MINOR TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

This is a clinical trial, which is a research study to answer specific medical questions.
The information from this study may also help future patients. The Study doctor (the person in charge of the research) will explain the study to you. This research study will include only people who choose to take part in the study. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

A. Why am I here?

We are inviting you to join our study because you have severe sickle cell disease. You are now receiving blood transfusions, hydroxyurea and/or pain medicines. There is another treatment called hematopoietic cell transplant or bone marrow transplant (HCT/BMT). A transplant uses blood-making cells from another person (donor) to replace your cells that are not healthy (the sickle red blood cell). A donor is the name for a person who gives some of their blood-making cells for a transplant and their tissue has to match your tissue. Only 3 out of 10 persons will have a tissue-matched donor, so most people do not have a donor. In this study, if you have a donor, you will receive the treatment called HCT/BMT. If you don't have a donor, you will continue receiving blood transfusion, hydroxyurea, and/or pain medications.

B. Why are you doing this study?

We know transplant works to cure your disease, but we don't know if this is a better treatment than blood transfusions, hydroxyurea, and/or pain medicines.

C. What will happen to me if I receive a transplant?

Before your transplant, you will have check-ups with the study doctors and find out if you have a donor. If you have a donor, you will get a small tube put in your chest in the operating room (you will be asleep for this). The small tube makes it easier for you to get your medicines. It will also make it easier for drawing blood for tests because you will not be poked.

We will give you medicines that will help make the cells from your donor grow in your body. These medicines might make you feel sick. You might throw up, lose your hair, or get sores in your mouth.

After you're done taking the medicines, you will get cells from your donor. This is your transplant. Your donor can be your sister or brother (related) or someone you don't know (unrelated). Your new cells will come from your donor's blood or bone marrow. The cells will make new and healthy cells in your body.

Sometimes the donor cells can cause a problem called graft versus host disease (GVHD). GVHD happens when the donor cells attack your body. It can give you diarrhea, a skin rash, make you feel sick and throw up, or make you not feel hungry. Your doctors will give you medicines to try to make sure you don't get GVHD.

You will stay in the hospital for several days before your transplant and for about 4 weeks after your transplant. After you go home, you will need to go back to see your doctor often.

It is possible that your disease will come back. If this happens, your doctor will find another way to treat you.

You will be followed for two years with tests for follow up scheduled weekly for the first 100 days and then every 3 months.

D. What will happen to me if I do not receive a transplant?

If you don't have a donor, you will continue receiving blood transfusion, hydroxyurea, and/or pain medications.

You will be followed for two years with tests for follow up scheduled every 3 months.

E. Will it hurt?

For your transplant, we will put a small tube in your chest. It might hurt a little and you might bleed a little. Your doctor and nurses will make sure you feel as little pain as possible.

F. Will the study help me?

We know HCT/BMT can cure sickle cell disease. What we don't know is whether some of the problems from transplant like GVHD can cause more harm than if you did not have a transplant and continued to receive the care you are receiving now.

G. 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.

H. Do I have to be in this study?

You don't have to be in this study. Your doctor and nurses will not be mad at you if you don't want to join. If you decide you don't want to be in this study, you should talk to your doctor, nurses and parents about other ways to treat your disease.

You can say yes now and change your mind later.

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

Writing your name on this page means that you agree to be in the study and know what will happen to you. If you decide to quit the study, all you have to do is tell your doctor.

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

_____	_____
Printed Name of Child	Date
_____	_____
Signature of Child	Age of Child

Certification of Counseling Healthcare Professional: I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

_____	_____
Printed Name of Person Obtaining Assent	Role in Research Study
_____	_____
Signature of Person Obtaining Assent	Date

APPENDIX B-2

INFORMED CONSENT AND ASSENT FORMS FOR TRANSPLANT AND ADDITIONAL FOLLOW UP AS PART OF A RESEARCH STUDY

Informed Consent form for Transplant and Additional Follow Up as Part of a Research Study

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR AN ADULT TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

This is a clinical trial, which is a research study to answer specific medical questions. The information from this study may also help future patients. The Study doctor (the person in charge of the research) will explain the study to you. This research study will include only people who choose to take part. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

1. Introduction

You previously agreed to be part of a research study at [Insert institution]. The people who take part in research studies are called "participants". This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. You are being asked to sign this consent form because you have been assigned to the "donor arm" of the clinical trial. Before you decide if you would like to participate on the "donor arm" of the study, we want you to know why we are doing this study. Being in this study is voluntary. You do not have to take part in this study. If you decide not to participate on the "donor arm" we will continue follow you for two years unless you tell your doctor you do not want to be followed. Do not join this study unless all of your questions are answered.

After reading and discussing the important information in this consent form you should know:

- Why this research study is being done
- What will happen during the study
- Any possible benefits to you
- The possible risks to you
- How your personal health information will be treated during the study and after the study is over
- Whether being in this study could involve any costs to you
- What to do if you have problems or questions about this study

Please read, or have read to you, this consent form carefully. After you finish, talk with the study doctor and ask questions. You may also want to talk to family, friends, your primary care doctor or other health care provider about joining this study. If you decide that you would like proceed with HCT/BMT, you will be asked to sign this form. You will be given a copy of the signed form to keep.

Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to read and discuss with family or friends before making your decision. There are also names and telephone numbers of people you can call to get answers to any questions you may have now or at any time during or after the study. You may change your mind about staying in the study at any time. However, due to the nature of the treatment provided during this study, it might not be safe for you to immediately stop being in the study. If you have any questions about your staying in the study, please talk with the study doctor or study team.

This research study is sponsored by National Heart, Lung, and Blood Institute of the National Institutes of Health (the "Sponsor"). [Insert institution] is being paid by the Sponsor to conduct this study.

If you choose to take part in this study, it is important that you give a true and complete medical history. You must be honest about your past and present use of medications. Information that is untrue or incomplete could have very serious effects on your health and safety during the study.

2. Background

Your doctor has already explained your Sickle Cell Disease (SCD) and how a hematopoietic cell transplant (HCT/BMT) (also referred to as a bone marrow transplant or BMT) can be used to treat your SCD when you first joined the study. The HCT/BMT replaces the defective Sickle blood cells with blood cells from a healthy donor who could be a sibling or an unrelated donor with a tissue-type match that is similar to yours. HCT/BMT may stop the disease and its health problems. HCT/BMT for SCD is successful in children but has not yet been tested in very many adults.

In this study, we assign patients to two treatment options: HCT/BMT or standard of care (this is the same treatment you now receive for your SCD). The treatment is assigned based on whether you have a tissue-type matched (also known as HLA-matched) donor; if you have a donor, you are assigned to the donor treatment arm and will be offered HCT/BMT. If you do not have a donor, you are assigned to the no donor treatment arm and will continue with on-going care. By comparing the health outcomes for patients who receive HCT/BMT to those patients who receive standard of care (regular/routine care), we will be able to determine whether the two treatments are the same, or if one is better than the other.

The study will recruit 200 subjects with severe SCD from approximately 40 hospitals in the United States. Approximately a third of subjects (60 subjects) will be assigned to the donor arm and are eligible for transplant (HCT/BMT). The remaining 140 subjects will be assigned to the 'no donor arm' and will continue to receive ongoing standard of care treatment for SCD.

We found a tissue-type matched donor for you. Therefore, you are assigned to the donor treatment arm and will undergo a hematopoietic cell transplant if you sign this consent form.

Your doctor already determined you were eligible for this study, but to be eligible for transplant:

- Your liver must be healthy enough for transplant
- Your brain MRI must show that you have not had a recent neurologic event (such as stroke) within 30 days of starting transplant conditioning. If you did have a neurologic event, your transplant will be put on hold for 6 months. After the 6 months, the brain MRI will be repeated to see if your brain has healed.
- You must not have HLA (tissue-specific) antibodies against your donor
- You must be willing to use approved contraception until you have stopped taking all the medicines that work against your immune system
- Your donor must be healthy enough to donate and willing to donate hematopoietic cells.

3. Purpose

The purpose of this research study is to:

- To compare outcomes in patients with SCD who undergo HCT/BMT with those who do not undergo HCT/BMT because of the lack of a donor.

- To learn if it is possible and safe to treat persons with severe SCD by HCT/BMT from related and unrelated donors and to document serious side effects due to HCT/BMT (both expected and unexpected).

For 2 years from enrollment, you will undergo study-related tests and results will be made available to study team. Between years 3 and 10 from enrollment, we will ask your doctor annually whether you are alive or dead and the date of last contact with your doctor. If you are not alive, we will ask for the date of death and the cause of death. If you doctor has lost contact with you, we will search the National Death Index, maintained by the government to record all deaths that occur in the U.S. Through the National Death Index, we will obtain the date of death and the cause of death.

4. Study Treatments and Tests

We found a tissue-type matched donor for you, so you have been assigned to the donor arm. You have already signed a consent which told you about the study procedures and follow up. This consent form will go over transplant and additional donor-arm specific follow up.

Before your transplant:

- Before your transplant, the BMT doctor will need to determine if you are healthy enough for transplant. These transplant-related screening assessments include:
    - If you are a female who can bear children, a blood pregnancy test (about 1 teaspoon of blood will be drawn for this purpose)
    - MRA/MRI of the brain (tests that show a detailed view of the brain and its blood vessels)
    - MRI of your liver may be required if you meet certain criteria based on this history of your SCD.
        - A liver biopsy may be required based on the results of your [liver] MRI.
- If you are determined to be healthy enough, you will proceed to transplant. If you are not healthy enough, you will not have a transplant and will continue receive standard of care from your SCD doctor.

Preparation for your transplant and transplant conditioning:

- Transplant Conditioning is the chemotherapy and other medicines given to prepare you to receive donor hematopoietic cells. It will help stop your immune system from attacking the donor cells and blocking engraftment or the donor cells ‘taking’. You will receive these medications before the HCT/BMT. These medications will be given in the hospital.
- If you are taking hydroxyurea, this medication will be discontinued at least one week before you start the conditioning therapy.
- To help with providing medicines, blood transfusions and obtaining blood for lab tests, a central venous catheter will be used. This is a hollow tube that is placed by a surgeon or radiologist, usually in the operating room. The tube is placed in the chest and allows medicines, transfusions, etc. to be given painlessly into the vein without the need for repeated sticking of needles in your arms. Once the catheter is placed, it will need daily care at home with cleaning and injection of medicines to prevent catheter-related blood

clots. The doctor doing the procedure and the anesthesiologist will describe the risks of the procedure before the surgery. You or your family members will be instructed on the care of this catheter.

- Transplant Conditioning Regimen:
  - [Insert 1, Conditioning Regimen Drugs, from Appendix B-3, B-4, or B-5]

Transplant and Post-Transplant Care:

- On the day of transplantation, you will receive the hematopoietic cell infusion that will be given through the central venous catheter. Your blood pressure, heart rate, respiration rate, and temperature, will be taken before and during the infusion. The study doctor may also give you medications before the infusion to prevent side effects or discomfort.
- After transplant, you will receive additional medications to help prevent a condition called graft-versus-host disease (GVHD). GVHD will be explained more later on in this document.
  - [Insert 2, GVHD Prophylaxis Drugs, from Appendix B-3, B-4, or B-5]

Additional Donor Arm Follow-Up:

- We will study the side effects of transplant (BMT) including those that are expected and unexpected in addition to the assessments described in the consent form you already assigned. These additional follow up assessments include:
  - Weekly physicals and GVHD assessments from day 7 to day 100 post-transplant.
  - White blood cell chimerism assessment at day 28, day 100, 1 year, and 2 years.
  - Red blood cell chimerism assessment for research at day 100 and 2 years
  - MRA/MRI of the brain (tests that show a detailed view of the brain and its blood vessels) at 2 years

5. Risks and Discomforts

You may experience discomfort, injury, and other risks as a result of taking part in this study, some of which are not currently known at this time. You may also learn medical information about you that you were previously unaware of and would rather not know. Also, your condition may not get better or may get worse during this study.

By taking part in this research study, you are at risk to a number of complications, some of which can be severe and sometimes fatal. The most serious and commonly encountered include:

Graft-versus-Host Disease (GVHD):

This condition results from white cells called T cells in the donor's hematopoietic cell cells recognizing your body as foreign and attacking it. You are more likely to get GVHD if the donor's tissue type does not match your tissue type well. There are two forms of GVHD: acute GVHD (usually occurs in the first 3 months after transplant) and chronic GVHD (usually occurs later and lasts longer). Acute GVHD may produce a skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened skin, joint stiffness, dry eyes, dry mouth, liver disease, weight loss, diarrhea and an increased risk of infection. Some patients

who have GVHD have developed collections of fluid around the heart (known as a pericardial effusion) or other body spaces such as around the lungs. These fluid collections may interfere with heart or lung function and may require surgical drainage or other treatments. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a skin biopsy (i.e., taking a small sample of skin tissue to look at under the microscope) and possibly an intestinal biopsy and rarely a liver biopsy.

There is at least a 10-20% chance that you will develop GVHD after the transplant. The risk of GVHD is higher after an unrelated donor transplant. You will be watched closely for this complication and given treatment to treat it further if it occurs despite the medicines given to prevent it. In most cases, GVHD can be successfully treated. If GVHD does not respond to the medicines listed above, treatment can involve combinations of many other medicines with different side effects. Chronic GVHD can also occur 3 or more months after transplantation and may be associated with a prolonged course. GVHD can range from mild to life-threatening. Treatment may be necessary for many years as GVHD symptoms can last for many months or years. Prolonged treatment for chronic GVHD can result in a weak immune system and infections and may need frequent medical care and hospitalization. It is possible that GVHD can leave you with chronic medical problems which are worse than symptoms or disability you currently experience due to sickle cell disease. Sometimes GVHD is severe or difficult to treat and may lead to death.

Susceptibility to bacterial and viral infections in the early post-transplant period:

In the early post-transplant period, you will have an increased chance of getting bacterial or viral infections. This is because your ability to fight infections will be greatly limited due to the drugs given to prepare you for the BMT/HCT.

Potential risk of reversible brain injury RPLS/PRES and bleeding in the brain:

Patients with sickle cell disease who have a HCT/BMT have a higher than expected occurrence of a usually uncommon (< 5%) complication called reversible posterior leukoencephalopathy syndrome (RPLS) also known as posterior reversible encephalopathy syndrome (PRES) a form of injury to the brain, which is usually reversible. Patients with RPLS/PRES have confusion and other changes in their ability to think. Sometimes, they experience seizures, sleepiness or, rarely, loss of consciousness. RPLS is diagnosed with an MRI of the brain. It is a disorder that is sometimes seen in patients with sickle cell disease even if they do not have a transplant. In transplant patients, it is usually caused by some of the drugs used to prevent or treat graft versus host disease. It can often, but not always, be prevented by very careful control of blood pressure. It is treated by changing graft versus host disease drugs, controlling blood pressure and/or giving anti-seizure medicines. It is likely that about a quarter of the patients are at risk to develop RPLS/PRES. All sickle cell patients who develop RPLS/PRES typically can be successfully treated for this complication. We do not anticipate RPLS/PRES in any patient more than 6 months from their date of transplant. We believe that patients who are on prednisone or other corticosteroids, or immunosuppressive drugs such as cyclosporine or tacrolimus or have high blood pressure are more likely to develop RPLS/PRES.

A very small number of patients with sickle cell disease have experienced bleeding in the brain after an HCT/BMT. While this complication is rare, it is very serious because it can cause permanent brain damage or death. Your doctors will keep your platelet count in a safe range and monitor you carefully to keep you safe and prevent bleeding in the brain.

If you experience any of these side effects or changes in mental status, you should contact your transplant physician right away, since early treatment is important. It is also important that any blood pressure medication be taken as prescribed to decrease the risk of RPLS/PRES.

Potential risk of drugs used to ensure engraftment of new hematopoietic cells:

To reduce the risk that the new hematopoietic cells will not "take" or grow, you will receive the medications listed previously, called the conditioning regimen, before transplantation. These drugs have possible side effects which include:

[Insert 3, Conditioning Regimen Risks, from Appendix B-3, B-4 or B-5]

Potential Side Effects of Drugs used to prevent GVHD:

Although we have learned much about how to prevent the disease, graft-versus-host disease may be difficult to treat once it occurs and the complications associated with it can be life-threatening. You will be given drugs to prevent graft-versus-host disease. These drugs have possible side effects which include:

[Insert 4, GVHD Prophylaxis Risks, from Appendix B-3, B-4 or B-5]

Damage to the vital organs in your body

The conditioning or GVHD treatment could result in problems in the heart, lungs, liver, intestine, kidneys and bladder, brain etc. Lung problems can be the result of infections or chemotherapy and sometimes as a complication of GVHD. Some patients can have veno-occlusive disease of the liver (VOD). This complication usually results from high doses of chemotherapy. Patients with VOD become jaundiced (yellowish skin), have liver function abnormalities, fluid retention, abdominal swelling, and abdominal pain. If organ damage symptoms are severe, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although many patients recover completely, these complications may cause permanent damage or even death.

Serious infections

Full and complete recovery of your immune system may take many months following the initial recovery of your cell counts. During this time, there is an increased risk of infections. You will be prescribed certain medications to reduce the chance of those infections. However, preventive treatments are not always effective. 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 are fatal.

Recurrence of disease and graft rejection.

There is a risk that the new marrow will fail to “take” and grow after transplantation. This is called graft rejection. If this happens, your own marrow will recover meaning that symptoms of your

sickle cell disease such as pain crises and other complications will return. Your blood will be evaluated frequently after transplantation to determine if the new donor hematopoietic cells are recovering. In the event that your marrow does not recover as expected, stimulating the hematopoietic cells by drugs, performing second HCT/BMT or giving hematopoietic cells from another donor are treatment options. If you develop graft rejection, you will stop being in this study but you will continue to receive the standard medical care. Delay or failure of hematopoietic cell recovery increases the risk period of infection and the need for blood transfusions.

Central venous catheter complications
The most common complications associated with central venous catheters are blood clots in the catheter and infection. If clots form, a medicine will be injected to dissolve the clot. If it cannot dissolve, the catheter may need to be replaced. Infections will be treated with medicines; sometimes, removal of the infected catheter is required and a new catheter will need to be placed.

Pregnancy:
For Women:
The treatment on this study can affect an unborn child. You should not become pregnant or breast feed your baby while being treated in this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use an effective method to avoid pregnancy or you must not have sex. The study doctor will talk to you about acceptable methods of contraception to avoid pregnancy while you are being treated in this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated in this study. Since treatments may alter/disrupt normal menstrual cycles, resulting in missed or absent periods, natural methods of family planning should not be used. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If you become pregnant during the research study, please tell the study doctor and your doctor immediately.

If you are nursing a baby, the medications used in this research could pass into the breast milk. You should not nurse your baby for the whole time you are getting the study medicines. You may need to continue this for a while, even after you finish the treatment, so talk to your doctor about the length of time you need to avoid nursing.

For Men:
The treatment on this study can damage testicular function. You should not father a child while in this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use an effective method of contraception to avoid pregnancy or you must not have sex. The study doctor will talk to you about the acceptable methods to avoid pregnancy while you are being treated in this study. You will have to use the chosen method to avoid pregnancy or abstain (not have sexual intercourse) the whole time you are being treated in this study. Natural family planning and the rhythm method will not be permissible means of avoiding pregnancy during study participation. If you have questions about this or want to change your method to avoid pregnancy during therapy, please ask your doctor. If your partner becomes pregnant during the research study, please tell the study doctor and your doctor immediately.

Impact on reproductive hormone function and sexuality
High doses of chemotherapy can cause sterility (inability to have children) and decreased hormone levels. Some patients with chronic GVHD have reported impaired sexual function due to decreased sexual desire and vaginal dryness. Since the chemotherapy doses used in the preparative regimen for this study are lower, the risk of sterility may be lower. However, it is difficult to know the exact risk of sterility after transplant with the use of this conditioning regimen. Since there is a high risk of infertility after an HCT/BMT in both males and females we will refer you to a fertility preservation center to discuss your options. These may include storage of sperm/eggs or tissue from ovary or testes.

Risk of death
Some of the side effects of an unrelated donor transplant may be very severe and may cause death despite using all supportive care. Though all precautions will be taken to make the transplant as safe as possible for you, there is still a 10% - 20% chance of death following unrelated donor transplantation.

Oher Risks
As with any procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening. You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. Possible Benefits

You may or may not benefit from taking part in this study. If the transplant is successful, you may benefit by not having any further symptoms and complications of severe sickle cell disease. The information obtained from your participation in this study will help doctors treat future patients with severe sickle cell disease who require a transplant.

7. Other Treatments

You do not have to participate in this study. Your participation is ***voluntary***. If you choose not to participate in the study, you will not be missing out on any standard therapy for sickle cell disease. You will receive the same excellent care from the doctors and nurses whether or not you decide to take part in this study. In addition, other types of transplants are currently available to you. You may also choose to receive a transplant that uses a different combination of medications or a higher or lower dosage of the same medications. The different transplant treatment plans each will have different risks and benefits. Your doctors can discuss each type of transplant with you in greater detail.

8. Costs and Reimbursements

Several of the tests and treatments given in this study are considered standard care and will be billed to you or your insurer in the usual way. This study is also approved by Centers for

Medicare and Medicaid Services (CMS) for reimbursement. Standard costs include those of your hospitalization, doctor's visits, standard laboratory tests, medications, and the cost of the donor's hematopoietic cells. There will be no charge for research tests.

The study will pay for the research-related items or services that are provided only because you are in the study as outlined above. If you get a bill you think is wrong, call the researchers.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed for your care
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan or if you think your health plan may not cover these costs during the study, please talk to the researchers or call your health plan's medical reviewer. It is recommended that you work with your health care team to find out about costs in advance.

If you receive a bill, or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or [Insert institution] Patient Billing Services.

You and/or your health insurance will be charged, in the standard manner, for services and procedures provided for your routine care. Any deductibles, co-insurances or co-payments that are a part of your insurance coverage will apply.

9. Compensation of Payment

You will not receive additional compensation for participating on the transplant portion of this clinical trial. You will continue to receive compensation for the health related questionnaire and the electronic pain diary as was explained to you when you previously agreed to participate on this trial.

10. Physical Injury as a Result of Participation

[Insert institution] researchers and their associates who provide services at the [Insert institution] recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

In the event that this research activity results in an injury, treatment will be available, including first-aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to your insurance company. If you think that you have suffered a research-related injury, let the study doctors know right away. It is important that you tell your doctor, [Insert Investigator], 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 [Insert

telephone]. You will receive medical treatment if injured as a result of taking part in this study. Your insurance will be charged for this treatment. The study sponsor, the National Heart, Lung, and Blood Institute, does not offer financial compensation or payment if you are injured as a result in participating in this research study. However, you are not giving up any legal rights by signing this form.

It is possible that [Insert institution] may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below.

11. Rights as a Participant

Your participation in this research study, including the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for your participation in this research study will have no effect on your current or future relationship with the [Insert institution]. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a [Insert institution] hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your physician is involved as an investigator in this research study. As both your physician and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

You may choose to either take part or to not take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision is made, there will be no penalty and you will not lose any of your regular benefits. If you leave the study, you can still get medical care from your doctor and transplant center. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any legal rights to seek payment by signing this form.

If you have questions about your rights as a research participant or if you have questions, concerns or complaints about the research, you may contact the [Insert institution] Institutional Review Board (IRB) at the toll-free number [Insert IRB Number].

12. Ending Your Participation

You may withdraw your consent, at any time, for your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable

medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for your participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

If you are thinking about withdrawing from this study, talk with one of the research team members and your regular doctor first so they can help you decide what may be best for your medical care once you are off study. **However, withdrawal after initiation of treatment could be life-threatening or even fatal, and may not be reasonable.**

If you leave the study before the planned final visit, the study doctor may ask to have some of the end of study procedures done for your safety and well-being.

Your study doctor or NHLBI may decide to take you out of the study if:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in this study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

13. Privacy, Confidentiality, and Use of Information

By signing this consent form, you are giving the researchers your permission to obtain, use, and share information about you for this study, and are required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Information from your hospital or office health records that may be reasonably related to the conduct and oversight of the research study. This may include information about hospital admissions or visits during this study, so that we know about any possible problems or side effects. If health information is needed from your doctors or hospitals from other institutions, you will be asked to give permission for these records to be sent to the researchers.
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

Any information about you obtained from this research will be kept as confidential (private) as possible. Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations protect your privacy, restrict who is allowed to look at your records, and require security to protect your records. All records related to your involvement in this research

study will be stored in a locked file cabinet. Your identity on these records will be indicated by a unique study ID number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

We will do our best to make sure that the personal information in your medical record be kept private. However, we cannot guarantee total privacy. Your personal information may be given out 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.

Information gathered during this study and your medical records may be inspected and verified by staff of the study sponsor (the National Heart, Lung, and Blood Institute/National Institutes of Health), Office for Human Research Protections, [Insert institution], or the Institutional Review Board (IRB). Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records shared outside of [Insert institution]. For records shared outside of [Insert institution], you will be given a study ID number. The list that can match you to the study ID number will be kept in a locked file cabinet in [Insert location].

Organizations that may look at and/or copy your medical records and protected health information for research, quality assurance, and data analysis include:

- Members of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), which is conducting this study
- The EMMES Corporation, a research organization that is helping to coordinate this study
- The National Marrow Donor Program (NMDP) and the Center for International Blood and Marrow Transplant Research (CIBMTR), organizations involved in research on blood and marrow transplantation and in the coordination of this study
- The National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

> Authorized representatives of the sponsor of this research study, the National Institutes of Health, or the Office for Human Research Protections or the Blood and Marrow Transplant Clinical Trials Network will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the [Insert institution] cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.

Authorized representatives of the [Insert institution] or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of: (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

At the end of the study, the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI) will be given data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. The data and/or materials may be shared with other scientists who meet NHLBI requirements, including treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties.

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of seven years after final reporting or publication of a project. The study results will stay in your research record at (*insert Institution*) for ten years from enrollment. Beyond the funding period (5-years), the dataset will be transferred to the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin for extended follow up. Research information in your medical record will be kept indefinitely. Data regarding your clinical situation, including follow-up after 2 years, may be obtained from the CIBMTR, which captures information on all US transplants.

In accordance with the [Insert institution] Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

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.

14. Health Insurance Portability and Accountability Act (HIPAA)

HIPAA authorization to use and disclose individual health information for research purposes:

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *Bone Marrow Transplantation for Adolescents and Young Adults with Severe Sickle Cell.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results). The identities of individuals such as names and addresses will not be shared or de-identified to make sure information cannot be linked to you.

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain 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:

Members of the BMT CTN Data and Coordinating Center and BMT CTN #1503 Protocol Team

National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors

The National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research

The Blood Center of Wisconsin (BCW), which is a central lab that will do specialized testing on blood samples required during the study

Data Warehouse Consultants (DWC) which is an agent of Emory University that will manage the pain diary. DWC will have access to your phone number, email address, IP Address and data that is entered in the pain diary application.

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

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 research-related treatment that is provided through the study. However, 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 the 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 or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date. However, you can elect at any time to withdraw your authorization to participate in the study.

15. For More Information

If you'd like more information about this study, or if you have any problems while you're participating in this study, you can contact the study doctor or staff. They may be contacted at the telephone numbers listed here:

[Insert name and contact details]

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.

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VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, [Insert institution and number] to discuss problems, concerns, and answer any questions I have about my rights as a research participant, to obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Signature of Participant	Participant's Printed Name	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date

Assent to Participate in Transplant and Additional Follow Up as Part of a Research Study

[Insert site logo and/or address]

TITLE: A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

Principal Investigator: [Insert site PI]
Co-Investigators: [Insert site co-I]

Study Coordinators: [Insert site study coordinator/s]

[Insert site department/facility name, address, and phone number]

Source of Support: National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (the NIH), Bethesda, Maryland

CONSENT FOR A MINOR TO BE A SUBJECT IN CLINICAL RESEARCH AND AUTHORIZATION TO PERMIT THE USE AND DISCLOSURE OF IDENTIFIABLE MEDICAL INFORMATION (PROTECTED HEALTH INFORMATION) FOR RESEARCH PURPOSES.

This is a clinical trial, which is a research study to answer specific medical questions.
The information from this study may also help future patients. The Study doctor (the person in charge of the research) will explain the study to you. This research study will include only people who choose to take part in the study. Please take your time to make your decision about taking part in the study. You may discuss your decision with family and friends. You should also discuss this with your healthcare team. If you have any questions, you can ask the Study doctor for more explanation.

A. Why am I here?

We are inviting you to join our study because you have severe sickle cell disease. You are now receiving blood transfusions, hydroxyurea, and/or pain medicines. There is another treatment called hematopoietic cell transplant or bone marrow transplant (HCT/BMT). A transplant uses blood-making cells from another person (donor) to replace your cells that are not healthy (the sickle red blood cell). A donor is the name for a person who gives some of their blood-making cells for a transplant and their tissue has to match your tissue. We have identified a donor for you and inviting you participate in this study to receive the treatment called bone marrow transplant HCT/BMT.

B. Why are you doing this study?

We know transplant works to cure your disease, but we don't know if this is a better treatment than blood transfusions, hydroxyurea, and/or pain medicines.

C. What will happen to me?

Before your transplant, you will get a small tube put in your chest in the operating room (you will be asleep for this). The small tube makes it easier for you to get your medicines. It will also make it easier for drawing blood for tests because you will not be poked.

We will give you medicines that will help make the cells from your donor grow in your body. These medicines might make you feel sick. You might throw up, lose your hair, or get sores in your mouth.

After you're done taking the medicines, you will get cells from your donor. This is your transplant. Your new cells will come from your donor's blood or bone marrow. The cells will make new and healthy cells in your body.

Sometimes the donor cells can cause a problem called graft versus host disease (GVHD). GVHD happens when the donor cells attack your body. It can give you diarrhea, a skin rash, make you feel sick and throw up, or make you not feel hungry. Your doctors will give you medicines to try to make sure you don't get GVHD.

You will stay in the hospital for several days before your transplant and for about 4 weeks after your transplant. After you go home, you will need to go back to see your doctor often.

It is possible that your disease will come back. If this happens, your doctor will find another way to treat you.

D. Will it hurt?

For your transplant, we will put a small tube in your chest. It might hurt a little and you might bleed a little. Your doctor and nurses will make sure you feel as little pain as possible.

E. Will the study help me?

We know HCT/BMT can cure sickle cell disease. What we don't know is whether some of the problems from transplant like GVHD can cause more harm that if you did not have a transplant and continued to receive the care you are receiving now.

F. 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.

G. Do I have to be in this study?

You don't have to be in this study. Your doctor and nurses will not be mad at you if you don't want to join. If you decide you don't want to be in this study, you should talk to your doctor, nurses, and parents. You will receive the care you are receiving now (pain medication, blood transfusion, or hydroxyurea).

You can say yes now and change your mind later.

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

Writing your name on this page means that you agree to be in the study and know what will happen to you. If you decide to quit the study, all you have to do is tell your doctor.

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

_____	_____
Printed Name of Child	Date
_____	_____
Signature of Child	Age of Child

Certification of Counseling Healthcare Professional: I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

_____	_____
Printed Name of Person Obtaining Assent	Role in Research Study
_____	_____
Signature of Person Obtaining Assent	Date

APPENDIX B-3

Consent Information for Conditioning Regimen A

APPENDIX B-3

CONSENT INFORMATION FOR CONDITIONING REGIMEN A

Insert 1, Conditioning Regimen Drugs

- The first medication you will be given for conditioning is called **fludarabine**, which will be given intravenously or IV (using the central venous catheter) for a total of 5 days prior to the transplant.
- The second medication is called **busulfan**. This drug will also be given IV through the central catheter for 4 days prior to the transplant.
- The third medication is called **anti-thymocyte globulin (ATG)**, and will also be given IV. The ATG will also be given for 5 days before the transplant.

Each of these drugs are routinely used as part of a conditioning regimen before transplant and to prevent graft versus host disease.

Insert 2, GVHD Prophylaxis Drugs:

- The first medication is called **methotrexate.** Methotrexate will be given on Days 1, 3, 6, and 11 following the bone marrow transplantation.
- The second medication that you will receive is a class of medicines called a **calcineurin inhibitor (Cyclosporine A or Tacrolimus)**. The calcineurin inhibitor will be given IV starting on Day 3 before the bone marrow transplantation and will be given until Day 180. After Day 180, a tapering of this medicine (gradual decreasing of the amount given) will start and will continue until it has been stopped. The dose may be modified by the study doctor if there is evidence of GVHD or if there is worry about the possibility of a graft rejection.

Insert 3, Conditioning Regimen Risks:

Fludarabine: Can cause rare side effects such as: temporary blindness, confusion, and coma. Infrequent side effects such as poor kidney function, common side effects such as mouth sores and likely side effects such as nausea, vomiting, and diarrhea.

Fludarabine

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Anemia due to decreased number of red cells Infection due to decreased number of white blood cells Bleeding due to decreased numbers of platelets	Pneumonia Diarrhea Mouth sores Skin rash Fever Swelling of hands and feet	Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet Changes in vision Agitation/nervousness

Tiredness Nausea Vomiting Weakened immune system		Confusion Cough Difficulty breathing Weakness Severe brain injury and death

Busulfan: Can cause rare side effects such as: infertility (inability to have children) and lung injury when used at high doses or for prolonged periods of time. Infrequent side effects such as seizures, common side effects such as sores in the mouth and darkening of the skin, and likely side effects include nausea, vomiting, and hair loss.

Busulfan

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Loss of appetite Nausea Vomiting Skin breakdown if drug leaks from vein Anemia due to decreased number of red cells Infection due to decreased number of white blood cells Bleeding due to decreased numbers of platelets Mouth sores Temporary hair loss	Diarrhea Inflammation of the lung Weakness Weight loss	Low blood pressure Excessive perspiration Allergic reaction Damage/ scarring of lung tissue Sterility Seizure

Anti-Thymocyte Globulin: Is an antibody (made in rabbits) which can cause rare side effects such as seizures and increased risk of infection, infrequent side effects such as joint pain or allergic reaction (with low blood pressure, fast heart and breathing rate, difficulty breathing, and hives) and anemia, and common side effects such as fever and rash.

Anti-Thymocyte Globulin

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*

Fever Chills Anemia due to decreased number of red cells Infection due to decreased number of white blood cells Bleeding due to decreased numbers of platelets Weakened immune system	Nausea Vomiting Diarrhea Rash Headache Sweating Back pain Severe itching Allergic reaction of skin and blood vessels Tiredness Loss of appetite	Abdominal pain Dizziness High blood pressure Blisters Pain in the muscles Herpes simplex infection Inflammation of the throat

Insert 4, GVHD Prophylaxis Risks:

Calcineurin inhibitor (Cyclosporine or Tacrolimus): Can cause rare side effects such as temporary blindness, seizures, confusion and coma, common side effects such as poor kidney function and in some cases a need for dialysis (rare), increased risk of infection, swelling of the gums, infrequent side effects include numbness/tingling/tremors in hands and feet, and some likely side effects include high blood pressure, increased body hair, and chemical imbalances.

Cyclosporine: This drug may be used for all patients.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
High blood pressure Kidney problems Headaches Nausea Vomiting Stomach pain or indigestion Swelling of the hands or feet	Tremors Increased hair growth	Muscle cramps Numbness and tingling of the hands or feet Seizure

Tacrolimus: This drug may be used for all patients.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients.*

		They may be serious if they occur.)
Anemia Loss of appetite Diarrhea High potassium levels High blood pressure Nausea Fever Headache High blood sugar	Hair loss Vomiting Tingling sensation in the extremities Itching Rash Abdominal pain	Confusion Painful joints Increased sensitivity to light Blurred vision Insomnia Infection Jaundice Kidney injury Seizures

Methotrexate: Can cause depression of the white blood count early after transplant, transient alteration in liver function and can result in severe mouth sores.

Methotrexate

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
High levels of liver enzymes	Nausea Vomiting Loss of appetite Diarrhea Mouth sores Sensitivity to sunlight Increased risk of sunburn Decreased number of red and white blood cells and platelets	Hair loss Dizziness Redness, tenderness, darkening, and peeling of skin Blurred vision Allergic reaction Damage to nerve tissue Kidney damage Seizures Decreased lung function Decreased liver function - temporary Bone and tissue damage Loss of memory, concentration, balance, and walking Poor nervous system function

APPENDIX B-4

Consent Information for Conditioning Regimen B

APPENDIX B-4

CONSENT INFORMATION FOR CONDITIONING REGIMEN B

Insert 1, Conditioning Regimen Drugs

- The medication you will be given for conditioning is called **Alemtuzumab**, which will be given intravenously or IV (using the central venous catheter) for a total of 5 days prior to the transplant.
- After that, you will get a low dose of **total body irradiation (TBI).** A single dose will be given while you are put in front of a machine two days before your transplant.

- This conditioning regimen is routinely used before transplant.

Insert 2, GVHD Prophylaxis Drugs:

- The medication called **Sirolimus** will be given to you one day before your transplant until Day 180. After Day 180, a tapering of this medicine (gradual decreasing of the amount given) will start and will continue until it has been stopped. The dose may be modified by the study doctor if there is evidence of GVHD or if there is worry about the possibility of a graft rejection.

- This drug is routinely used for GVHD prevention.

Insert 3, Conditioning Regimen Risks:

Alemtuzumab

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 2%)	Rare, but Serious (May happen in 2% or fewer patients)
• Infection, which may cause fever and chills • Joint pain • Low platelet levels, which may cause bruising, bleeding • Low red blood cell counts, which may cause tiredness or may require blood transfusions • Low white blood cells, which may cause increased	• Cough • Feeling anxious • Feeling tired • Headache • Hypertension • Irregular heartbeat, most commonly fast heart rate • Muscle stiffness, spasms, tremor or pain • Problems sleeping • Rash, itching	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, dizziness, swelling of the face or throat • Heart problems including heart enlargement, or impaired heart pumping • Inflammation of the brain

infections and slower wound healing • Nausea, vomiting, abdominal pain, diarrhea, loss of appetite • Reaction to the medication infusion, which may include itching, fever, chills, low blood pressure and problems breathing • Sweating • Swelling of ankles and feet • Thyroid function decreased		• Inflammation of the gallbladder

Low Dose TBI

Common, some may be serious (>20%)	Occasional, some may be serious (4 - <20%)	Rare and serious (3% or fewer)
• Anemia (low red blood cells) which may require blood transfusions • Infection, especially when white blood cell count is low • Low platelet counts, which may cause bruising or bleeding • Mouth sores • Nausea, vomiting, stomach pain, diarrhea	• Eye cloudiness • Hair loss • Inability to have children • Painful swelling of the salivary glands under the ears for a few days • Redness of the skin	• A new cancer resulting from treatment of a prior cancer • Back pain • Difficulty swallowing • Hormone problems (such as thyroid disease or diabetes) • Kidney problems • Learning problems • Liver problems • Lung inflammation • Risk of developing other cancers in the future • Slowing of growth (body height)

Insert 4, GVHD Prophylaxis Risks:

Sirolimus

Common, some may be serious (>20%)	Occasional, some may be serious (4 - <20%)	Rare and serious (3% or fewer)
• Change of lab values that may need to be corrected: high cholesterol, high triglycerides • Constipation, diarrhea, nausea, , abdominal pain • Headache • High blood pressure • Increased creatinine levels • Low platelet levels, which may cause bruising, bleeding • Low red blood cell counts, which may cause tiredness or may require blood transfusions • Painful Joints • Rash, skin breakouts • Swelling of the body	• A new cancer resulting from treatment of earlier cancer • Blood clots in the veins that can cause blood clots in the lungs and legs especially • Brittle bones that break easier • Change of lab values that may need to be corrected: low potassium, high glucose • Damage to lungs, which may cause shortness of breath, fluid arounds lungs • Embolism and clotting of the small blood vessels in the brain and kidneys and other organs • Fast heart rate • Low white blood cells, which may cause increased infections and slower wound healing • Mouth sores	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

APPENDIX B-5

Consent Information for Conditioning Regimen C

APPENDIX B-5

CONSENT INFORMATION FOR CONDITIONING REGIMEN C

Insert 1, Conditioning Regimen Drugs

- The first medication you will be given for conditioning is called **alemtuzumab** which will be given intravenously or IV (using the central venous catheter) for three days in a row about 20 days before the transplant.
- The second medication is called **fludarabine**. This drug will also be given IV through the central catheter for 5 days about a week before the transplant.
- The third medication is called **melphalan** and will also be given IV for one day three days before the transplant.

Each of these drugs is routinely used as part of a conditioning regimen before transplant.

Insert 2, GVHD Prophylaxis Drugs:

- The first medication is called **methotrexate.** Methotrexate will be given on Days 1, 3, and 6 following the transplant.
- The second medication that you will receive is **tacrolimus**. Tacrolimus will be given IV starting on Day 3 before the transplant and will be given until Day 180. After Day 180, a tapering of this medicine (gradual decreasing of the amount given) will start and will continue until it has been stopped. The dose may be modified by the study doctor if there is evidence of GVHD or if there is worry about the possibility of a graft rejection.

Insert 3, Conditioning Regimen Risks:

Alemtuzumab

Likely (May happen in more than 20% of patients)	Less Likely (May happen in 20% or fewer patients, but more than 2%)	Rare, but Serious (May happen in 2% or fewer patients)
• Infection, which may cause fever and chills • Joint pain • Low platelet levels, which may cause bruising, bleeding • Low red blood cell counts, which may cause tiredness or may require blood transfusions • Low white blood cells, which may cause increased	• Cough • Feeling anxious • Feeling tired • Headache • Hypertension • Irregular heartbeat, most commonly fast heart rate • Muscle stiffness, spasms, tremor or pain • Problems sleeping • Rash, itching	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, dizziness, swelling of the face or throat • Heart problems including heart enlargement, or impaired heart pumping • Inflammation of the brain

infections and slower wound healing • Nausea, vomiting, abdominal pain, diarrhea, loss of appetite • Reaction to the medication infusion, which may include itching, fever, chills, low blood pressure and problems breathing • Sweating • Swelling of ankles and feet • Thyroid function decreased		• Inflammation of the gallbladder

Fludarabine: Can cause rare side effects such as: temporary blindness, confusion, and coma. Infrequent side effects such as poor kidney function, common side effects such as mouth sores and likely side effects such as nausea, vomiting, and diarrhea.

Fludarabine

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Anemia due to decreased number of red cells Infection due to decreased number of white blood cells Bleeding due to decreased numbers of platelets Tiredness Nausea Vomiting Weakened immune system	Pneumonia Diarrhea Mouth sores Skin rash Fever Swelling of hands and feet	Numbness and tingling in hands and/or feet related to irritation of nerves of the hand and/or feet Changes in vision Agitation/nervousness Confusion Cough Difficulty breathing Weakness Severe brain injury and death

Melphalan

Common, some may be serious (>20%)	Occasional, some may be serious (4 - <20%)	Rare and serious (3% or fewer)
• Anemia (low red blood cells) which may require blood transfusions • Diarrhea • Feeling of being tired • Infection, especially when white blood cell count is low • Nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Swelling of the body	• Inflammation of blood vessels • Kidney problems which may require dialysis • Liver problems which may cause yellow eyes and skin • Low platelet counts, which may cause bruising or bleeding • Scarring of the lungs which may cause shortness of breath	• A new cancer resulting from treatment of a prior cancer • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness

Insert 4, GVHD Prophylaxis Risks:

Methotrexate: Can cause depression of the white blood count early after transplant, transient alteration in liver function and can result in severe mouth sores.

Methotrexate

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
High levels of liver enzymes	Nausea Vomiting Loss of appetite Diarrhea Mouth sores Sensitivity to sunlight Increased risk of sunburn Decreased number of red and white blood cells and platelets	Hair loss Dizziness Redness, tenderness, darkening, and peeling of skin Blurred vision Allergic reaction Damage to nerve tissue Kidney damage Seizures Decreased lung function

		Decreased liver function - temporary Bone and tissue damage Loss of memory, concentration, balance, and walking Poor nervous system function

Tacrolimus: This drug may be used for all patients.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients.)*	**Less Likely** *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients.)*	**Rare, but Serious** *(These possible risks have been reported in rare occurrences, typically less than 2% of patients. They may be serious if they occur.)*
Anemia Loss of appetite Diarrhea High potassium levels High blood pressure Nausea Fever Headache High blood sugar	Hair loss Vomiting Tingling sensation in the extremities Itching Rash Abdominal pain	Confusion Painful joints Increased sensitivity to light Blurred vision Insomnia Infection Jaundice Kidney injury Seizures

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

Hematopoietic progenitor cell transplantation (HCT) remains the only curative therapy for severe sickle cell disease (SCD) and is associated with high rates of survival with stabilization of organ function and amelioration of sickle cell related complications. The impact of SCD on the long term survival and outcomes in SCD patients remains unclear because of the lack of studies comparing outcomes between SCD patients who undergo HCT or standard of care. BMT CTN 1503 STRIDE 2 is the first ever comparative clinical trial of a well-characterized group of adult patients with SCD biologically assigned to receive HCT or standard of care according to the availability of a suitable donor. As such it provides a unique opportunity. Biological specimens from patients enrolled in this study, therefore, represent a valuable resource to interrogate mechanisms of SCD related and HCT related complications and the long term effects of HCT.

A. Required Research Samples for Erythroid Chimerism Testing

Sickle cell disease (SCD) is a common and severe autosomal recessive disorder caused by a missense mutation in the hemoglobin gene (HBB) resulting in hemoglobin S. Nonmyeloablative allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly being used to treat severely affected patients. Mixed chimerism is observed in a large proportion of patients after HSCT. Most patients transition to complete donor chimerism. Some patients have long-term persistent mixed chimerism without need of red cell support even with a low percentage of donor-derived nucleated cells since an adequate amount of the normal HBB transcript, HbA, is being made.

Several studies have demonstrated that chimerism measured in the nucleated cell compartment does not always reflect the engraftment in the erythroid lineage. Assessment of the chimerism in the erythroid lineage may be a better indicator of donor erythropoiesis. As red cells do not contain DNA, chimerism in the erythroid compartment can be monitored using quantitative measurements of HbA and HbS transcripts produced from the hemoglobin gene (HBB) expressed in red cell progenitors.

Required molecular testing will be performed on Day +100 and Day +730 post-transplant samples to monitor erythroid chimerism and the effects of allogenic transplantation in SCD patients. ***Sample collection is limited to study patients assigned to the allogeneic donor arm of the trial***. Either peripheral blood or marrow aspirate samples are acceptable sample types to be submitted for this required testing. Research samples will be scheduled for collection on Day +100 (±14) and on Day +730 (±14) post-transplant. Biologic samples will be shipped on the day of collection to the Molecular Diagnostics Laboratory at the Blood Center of Wisconsin.

Required Erythroid Chimerism Sample Collection Summary					
Tube	**Specimen Type**	**Specimen Purpose**	**Amount (mL)**	**Time Points**	**Sample Shipping**
BD Vacutainer® EDTA Tube	Whole Blood or Bone Marrow Aspirate	Research Sample (Erythroid Chimerism)	10 mL (blood) Or 3-5 mL (marrow)	Day 100 & Day 730 Post-Transplant	Ambient

Detailed procedures regarding specimen collection schedules, collection procedures, and sample shipping instructions will be provided in the BMT CTN 1503 MOP.

B. *Optional* Research Samples for Planned and Future Laboratory Studies

Peripheral blood and urine samples will be collected on all consenting study patients receiving biologic assignment to either arm of the trial and shipped to the Children's Healthcare of Atlanta (CHOA) Cellular Therapies Lab associated with the CHOA Biorepository for processing and sample storage. The samples will be used for planned lymphocyte population analysis and for future BMT-related cellular, proteomic, transcriptomic and DNA-based genetic studies and sickle cell disease related research.

The optional peripheral blood (31.5 mL) and urine (50 mL) research samples will be collected on all consenting study patients at two study time points:

- At the time of biologic assignment. ***Baseline*** research samples will be collected ***within 14 days after*** biologic assignment and prior to the initiation of study arm-specific therapy.
- Day +730 (±14) post-biologic assignment

Samples will be shipped on the day of collection to the CHOA Biorepository for processing and long-term sample storage. Detailed procedures regarding specimen collection schedules, collection procedures, sample tube centrifugation and shipping instructions will be found in the BMT CTN 1503 MOP.

Optional Research Sample Collection Summary						
Tube	Specimen Type	Specimen Purpose	Amount (mL)	Time Points	Clinical Site Blood Tube Centrifugation Required	Stored Biospecimen Type
BD Vacutainer® SST Serum Tube	Whole Blood	Research Sample (Serum)	5	Baseline & Day 730	YES	Serum
BD Vacutainer® PPT™ Plasma Preparation Tube	Whole Blood	Research Sample (Plasma)	5		YES	EDTA Plasma

Optional Research Sample Collection Summary						
Tube	Specimen Type	Specimen Purpose	Amount (mL)	Time Points	Clinical Site Blood Tube Centrifugation Required	Stored Biospecimen Type
BD Vacutainer® CPT™ Mononuclear Cell Preparation Tube	Whole Blood	Research Sample (PBMC)	8	Post-Biologic Assignment	YES	PBMC
BD Vacutainer® EDTA Tube	Whole Blood	Research Sample (Whole Blood)	6		No	Whole Blood
PAXgene Blood RNA Tube	Whole Blood	Research Sample (PAXgene)	2.5		No	Blood RNA Lysate
Cyto-Chex BCT	Whole Blood	Research Sample (Cyto-Chex)	5		No	N/A
Polypropylene Centrifuge Tube	Urine	Research Sample (Urine)	50		No	Urine

APPENDIX D

BUSULFAN DOSING CALCULATION

APPENDIX D

BUSULFAN DOSING CALCULATION

Busulfan dose will be targeted to achieve a concentration at steady state (Css) of 600-900 ng/ml (target 750 ng/ml) or a daily area under the plasma concentration curve (AUC) of 3507–5261 µM•min (target 4384 µM•min) on the subsequent day. The total regimen AUC will be in the range of 14,000 – 21,000 µM•min.

Css does not change according to the dosing interval, but AUC does. Css can be converted to AUC using the following formula:

$$\text{Css (ng/mL)} = \frac{\text{AUC (in umol*min/L) * molecular weight}}{\text{Dosing interval (in min)}}$$

Busulfan MW = 246.3 g/mol

For Q24H dosing, the dosing interval in minutes in 24 hours = 1440 min)

So an AUC of 4400 umol*min/L Css can be calculated as follows:

$$\text{Css (in ng/mL)} = \frac{4400 * 246.3}{1440} = 753 \text{ (rounding to the nearest ng/mL)}$$

APPENDIX E

METHOTREXATE DOSING ADJUSTMENT GUIDELINES

APPENDIX E

METHOTREXATE DOSING ADJUSTMENT GUIDELINES

Dose reduction of methotrexate due to worsening creatinine clearance after initiation of conditioning regimen, elevated serum bilirubin or oral mucositis is allowed according to institutional practice. The Table below offer doing guidelines based on serum bilirubin and creatinine.

Table 1. Dosing Guidelines for Methotrexate

Laboratory parameters	MTX dose				
	Full	75%	50%	25%	Hold dose
Serum bilirubin	< 2.0	NA	2.1-3.0	3.1 – 5.0	>5.0 mg/dL
Serum creatinine	<1.5	1.5 – 1.7	1.8 - 2.0	NA	>2

APPENDIX F

GUIDELINES FOR PREVENTION AND MANAGEMENT OF PRES

APPENDIX F

GUIDELINES FOR PREVENTION AND MANAGEMENT OF PRES

Mission Statement:
To describe the pathophysiology, clinical diagnosis, prevention and management of Posterior reversible encephalopathy syndrome (PRES). PRES is a disorder of reversible subcortical vasogenic brain edema with a constellation of acute neurological symptoms and brain imaging findings of vasogenic edema predominantly involving the bilateral parieto-occipital regions. Patients with sickle cell disease are particularly susceptible to PRES.[63,64]

Pathophysiology
PRES results from endothelial injury related to abrupt blood pressure changes or direct effects of cytokines on the endothelium, which leads to the breakdown of the blood–brain barrier and subsequent brain edema. With early diagnosis and appropriate management, PRES is reversible, both radiographically and clinically, and generally has a favorable prognosis.

Clinical Presentation
Clinical presentation of PRES include[65-71] seizure (60–75%), encephalopathy (50–80%), headache (50%), visual disturbances (33%), focal neurological deficit (10–15%), and Status epilepticus (5–15%). Symptoms typically occur in the setting of renal failure, blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and pre-eclampsia or eclampsia.[67] Calcineurin inhibitor (CNI)-induced PRES may occur with elevated blood pressure within days to weeks of CNI initiation and typically occurs without elevated medication levels.[72] Clinical and radiographic recovery occur in 75–90% of patients with a mean time to full clinical recovery range of 2–8 days, although some patients can take several weeks to achieve full recovery.[72-75] Concomitant GVHD with the use of steroids is an important risk factor for PRES.[76]

Imaging
Brain imaging is useful to confirm the diagnosis of PRES and to exclude alternative diagnoses. Although vasogenic edema can be visualized using non-contrast CT in some patients, brain MRI (particularly T2-weighted sequences such as fluid-attenuated inversion recovery [FLAIR]) is much more sensitive.[73,77] Brain imaging usually reveals vasogenic edema in the parieto-occipital regions of both cerebral hemispheres. The subcortical white matter is always affected, and the cortex is also often involved. The edema is usually asymmetric, but almost always bilateral. Three primary descriptive variations exist in approximately 70% of patients: a dominant parieto-occipital pattern, holo-hemispheric watershed pattern, and superior frontal sulcus pattern. Neither the pattern nor the severity of brain edema, is associated with the type or severity of clinical presentation.[67,73]

Differential Diagnosis
The symptoms and signs are non-specific, thus necessitating brain imaging with the primary intent to exclude alternative diagnoses. However, the diagnosis of PRES is not solely radiological; the clinical context and the judgment of the clinician are crucial to making the correct diagnosis.

Differential diagnoses to be considered include infectious encephalitis, vasculitis, post transplant lymphoproliferative disorder and progressive multifocal leukoencephalopathy.

Risk Factors in HCT/BMT Predisposing to PRES

Incidence of PRES in allo-HCT/BMT is 7-9% with greater risks with myeloablative than with non-myeloablative regimens (16%vs 3%). PRES commonly occurs in the first month following HCT/BMT and is associated with increased HLA mismatch and with acute GVHD. Low –level neurotoxicity such as tremors, anxiety, and psychiatric dysfunction has been observed in 10%-40% of patients receive CNIs. Cyclosporine can induce endothelial injury/dysfunction leading to enhanced vasoconstrictive effects, increased sympathetic activation, and coagulation effects. Blood levels of Cyclosporine do not appear to correlate with severe neurotoxicity or PRES. Immune challenge from the transplant such as rejection and GVHD, effects of chemotherapy, and sepsis may all contribute to the risk of PRES. Discontinuation or switch of CNIs usually results in clinical improvement.

Unique Risk for PRES in Patients with SCD Undergoing HCT/BMT

Patients with SCD have impaired dynamic cerebrovascular auto regulation with decreased ability to buffer the transfer of blood pressure surges to cerebral tissue[78] as well as reduced cerebrovascular reserve capacity or vasodilatory capacity.[79] This may place them at unique risk for developing PRES. PRES has been reported in patients with SCD following severe acute chest syndrome, blood transfusion, hyper-transfusion with rapid increase in hemoglobin, recent use of

TABLE I

Medians and 90th Percentiles of Systolic and Diastolic Blood Pressure for Sickle Cell Anemia Subjects in the Cooperative Study of Sickle Cell Disease (CSSCD)

Age (Years)		2–3	4–5	6–7	8–9	10–11	12–13	14–15	16–17	18–24	25–34	35–44
Females N		257	97	72	68	57	71	89	81	227	199	66
SYS	Median	90	95	96	96	104	106	110	110	110	110	110
BP	90th	100	110	110	110	110	118	120	122	122	125	130
DIA	Median	52	60	60	60	60	62	70	70	64	68	70
BP	90th	62	70	70	70	74	74	80	78	80	80	84
Males N		276	111	78	66	75	61	75	53	179	166	41
SYS	Median	90	95	100	100	100	110	108	112	112	114	110
BP	90th	104	110	108	116	112	120	120	128	130	130	132
DIA	Median	54	60	60	60	60	64	64	70	68	70	70
BP	90th	66	68	68	70	70	72	78	80	80	80	84

SYS BP = systolic blood pressure; DIA BP = diastolic blood pressure.**Pegelow, C et al Am J Med 102 p171-177) 1997**

corticosteroids, hypomagnesaemia, and in the absence of any precipitating factors.[80-84] The prevalence of seizures in children with SCD is 10 times that of the general population.[85-87] The observation of neurological complications in 30% of patients including intracranial hemorrhages in 38% of those with a previous history of stroke in an early series of patients with SCD undergoing HCT/BMT led to the universal adoption of measures for the prevention of PRES.[64] Measures for prevention of PRES include extended duration of anticonvulsant prophylaxis, intensified antihypertensive management and aggressive platelet support.[64]

Prevention of PRES in HCT/BMT for SCD
Prevention of PRES requires careful attention to the following measures (Table 2):

a. **Control of blood pressure.** Blood pressure in patients with SCD has been reported to be lower than published standards for age, sex, and race-matched controls .[88-90] Decreased survival has been observed for patients with SCD whose systolic or diastolic pressures were above the 90th percentile for HbSS subjects.[85] Pressures above the 90th percentile for HbSS may overlap levels considered normal in non-SCD patients. Blood pressures may be elevated with fluid infusions or use of medications such as corticosteroids or CNIs. Supportive care orders must indicate the importance of keeping BP within 10% above the median for age for HbSS patients as described by Pegelow et al (Table I)[88] or the baseline BP for the patient, whichever is lower. Mean arterial pressure (MAP) should be maintained at <70mmHg. Close monitoring and aggressive management with anti-hypertensive agents will be required to prevent PRES.

b. **Maintenance of adequate platelet count**. Thrombocytopenia and coagulopathy may be associated with increased risk of PRES-related ICH.[64,90] It is therefore recommended to keep platelet count> 50, 000/μL.

Table 2. Measures for Prevention of PRES

Measure	Action
Control of Blood pressure	Physician to be notified and PRN anti-hypertensives to be administered if systolic or diastolic BP exceeds 10% above median for age in HbSS patients or > 10% baseline for patient, whichever is lower.
Maintenance of adequate platelet count.	Transfuse to keep Platelets> 50, 000/μL
Maintenance of euvolemic state	Avoid rapid fluid shifts. Maintain weight as close to baseline as possible.
Maintenance of adequate magnesium level	Maintain serum magnesium level ≥ 1.8mg/dL (0.75mmol/L) when lab normal range (1.7–2.4 mg/dL or 0.7–1 mmol/L)
Prevention of seizures	Institute anticonvulsant therapy before Busulfan and continue through the duration of administration of any calcineurin inhibitor.

c. Maintenance of euvolemic state. Large fluid shifts should be avoided.[86] Close attention must be paid to fluid balance since fluid overload with weight gain associated with increased blood pressure and consequently, increased risk of PRES.

d. **Maintenance of adequate level of serum Magnesium**. The association between hypomagnesemia and cyclosporine toxicity was first observed during the initial clinical trials of the drug for GVHD prophylaxis.[91] Severe hypomagnesemia can also present with clinical and radiological features similar to PRES.[92,93] Magnesium sulphate is considered the drug of choice in the treatment of PRES associated with Eclampsia.[94] It is therefore recommended that patients receive magnesium supplementation in order maintain patient Maintain serum magnesium level ≥ 1.8mg/dL (0.75mmol/L) when lab normal range (1.7–2.4 mg/dL or 0.7–1 mmol/L). Maintenance of mild hypermagnesemia with serum Magnesium 2-3mg/dL may be advisable, but maybe difficult to achieve because of side effects of P.O Magnesium. Bioavailability of magnesium in the aspartate, citrate, lactate, diglycinate and chloride forms is higher than magnesium oxide or sulfate.[95-99].

Table 3. Measures for Treatment and Management of PRES

Measure	Action
Supportive care	Immediately admit to ICU and initiate management as below while evaluating cause for neurological manifestations. High index of suspicion and early diagnosis are key. Obtain MRI with FLAIR. Monitor neurological status closely.
Removal of drug precipitating PRES	Stop cyclosporine or tacrolimus immediately. After 48 hours washout period may consider adding sirolimus. Tacrolimus may then be started in place of cyclosporine. Caution is advised in adding steroids because of the risk of hypertension and progression of PRES.
Control of Blood pressure	Institute intravenous medications to control Blood pressure. Labetalol is drug of choice. Decrease BP by 25% over 6 hours. Gradual reduction of BP thereafter.
Maintenance of adequate platelet count.	Transfuse to keep Platelets > 50, 000/μL
Maintenance of euvolemic state	Avoid rapid fluid shifts. Maintain weight as close to baseline as possible. Close attention to intake and output. Avoid hypertransfusion. Keep Hb <12g/dL.
Maintenance of adequate magnesium level	Correct hypomagnesemia. Maintain serum magnesium level ≥ 1.8mg/dL (0.75mmol/L) when lab normal range (1.7–2.4 mg/dL or 0.7–1 mmol/L)
Treatment of seizures	Institute anticonvulsant therapy immediately.

Table 3. Measures for Treatment and Management of PRES	
Measure	**Action**
Management of concurrent illness	Treat sepsis, or fluid overload.
Rehabilitation	Consider early introduction of physical and occupational therapy as appropriate

Treatment and Management of PRES

The management of PRES consists of eliminating the precipitating cause, control of blood pressure and the institution of comprehensive supportive measures (Table 3). If PRES is caused by a specific medication such as Cyclosporine or Tacrolimus, this medication should be discontinued. Failure to do so can perpetuate the syndrome. Alternative immunosuppression might be considered, but corticosteroids should be avoided. Following a suitable period for washout of cyclosporine, tacrolimus and/or sirolimus may be added. If steroids are added, careful consideration must be given to aggressive management of blood pressure. While it is important to treat the hypertension, the initial goal in treating patients with severe hypertension is to reduce blood pressure by 25% within the first few hours. Pronounced fluctuations of blood pressure should be avoided, and continuous infusions of intravenous drugs might be required. Excessive or rapid blood pressure reduction could provoke cerebral ischemia. Seizures are treated with antiepileptic medications. Other underlying disorders, such as sepsis, and flare-ups of autoimmune disorders, should be treated.

Prognosis

Despite its name, PRES is not always fully reversible. Early diagnosis and prompt management is crucial since the most severe forms of the PRES result in death, or chronic neurological sequelae. Severe neurological injury and death can be attributed to intracranial hemorrhage, posterior fossa edema with brainstem compression, acute hydrocephalus, or marked diffuse cerebral edema and increased global intracranial pressure. Persistent neurological sequelae are reported in 10–20% of patients with PRES.

APPENDIX G

ELIGIBILITY REVIEW COMMITTEE

APPENDIX G

ELIGIBILITY REVIEW COMMITTEE

Potential BMT CTN 1503 participants may be screened and approved for protocol eligibility on an as needed basis by a three member review panel comprised of experts in sickle cell disease and transplantation. All participants enrolled under the neurologic deficit SCD severity criteria will be reviewed by the ERC; participants enrolled under the other SCD severity criteria will be reviewed on an ad hoc basis if deemed necessary by the BMT CTN 1503 Protocol Leadership. Potential participants requiring review are reviewed by the ERC after consultation with a transplant physician at a participating clinical site and informed consent for screening. The ERC's confirmation of eligibility and approval for initiation of HLA typing in the interest of proceeding to biologic assignment is based on data contained in the patient registration (Segment 0) forms as well as uploaded source documentation. All of the following items must be completed in AdvantageEDC prior to review:

1. Completion of Segment 0 Enrollment Form

2. Upload of de-identified source documentation establishing all of the following eligibility criteria have been achieved:

    a. Baseline History & Physical Examination with study physician including documentation of performance score and vital signs to include pulse oximetry with a baseline O2 saturation of ≥ 85% on room air.

    b. Eligibility labs establishing acceptable organ function as outlined in Section 2.3.1.1.

    c. Echocardiogram results confirming left ventricular ejection fraction (LVEF) > 40%; or LV shortening fraction > 26% by cardiac echocardiogram or by MUGA scan;

    d. Progress notes, admission notes and/or similar documentation from the participant's medical records denoting a past medical history including one or more of the following SCD complications:

        i. Clinically significant neurologic event (stroke) or neurological deficit lasting > 24 hours;

        ii. Two or more episodes of acute chest syndrome (ACS) in the 2-year period preceding referral despite adequate supportive care measures (i.e. asthma therapy and/or hydroxyurea [HU]);

        iii. An average of three or more vaso-occlusive crises per year in the 2-year period preceding referral despite adequate supportive care (i.e. a pain management plan and/or treatment with HU);

        iv. Regular red blood cell (RBC) transfusions, defined as 8 or more transfusions per year for ≥1 year or ≥ 20 cumulative transfusions to prevent vaso-occlusive clinical complications (i.e. pain, stroke, or ACS);

v. An echocardiographic finding of tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec.

vi. Chronic Pain on a majority of days for ≥ 6 months

All uploaded source documentation must be de-identified, including redaction of all participant identifiers and/or PHI (name, patient initials, medical record number, date of birth) as well as redaction of institutional name and physician/advanced practice provider name(s).

Following completion of Segment 0 enrollment form and upload of source documentation, the DCC protocol coordinator will be notified via email. The protocol coordinator will review the data and source documentation in AdvantageEDC within 24 business hours. If all case information is present, the protocol coordinator will alert the ERC reviewers and the Protocol Officer. The panel then has 5 business days to review the case and confirm eligibility. The turn-around-time for review and adjudication should be no longer than 5 business days. In the event the case under review and an ERC member are from the same clinical site, the ERC member is recused and a substitute from another site is assigned to the ERC. In the event there is a discrepancy, the Protocol Officer or the Medical Monitor (if the Protocol Officer has a conflict) will adjudicate. This adjudication may require a teleconference call with the ERC members tasked with reviewing the case. The protocol coordinator will notify the enrolling center in writing once the panel has completed their review for patients requiring ERC review. Please refer to the BMT CTN 1503 MOP for additional information on the ERC.

For participants not reviewed by the ERC, successful enrollment into Segment 0 of AdvantageEDC will confirm eligibility and no further notification will be provided. All relevant source documents related to patient eligibility must be uploaded to the enrollment form regardless of ERC review requirement.

APPENDIX H

GUIDELINES FOR PRE-AND POST- TRANSPLANT CARE FOR PATIENTS WITH SICKLE CELL DISEASE

APPENDIX H:

Pre- and Post- Transplant Guidelines Specific for Sickle Cell Disease

1. Blood pressure management: Probably the single most important effector in preventing PRES and seizures after BMT for SCD is the prompt and effective treatment of systemic hypertension. Refer to Appendix F of the protocol for additional information on hypertension parameters in this population.
    a. Parameters for treating hypertension should be included in the admission order set; in SCD patients, it is recommended to have strict guidelines for ceiling systolic/diastolic BPs that prompt a call to MD and administration of a short-acting anti-hypertensive drug.
    b. A typical anti-hypertensive order might be nifedipine orally or hydralazine intravenously.
    c. Do not 'repeat BP until normal' or wait until the patient is 'calm' before treatment; instruct the nursing staff to call MD and institute treatment promptly. An in-service presentation or other targeted education for nursing staff about this issue can be helpful.
    d. Patients who receive >2 – 3 doses of prn nifedipine in a 24 – 48 hour period should begin a long acting Calcium-channel blocker, such as amlodipine once or twice daily, or another anti-hypertensive agent that is administered on a scheduled basis.
    e. Patients who develop GVHD that is treated by a combination of a calcineurin inhibitor and corticosteroids should receive empirical anti-hypertensive therapy; these patients often will require multi-drug combinations for strict control of hypertension.
    f. Some patients as above will need combination anti-hypertensive therapy for adequate BP control – secondary agents such as clonidine, enalapril, and/or a beta-blocker should be considered to ensure there is adequate control. Nephrology consultation can be very helpful with management of these challenging cases.
2. Other Neurological guidelines: refer to the Appendix F of the protocol about prompt repletion of magnesium and the importance of maintaining platelet >50,000/mm^3 to prevent intra-cranial hemorrhage, which are also very important for preventing neurological events after BMT.
3. RBC transfusions: An exchange transfusion before BMT to reduce the HbS < 30% is required. At a minimum, patients should receive ABO compatible RBC units, but extended antigen matching for C, E, Kell, and rH phenotype of the recipient also is recommended to prevent RBC alloimmunization.
    a. In patients who have extensive RBC alloimmunization, it is necessary to have access a sufficient number of compatible RBC donors or units in the blood bank pre-BMT to support the patient through recovery after BMT; in some cases, this will limit the feasibility of myeloablative BMT.
    b. In patients who have RBC alloimmunization before BMT, it is recommended that extended phenotypically-matched RBC units should be administered before and after BMT to reduce the risk of developing a new allo-antibody.
    c. The routine post-transplant administration of corticosteroid or IVIg in patients with existing RBC alloimmunization is not recommended due to uncertain efficacy and in the case of corticosteroids, the potential for exacerbating hyper tension.

4. Pain control: Many patients will have a history of acute and chronic pain related to SCD that can strongly influence the treatment and control of pain after BMT. In addition, patients with chronic pain syndrome treated previously by BMT can experience pain with extended opioid treatment with a taper that can extend months after transplant.
    a. Create a pain management plan that is tailored to an individual's past experience; if a pain plan has been effective, it is important to extend this experience through BMT.
    b. Expectation of a rapid opioid taper after acute painful stimuli related to transplant complications might not be reasonable in some cases; instituting a gradual taper and seeking advice from Pain Management specialty services should be considered.
    c. Routine use of non-steroidal anti-inflammatory drugs should be deferred until after platelet engraftment.

APPENDIX I

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