Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Adolescents and Young Adults with Severe Sickle Cell Disease

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Study Plan

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Executive Summary

Title:	Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Adolescents and Young Adults with Severe Sickle Cell Disease
Principal Investigator:	Mary Eapen MBBS MS
Eligibility Criteria:	Patients with sickle cell disease (HB SS, HB S beta thalassemia or HB SC) aged 15 – 50 years with severe signs or symptoms indicating poor prognosis and warranting transplantation. These could include one or more of include the following: • Stroke • Neurological deficit lasting > 24 hours • Recurrent acute chest syndrome (ACS) • Recurrent pain crises • Red blood cell (RBC) transfusions to prevent vaso-occlusive clinical complications (i.e. pain, stroke, or ACS) • High tricuspid valve regurgitant jet velocity (TRJV) Donors may be HLA-matched siblings, mismatched siblings or other relatives (parent, offspring or another relative mismatched to the recipient at 1 or more HLA loci), HLA-matched or mismatched unrelated donors. Donors may donate bone marrow, peripheral blood or umbilical cord blood. Donors with sickle cell trait are eligible to donate.
Accrual Objective:	This study will accrue 200 patients receiving allogeneic transplant and 450 – 500 receiving standard of care therapies for severe sickle cell disease
Primary Endpoint:	Compare the probabilities of 5-year overall survival between patients who received an allogeneic HCT and those who received standard of care. Each case will be compared to its matched control(s).
Secondary Endpoints:	Secondary endpoints are transplant-related and reported only for patients who receive HCT. The following endpoints will be studied: • 5-year probabilities of disease-free survival • 1- and 2- year incidence of graft failure • Day-100 and 6-month incidence of grade II-IV and III-IV acute graft versus-host disease (GVHD)

- 1, 2 and 5- year incidence of chronic GVHD

Additionally, primary and secondary outcomes will be reported by donor type:

- HLA-matched sibling
- HLA-mismatched relative
- HLA-matched adult unrelated donor
- HLA-mismatched adult unrelated donor
- HLA-matched or mismatched unrelated umbilical cord blood

Study Design: This observational study will compare survival of a prospectively enrolled cohort of HCT recipients to that of an established cohort of non-HCT controls. Each HCT recipient will be matched to 1 - 3 non-HCT controls on age (+/- 5 years) and time of onset of the indication for allogeneic HCT (within the same calendar year or the previous calendar year).

Patients undergoing allogeneic HCT will receive HCT at a transplant center in the United States (US) and be reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) using well-established data collection procedures on standardized CIBMTR Comprehensive Report Forms (CRF) including the standard Sickle Cell Disease specific and a study-specific supplemental Form. Data on historical non-HCT controls will be collected from 4 US academic centers through a database that contains relevant disease-specific information with longitudinal follow-up.

CMS Coverage with Evidence Development (CED) Requirements

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects:

The principal purpose of the study is described in Chapter 2.

The primary objective is to compare overall survival at 5 years of patients receiving HCT versus standard of care.

Secondary objectives are limited to HCT recipients. In this population, we will describe transplant outcomes by donor type: overall survival, disease-free survival, neutrophil and platelet recovery, graft failure, acute and chronic GVHD.

b. The rationale for the study is well supported by available scientific and medical evidence:

The rationale for the study is described in Chapter 1 Severe

SCD is associated with higher than normal mortality rates, estimated to be 4.4 deaths per 100 person years. Several published reports show allogeneic HCT is curative but this treatment is associated with complications related to the transplant procedure that can potentially result in early death.

We hypothesize that HCT recipients will experience mortality that may exert an early impact on survival but that rate will plateau by 2 years. On the other hand, those receiving standard of care will not be susceptible to early death, but will gradually succumb to the cumulative effects of their disease with a mortality rate much higher than in the general population. The goal of this study is to test whether 5-year overall survival after HCT is higher by at least 10% compared to standard of care.

c. The study results are not anticipated to unjustifiably duplicate existing knowledge:

Existing knowledge is summarized in Chapter 1. There is a CMS approved clinical trial that is accruing patients. This trial has a similar objective in that it compares survival after HCT (from HLA-matched sibling or HLA-matched unrelated donor and using intensive pretransplant conditioning regimen) to standard of care. This proposal will complement the findings of that clinical trial in that patients not eligible for the clinical trial may be offered an HCT on this study, thereby providing CMS with data on a broader spectrum of patients and HCT approaches. Such examples include patients who are unable meet the trial specified inclusion criteria or tolerate the trial prescribed intensive transplant conditioning regimen, those without an HLA-matched related or unrelated donor and those who are not geographically close to a center with that trial open. The current study will provide access to a rigorously designed trial to most patients who meet CMS's eligibility criteria for reimbursement under CED.

d. The study design is methodologically appropriate and the anticipate number of enrolled subjects is sufficient to answer the research questions being asked in the National Coverage Determination.

The study design was developed by experienced statisticians and subject matter experts and uses established methods for case-control studies. It is adequately powered to address the primary objective described above and has the power to evaluate multiple

secondary endpoints. It is similar in design to the recently approved CED study of allogeneic transplantation for myelofibrosis.

e. The study is sponsored by an organization or individual capable of completing it successfully.

The CIBMTR is a longstanding, federally funded clinical research organization with wide participation by the HCT and hematology community and more than 1000 peer-reviewed publications, and which is already performing three CED studies for CMS.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. All aspects of the study are conducted according to appropriate standards of scientific integrity.

The study protocol will be reviewed for compliance with all applicable Federal regulations concerning the protection of human subjects as detailed in 45 CFR Part 46 and scientific integrity by a central Institutional Review Board (IRB).

Data collection for HCT recipients is performed under a protocol approved by the National Marrow Donor Program IRB.

Data collection for non-HCT recipients (standard of care) is performed under a protocol approved by the Johns Hopkins Medical Institute IRB.

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.

Stopping rules are described in Chapter 5

Stopping guidelines for patients assigned to the donor arm: Patients will be monitored for death by day-100. The stopping rule for unacceptable day-100 mortality considers all patients together and we will consider stopping the study if the mortality at day-100 exceeds 10%. This will be evaluated after every 50 cases and stopping for excess mortality is recommended if 10 or more out of the first 50 patients die within 100 days of the transplant (10/50 or 16/100 or 22/150 or 28/200).

Stopping guidelines for patients assigned to the no donor arm: None; patients are receiving standard of care as prescribed by their treating physician

h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements

See Chapters 2, 3 and 5 of Study Protocol.

The primary objective of the study is to compare overall survival at 5 years of patients receiving HCT versus standard of care.

i. Study is not designed to exclusively test toxicity or disease pathophysiology in healthy subjects:

Not applicable

j. This study is registered at Clinical Trials.gov:

NCT01166009

k. Method and timing of public release of all pre-specified outcomes to be measured.

Regardless of the outcomes, the results of this study will be incorporated into a primary manuscript and submitted to a peer-reviewed journal within 12 months of completing the final analysis. Final analysis will be conducted when all patients enrolled in this study have been followed for a minimum of 5-years from date of enrollment (i.e., date of transplant). In addition, results will be made public via abstracts submitted to the American Society of Hematology meetings or a similar appropriate meeting

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally under underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why criteria are necessary.

- Inclusion and exclusion criteria are described in Chapter 2
- Gender: women and men with severe SCD are eligible
- Minorities: the study benefits patients with severe SCD the majority of whom are of African-American descent. The advantage of this protocol is its broad accessibility to a representative sample of US patients with SCD.
- Medicare beneficiaries: some are Medicare beneficiaries; data on type of health insurance will be captured.
- Retention of study participants: Data on HCT recipients and non-HCT recipients are reported to existing well-supported databases. Reporting on HCT recipients is

mandatory in accordance with the Stem Cell Therapeutic Outcomes Database mandated through Congressional legislation. Non-HCT recipients are followed at 4 large sickle cell centers in the US.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicare eligibility.

The study design targets a young adult population with sickle cell disease with complications that predict a future with significant morbidity and probably early mortality. If the hypothesis that transplantation extends a survival benefit in this population is established by the study, then a beneficiary subpopulation would be established that mimics the eligibility criteria employed in the study. Due to the disability experienced by young adults with severe sickle cell disease as delineated by the eligibility criteria of the study, it is likely that several of these individuals satisfy existing criteria for Medicare coverage ensuring generalizability.

Study Glossary

Acronym	Meaning
ACS	Acute Chest Syndrome
ATT	Average Treatment effect among Treated
BMT	Bone marrow transplant
BM	Bone marrow
BMTCTN	Blood and Marrow Transplant Clinical Trials Network
CDC	Center for Disease Control
CED	Coverage with Evidence Determination
CIBMTR	Center for International Blood and Marrow Transplant Research
CMS	Center for Medicare and Medicaid Services
CRF	Comprehensive Report Forms
CSSCD	Cooperative Study for Sickle Cell Disease
EBMT	European Group for Blood and Marrow Transplant
FEV1	Forced Expiratory Volume in one second
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplant
HLA	Human leukocyte antigen
IRB	Institutional Review Board
ITT	Intent-to-Treat
Kg	Kilogram
Mg	Milligram
MSH	Multi-center Study of Hydroxyurea
NMDP	National Marrow Donor Program
PB	Peripheral blood
PFT	Pulmonary Function Test
Pre-TED	Pre- Transplant Essential Data Form
RBC	Red Blood Cell
SCD	Sickle Cell Disease
TRJV	Tricuspid regurgitation jet velocity
UCB	Umbilical cord blood
US	United States
Walk-PHaSST	Pulmonary hypertension and sickle cell disease with sildenafil treatment trial

1.0 Background and Rationale

1.1 Introduction

Approximately 80,000 to 100,000 persons in the United States are affected by sickle cell disease (SCD). SCD is caused by a single point mutation in codon 6 of the β- globin chain. This mutation directs an amino acid substitution of valine for glutamic acid, which promotes the formation of long hemoglobin polymers under hypoxic conditions. This propensity for polymer formation deforms the red blood cell (RBC) and causes significant alterations in red cell integrity, rheologic properties, and life span. The presence of SCD with chronic hemolysis is directly or indirectly responsible for the vasculopathy that forms in virtually all body organs. This disease burden has a considerable impact on individuals affected and health-care systems. In the United States alone, the medical cost of caring for approximately 80,000 affected individuals exceeds $1 billion. Since the first clinical trial of HLA-matched sibling bone marrow transplant (BMT) in children with severe SCD, BMT from HLA-matched siblings is accepted treatment for children and adolescents with severe SCD.[1,2]

The course of SCD has dramatically changed over the last 40 years.[3] Currently children born with SCD are expected to live through adolescence and young adulthood with > 95% expected to reach their 18th birthday.[4] A recent prospective study of children with severe disease reported a 15 year estimated survival of 99% when placed on hydroxyurea therapy.5 In comparison, children from the same cohort with less severe disease that were not placed on hydroxyurea therapy had an overall survival of 95%.[5] These results are similar to a Brazilian cohort that also showed children with severe SCD on hydroxyurea therapy had a better survival compared to those with less severe disease but were not on hydroxyurea, (99·5% vs. 94·5%, P = 0·01), for a median of 2 years (range 0·1-6·5). Taken together, these studies suggest that with appropriate anticipatory guidance for splenic sequestration, prompt management of fever, routine vaccinations, and penicillin prophylaxis, SCD in children is no longer life threatening.

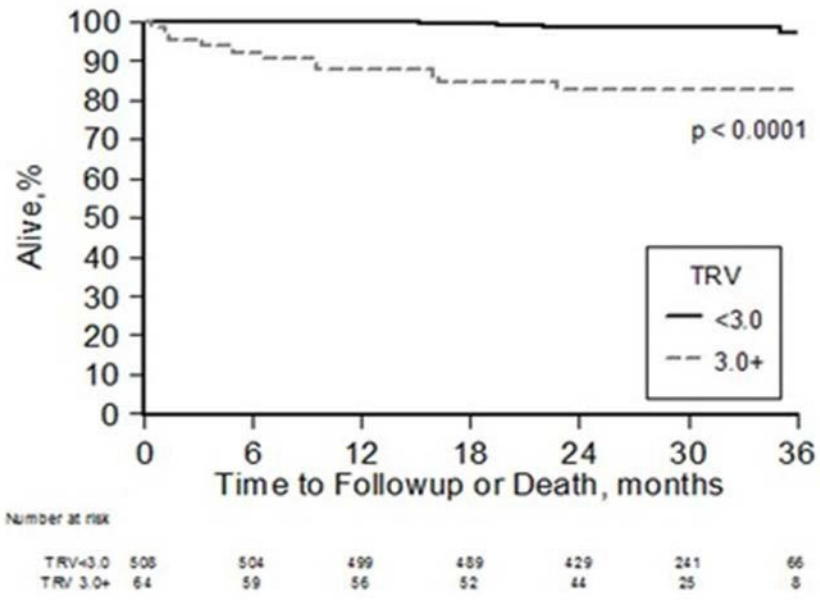
1.2 Progressive Disease with a high mortality rate for adults with SCD

In contrast to children where advances in medical care, public health and anticipatory guidelines have decreased mortality, the mortality rate for adults with SCD has remained unchanged in large population based studies. Cardiopulmonary organ dysfunction and chronic kidney injury have a large effect on morbidity and premature mortality, and typically accelerate in the second decade of life. These processes culminate in the development of pulmonary hypertension, left ventricular diastolic heart disease, dysrhythmia, and sudden death.[6] In the most comprehensive study of SCD conducted, the Cooperative Study for Sickle Cell Disease (CSSCD), from 1977 to 1998, the average life span for men and women with SCD was 42 and 48 years, respectively.[7] Data from 1979 to 2005 from National Center for Health Statistic that included over 16,000 adults with SCD revealed that the median age of death was 38 and 42 years for men and women with SCD, respectively. With improvement in care for the adults, we know the biggest risk factors for earlier death in adults with SCD is cardiopulmonary disease and that there are no definitive strategies to abate the progression of

cardiopulmonary disease.[8,9] An elevated tricuspid regurgitant jet velocity (TRJV) was present in approximately 10% of adults in a follow up study of the walk-PHaSST screening cohort of 662 patients (median follow up of 29 months).[9] In that study, TRJV ≥3 m/sec was the predominant risk factor for death (Figure 1). Other factors associated with death include age (>47 years), males, chronic transfusion, increased hemolytic markers, elevated ferritin and elevated creatinine.[10] Currently there is no effective treatment for adults with TRJV ≥3.0 m/sec. Although hydroxyurea is recommended by the American Thoracic Society there are no randomized trials, either completed or on-going, to demonstrate the efficacy of hydroxyurea for pulmonary complications. Sidenifil versus placebo was introduced as a therapy for elevated TRJV in a double blind randomized controlled clinical trial; however, the trial stopped prematurely because of the increased rate of vaso-occlusive pain events in the active treatment arm.[11]

Figure 1. Kaplan Meier plot from the Walk PHaSST Cohort demonstrating the proportion alive in a cohort of adults with SCD that had TRJV ≥ 3 m/sec (n=64) and < 2 m/sec. (n=508).

A



B

In addition to elevated TRJV, other pulmonary complications of SCD, like acute chest syndrome, asthma, wheezing and smoking are identified as risk factors for mortality.[12] In another report that studied pulmonary function tests and mortality, lower FEV1 % (forced expiratory volume in 1 second) correlated with higher mortality with every 1% decrease of predicted FEV1 % associated with a 2% increase in the hazard of death.[13] Other measures of PFT, restrictive or obstructive lung disease were not associated with mortality in that study.

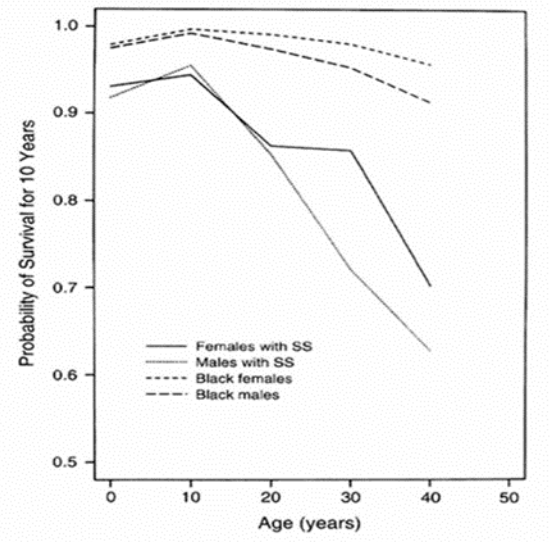
Likewise, renal disease, which is common in adults with SCD, is also associated with higher mortality. In a prospective population study conducted by the CDC between 2005

and 2009, the rate of death in SCD patients the first year after commencing dialysis for end stage renal disease was 26%.[14]

Adults with SCD experience recurrent episodes of debilitating pain. Pain is the result of vaso-occlusion that occurs in a large proportion of adults with SCD. In a prospective cohort study that documented daily pain in a diary Smith et al., demonstrated that 29.3% of adults with SCD reported pain almost every day in their diary days; whereas, only 14.2% reported pain in 5% or fewer diary days (adjusted).[15] Most importantly when a patient reported that they had vaso-occlusive pain episodes, referred to as crises in the manuscript, only 22% of episodes resulted in health care utilization; the remaining 78% of acute pain episodes resulted in the adult electing to manage the crises at home. The only FDA approved treatment for prevention of vaso-occlusive pain events in SCD is hydroxyurea. There are two large studies on use of hydroxyurea in adults with SCD with confirmation that hydroxyurea lowers the incidence of vaso-occlusion, acute chest syndrome and stroke with substantial improvement in long-term survival for those compliant with long-term hydroxyurea treatment.[7,16] These studies (17 year follow up) report 86% long-term survival in adults taking hydroxyurea compared to 64% for those who did not take hydroxyurea.[7] Long-term follow up has also demonstrated safety of long-term hydroxyurea treatment in that there are no reports of myelodysplastic syndrome or acute myeloid leukemia in these patients. Despite the reported success with long-term hydroxyurea therapy not all adults with SCD are receiving this drug and even in those who are receiving hydroxyurea, compliance vary. Further, the effectiveness of hydroxyurea in decreasing mortality in the subset of adults with severe pre-existing end organ disease is unclear.

Death in adulthood is frequently related to organ damage that is not preventable or easily managed with current medical measures.[17-19] SCD related complications such as leg ulcers, stroke, priapism, vascular necrosis, anxiety, and depression further worsen

Figure 2. Steep decline in probability of survival in adulthood in patients with sickle cell disease.



the health-related quality of life.[10,20] The mortality rate of patients with SCD is 5.8-20% in the first 10 years after transition to adult care. Premature death occurs at a median

age of 38 years, a statistic that has not changed in 20 years (**Figure 2**).[7] In the long-term follow-up 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.[21] Thus, the inexorable progression of disease and premature mortality in adulthood provides a strong rationale for intensifying the investigation and development of curative therapies in this group of patients.

1.3 HCT is a therapeutic option for SCD

Supportive health care measures instituted during childhood, which include newborn screening and pneumococcal prophylaxis, the administration of hydroxyurea and regular red blood cell (RBC) transfusions, have decreased the risk of serious infections and other life-threatening complications, resulting in improved survival to adulthood. This has, in part, shifted the demographics of SCD to include a growing proportion of young adults with chronic health impairments that adds to the burden of morbidity and mortality. Multiple studies have demonstrated that adults with SCD with co-morbidities especially cardiopulmonary complications have a shortened life span.

As an alternative to chronic supportive care, hematopoietic cell transplantation (HCT) from a human leukocyte antigen (HLA)-matched sibling donor has been used in children most whom have had a stroke.[1,2] With sustained donor engraftment after HCT, this treatment is curative. However, unlike supportive care therapy were death was attributed to disease severity, there are several risk factors associated with HCT treatment that can led to death independent of disease severity. In general, the risk of HCT associated complications is lowest when the donor is a human leukocyte antigen (HLA) matched sibling[1,2,22] and higher with HLA mismatched relatives[23] and HLA matched or mismatched unrelated donors.[24-26] Other risk factors include age at HCT,[22] co-morbidities prior to HCT including performance score,[27] and alloimmunization especially when considering HLA-mismatched related or HLA-matched or mismatched unrelated donor transplant (donor-directed HLA antibodies in the patient).[28,29]

Another limitation to HCT as a potentially curative treatment is the availability of a suitably HLA-matched donor. Based upon current estimates, about 15% of patients with SCD who might benefit from HCT have an HLA-matched donor. Therefore, most patients would have to rely on an HLA-mismatched relative or a HLA-matched or mismatched unrelated donor. A recent publication that examined for the likelihood of identifying suitable donors using the National Marrow Donor Program (NMDP) registry of donors estimated 18% of African – Americans are likely to identify an HLA-matched adult unrelated donor.[30] Consequently, if we were to consider offering HCT as a curative option to all patients who would benefit, we must anticipate that most potentially eligible patients would receive HLA mismatched related or unrelated donor HCT. Therefore, in any trials we would have to carefully balance the upfront risk of mortality associated with HCT versus the longer-term mortality risk from the severity of the disease. Only then can patients and their physicians make appropriate choice on the best available treatment option. To date, there are no reports that compared survival after HCT to survival in a comparable population with SCD (i.e., those who meet eligibility criteria for HCT trials). There is a phase II trial that is enrolling patients (aged 15 – 40 years) in

which eligible patients are assigned to a donor arm (based on availability of a HLA matched sibling or unrelated donor) or to a no donor arm (those without a HLA matched sibling or unrelated donor), BMT CTN 1503; NCT# 02766465 and approved by CMS as qualifying for CED. The primary endpoint of that trial is a comparison of survival at 2-years. However not all patients have an HLA-matched related or unrelated donor, patients may decline to participate in a trial that assigns treatment based on availability of a HLA-matched donor as opposed to transplantation with any available donor (i.e. HLA-mismatched donor if a HLA-matched donor is not available) or the treating physician may choose to offer HCT considering the clinical situation or for those who fail to meet trial-specified eligibility but may benefit from HCT. Additionally, that study employs intensive pre-transplant conditioning which may not be appropriate for SCD patients with organ toxicities.

1.3.1 HLA matched sibling HCT for SCD

The result of the first trial of HLA matched sibling bone marrow (BM) transplantation in children with SCD was published almost 2 decades ago.[1] That trial reported overall and event-free survival in 22 children. The 3-year overall survival rate was 91% and event-free survival was 73%. Three patients had graft failure with recurrent disease and 2 patients died from transplant-related complications. Since that publication there have been several reports supporting transplantation of BM and umbilical cord blood (UCB) from HLA matched siblings for SCD.[2,22,31] The results of UCB transplants from HLA matched siblings are also excellent and similar to that reported after BM transplants. In the recent publication on the worldwide experience on HLA-matched sibling transplant for SCD (n=998) the 5-year overall survival and event-free survival were 93% and 91%, respectively.[22] Although, most patients were aged <16 years at time of transplant and the median age at transplant was 9 years, 15% of the study population were aged 16 – 54 years (median age 20 years). Indications for HCT included stroke, vaso- occlusive crisis (chronic pain) and acute chest syndrome. BM was the predominant graft and most received myeloablative transplant conditioning, busulfan + cyclophosphamide was the predominant regimen. Multivariate analysis confirmed the adverse effect of age and peripheral blood (PB) grafts on mortality. For every 1-year increment in age, there was a 10% increase in the hazard ratio (HR) for death (HR 1.10, 95% confidence interval [CI] 1.06 – 1.14, p<0.0001). Peripheral blood transplants were associated with higher mortality compared to BM transplants (HR 2.62, 95% CI 1.17 – 5.89, p=0.02). The overall incidence of acute and chronic graft-versus-host disease (GVHD) was low, 15% and 14% respectively. But chronic GVHD risks were higher with transplantation of PB compared to BM (HR 2.00, 95% CI 1.11 – 3.12, p=0.02). In summary, the data support excellent survival after HLA-matched sibling transplant. Younger patients have better survival and BM and UCB are the preferred grafts for HLA matched sibling HCT.

1.3.2 HLA matched unrelated donor HCT for SCD

As fewer than 20% of patients with SCD who might benefit from HCT are expected to have an HLA matched sibling, the value of HCT as a curative option for SCD relies on using donors who are not matched siblings. One such option is an unrelated adult donor who is HLA matched to the patient. Approximately 20% of African-Americans are likely to identify a HLA matched adult unrelated donor through the NMDP’s donor registry.

This prompted the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) to conduct a phase II trial that utilized a reduced intensity transplant-conditioning regimen with BM grafts in patients with SCD aged 3 – 20 years (BMT CTN 0601; NCT # 00745420).[25,26] A reduced intensity transplant conditioning regimen was chosen to preserve fertility, and to lower the risks of end organ toxicity, that may occur after a more intense regimen. The indications for transplantation in that study included one or more of the following: 1) clinically significant neurologic event (stroke or neurologic deficit lasting longer than 24 hours and accompanied by an infarct on cerebral magnetic resonance imaging; 2) transcranial Doppler velocity >200 cm/s by the non-imaging technique or velocity >185 cm/s measured at a minimum of 2 separate occasions 1 month or more apart; 3) a minimum of 2 episodes of acute chest syndrome within the preceding 2-year period; and 4) a minimum of 3 episodes of new pain events per year in the preceding 2 years. The trial enrolled 29 patients who received BM from HLA-matched unrelated adult donors and their 1 and 2-year overall survival was 86% and 76%, respectively.[26] The corresponding event-free survival was 76% and 69%. Three patients experienced graft failure with autologous reconstitution. There were 8 deaths of which 7 were attributed to GVHD. Although this trial tested a reduced intensity pretransplant conditioning regimen, 2-year survival was only 76% and event-free survival 69%. Therefore, the regimen used in this trial is not recommended for widespread adoption without modification to lower GVHD rates, the predominant cause of death. That trial also had an UCB arm that was closed early for excess graft failure.[25] Another recent multi-center phase II trial enrolled 22 patients with SCD aged 16 – 40 years (median age 22 years) who underwent HLA matched related or unrelated donor HCT.[32] That trial used a myeloablative transplant- conditioning regimen (busulfan and fludarabine) with anti-thymocyte globulin and allowed only BM grafts. Event-free survival was 86% and overall survival, 90% at 1 year.[32] However, most patients received BM from HLA-matched siblings and the excellent survival may not hold true with use of more unrelated donor transplants.

1.3.3 HLA mismatched unrelated donor HCT for SCD

There are two reports on HLA mismatched unrelated donor HCT for SCD. Both used UCB as the graft of choice and graft failure was a limitation in both reports.[24,25] It is not surprising that graft failure rates are high with UCB transplants. The cell dose content of banked UCB units is at least 1 log lower than with BM grafts and both HLA mismatching between donor (UCB unit) and recipients and low cell doses are risk factors for graft failure. However, several new approaches including selecting better HLA-matched units, using double cord blood units and/or expansion techniques and/or novel preparative regimens show more promising results. Once engraftment occurs, GVHD rates are low, an advantage of this approach.

1.3.4 HLA mismatched related donor HCT for SCD

Lack of a HLA matched sibling or unrelated donor is a major barrier to HCT for SCD. So, for the approximately 60% of SCD patients who might benefit from HCT, grafts from a haploidentical relative would be useful. Administration of high dose cyclophosphamide (100 mg/kg) post-HCT after infusion of T-cell replete BM from haploidentical donors has been used successfully for hematologic malignancies[33] and is now being tested for non-

malignant diseases including SCD. Seventeen SCD patients received BM from a haploidentical relative or HLA-matched sibling.[23] The transplant conditioning regimen included low dose total body irradiation (200 cGy), low dose cyclophosphamide (29 mg/kg), fludarabine and anti-thymocyte globulin. GVHD prophylaxis included cyclophosphamide (100 mg/kg) given after BM infusion, tacrolimus and mycophenolate. Six patients (43%) had graft failure with recurrent disease. Although all patients are alive the high rate of graft failure was an obstacle. The regimen has been modified such that the total body irradiation dose is now 400 cGy and results are awaited. Others have also intensified the Hopkins approach to overcome graft failure. In a recent presentation at the American Society of Hematology annual meeting, 22 patients received hydroxyurea and azathioprine for 2 months prior to transplant and thiotepa (single dose) was added to the Hopkin's transplant regimen.[34] Nine percent of patients reported graft failure and 3 patients died. The 1 year overall survival was 86% and event-free survival was 82%.

1.4 When to consider allogeneic HCT in adolescents and adults?

The available data support allogeneic HCT as curative for SCD. But HCT is also associated with morbidity and mortality and there are reports that support continued use of hydroxyurea has improved survival. So, the question is whether the 15% - 20% early mortality associated with HCT would with longer follow up result in a survival advantage for those who received HCT compared to patients treated with supportive care including hydroxyurea and chronic red blood cell transfusion. Based on the available literature, HCT may result in an advantage long-term if there are few deaths beyond 2 years after transplant. There are relatively modest numbers of HCTs being performed for SCD and most transplants with donors other than HLA-matched siblings have occurred recently so little is known about survival beyond 5 years for these group of patients with SCD. In the recent joint publication from the CIBMTR and the European Group for Blood and Marrow Transplant (EBMT) with ~1000 SCD patients who received HLA-matched sibling HCT, although the overall survival at 5 years for 91%, deaths continued to occur beyond 5 years and accounted for 10% of all deaths in that study.[22] We also know the long-term survival of adults on hydroxyurea is 86% but there is an ~20% decrement in survival for those not taking hydroxyurea. Compliance with hydroxyurea life-long can be challenging, yet this is potentially lifesaving. We also have reports on long-term survival and late mortality for another non-malignant disease, severe aplastic anemia. Studies on long-term survivors for aplastic anemia suggest mortality rates reverts to that of an age- and sex- matched general population, 6 years after HLA-matched sibling transplants.[35] On the other hand, when the study population includes both long-term survivors with severe aplastic anemia who received HLA-matched sibling and HLA-matched or mismatched unrelated donor transplants, their mortality risk remains elevated compared to an age- and sex-matched population. However, late mortality is low and remains at less than 10% for those who survived disease-free for at least 2 years after transplantation.[36] Severe aplastic anemia and SCD are biologically very different; in severe aplastic anemia, end organ damage prior to transplantation is rare were as in SCD, it's more common and may affect late mortality risk. Only with longer

follow up of HCT recipients will we be able to study the effects of HCT and the underlying disease on longevity.

1.5 US Centers for Medicare and Medicaid Services decision

On January 27, 2016, the US Centers for Medicare and Medicaid Services (CMS) issued the Final National Coverage Decision Memorandum for Stem Cell Transplantation (multiple myeloma, myelofibrosis, SCD), administrative file CAG-00444R. In that memorandum, CMS stated it will modify the existing National Coverage Determinations Manual to cover allogeneic HCT for sickle cell disease, under its Coverage with Evidence Development (CED) mechanism while participating in an approved prospective clinical study. these three indications, including sickle cell disease.

The study must address the following question:

> Prospectively, compared to patients who do not receive allogeneic HCT, do Medicare beneficiaries with SCD who receive allogeneic HCT have improved outcomes as indicated by:
>
> - Acute and chronic GVHD
> - Other transplant related adverse events
> - Overall survival
> - Quality of life (optional)

The encouraging preliminary data on overall and disease-free survival from a phase II clinical trial,[32] allowed for the development of a phase II randomized trial that is comparing survival and SCD events of special interest between patients assigned to a donor arm (expected to undergo HCT from a HLA-matched sibling or unrelated donor) and a concurrent no donor arm (without a HLA-matched sibling or unrelated donor). Patients assigned to the no donor arm receive standard of care treatment. This study met the criteria for CED and is approved by CMS. The clinical protocol (BMT CTN 1503; NCT# 02766465) is available at www.bmtctn.net. CMS approval for this clinical trial is available at (https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/allo-scd.html).

The purpose of this CED application is to ensure that those patients who lack an HLA-matched sibling or HLA-matched unrelated donor have access to high quality clinical trials that qualifies for CMS reimbursement under CED and will generate data relevant to the majority of individuals with SCD. As fewer than a third of patients will have a suitable HLA-matched sibling and only another 20% will have a suitable HLA-matched unrelated donor, we anticipate a substantial number of patients will benefit from HLA-mismatched related or unrelated donor transplantation. Further, clinical trials are designed with relatively narrow inclusion criteria and there will be several patients who may have a HLA- matched sibling or an HLA-matched unrelated donor who may not meet the restrictive criteria for inclusion in the above-mentioned CMS approved clinical trial. Therefore, we believe this application for CED for allogeneic HCTs for adolescents and young adults with SCD will broaden access to HCT as well as generate generalizable knowledge.

2.0 Eligibility

Patients fulfilling the following criteria will be eligible for inclusion in this study:

2.1 SCD (Hb SS, Hb S beta thalassemia or Hb SC)

Aged 15.00 – 50.00 years with signs or symptoms indicative of poor prognosis and warranting transplantation.

These may include 1 or more of the following**:**

- Stroke
- Neurological deficit lasting > 24 hours
- Recurrent acute chest syndrome (ACS)
- Recurrent pain crises
- Red blood cell (RBC) transfusions to prevent vaso-occlusive clinical complications (i.e. pain, stroke, or ACS)
- High tricuspid valve regurgitant jet velocity (TRJV)

2.2 Donors

Donors may be HLA-matched siblings, mismatched siblings or other relatives (parent, offspring or another relative mismatched to the recipient at 1 or more HLA loci), HLA-matched or mismatched donors. Donors with sickle cell trait are eligible to donate. Donors may donate bone marrow, peripheral blood or umbilical cord blood. Choice of optimal donor is at the discretion of the transplanting institution.

2.3 Exclusion Criteria:

- Previous allogeneic HCT

3.0 Study Objectives

3.1 Primary

Compare the 5-year survival probabilities between patients who received allogeneic HCT to those who received standard of care using the intent-to-treat (ITT) principle.

- Arm 1: allogeneic HCT recipients
- Arm 2: non-allogeneic HCT treatment (best supportive care as determined by treating physician)

Note: the only outcome of interest for patients enrolled on Arm 2 is survival.

3.2 Secondary (allogeneic HCT recipients only; Arm 1)

All allogeneic HCT recipients (i.e., all donor groups together)

- Neutrophil and platelet recovery
- 1- and 2- year incidence of graft failure
- Day-100 grade II-IV and III-IV acute GVHD
- 1-, 2- and 5-year chronic GVHD
- 5-year disease-free survival

Both the primary and secondary outcomes will also be reported separately by donor type:

- HLA-matched sibling HCT
- HLA-mismatched relative HCT
- HLA-matched unrelated donor HCT
- HLA-mismatch unrelated donor HCT
- Umbilical cord blood HCT

3.3 Study Endpoints

3.3.1 Primary Endpoint

All patients (Arm 1 and Arm 2)

Overall survival: death from any cause is considered an event; all surviving patients will be censored at 5-years.

The start time for patients enrolled in this study is the date of allogeneic HCT. The study will use a time-matched control design. Each case (allogeneic HCT recipient) will be matched to at least 1 or a maximum of 3 controls (non- allogeneic HCT recipients) based on age (within the same decade) and at least 1 eligibility criterion for HCT as described in section 2.1 (within the same calendar year as the case). The start time for the controls will be the date of the allogeneic HCT of the corresponding case.

3.3.2 Secondary Endpoints Allogeneic HCT recipients only (Arm 1)

Neutrophil recovery: defined as achieving absolute neutrophil count ≥0.5 x 10^9/L for 3 consecutive days

Platelet recovery: defined as achieving platelets ≥20 x 10^9/L, unsupported by platelet transfusion for at least 7 days

Graft failure: defined as failure to achieve neutrophil count (ANC) >0.5 x 10^9/L (for 3 consecutive days) or sustained decline in ANC to <0.5 x 10^9/L after initial recovery or donor chimerism ≤5% or Hb S level >30% or second allogeneic HCT (includes infusion of hematopoietic cells from the donor with or without a second conditioning regimen).

Grade II – IV and III – IV acute GVHD and chronic GVHD: as per standard definitions

Disease-free survival: defined as being alive with sustained donor engraftment. Sustained donor engraftment is defined as donor chimerism >5% or Hb S level <30% (red blood cell transfusion independent).

4.0 Data Collection

4.1 Prospectively enrolled HCT recipients (Arm 1)

All data on allogeneic HCT recipients will be collected using the existing mechanism of the CIBMTR operating under the “CIBMTR Protocol for Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries”, (NCT01166009), (**Appendix A**). The most recent versions of the CIBMTR study forms can be found at www.cibmtr.org. In addition, a supplemental form

will be deployed to capture indications for transplant (as described in 2.1) that are not currently captured on CIBMTR standard Report Forms (**Appendix B**). Transplant centers pre-register all transplant recipients within 2 weeks of starting pre-transplant conditioning. The Pre-Transplant Essential Data Form (Pre-TED) captures information regarding primary disease, type of donor, type of graft, conditioning regimen and GVHD prophylaxis. For the purposes of this study, centers will be asked to complete Comprehensive Report Forms (CRF) for each transplant patient, which captures detailed information on patient, disease and outcome characteristics and outcomes. Within the HCT cohort, initial follow up forms are due three months' post- transplant and include a 100 day Post-HCT Data Form, Pre-and Post-HCT and disease specific Forms and a Product (graft) Form. These forms capture demographics, details of the patient's pre-transplant disease course including indication for HCT, the transplant regimen including the characteristics of the graft and GVHD prophylaxis, post-transplant supportive care and outcomes. Outcomes include disease response to HCT, GVHD, infections, organ dysfunction and survival. Follow up report forms will be required annually through year 6 post-HCT and include a general follow-up form and disease-specific follow-up from. Follow up forms will be required bi-annually thereafter and include a general follow-up form and a disease-specific follow-up form. Reminders of forms due for pre-registered patients and patients requiring follow-up report forms are sent to participating centers monthly. Standard CIBMTR procedures require that all contact with patients be done by the transplant center. **Appendix C** describes the CIBMTR procedures governing IRB oversight, consent and privacy as they relate to the transplant centers and this study. Keeping with CIBMTR procedures, upon approval of the final protocol, oversight for the study proposed in this application will be submitted to the IRB of record for the CIBMTR, the National Marrow Donor Program's IRB.

4.2 Concurrent non-HCT controls (Arm 2)

The data collection template for variables being collected for the non-HCT cohort for this study is shown in **Appendix D**. This database is held at the Johns Hopkins Medical Institute and will hold data from consenting patients from 4 US academic centers (Johns Hopkins Medical Institute, Case Western Reserve University, Children's Hospital of Oakland and Medical College of Wisconsin). Patients will be followed longitudinally for survival status (the only outcome variable for this CED application). The IRB at Johns Hopkins Medical Institute is the IRB of record for the 4 participating centers (**Appendix E**). De-identified data for the control population will be transferred securely from the Johns Hopkins Medical Institute to the CIBMTR and held in folder for this study. Survival status will be updated annually.

5.0 Statistical Analysis

5.1 Overview

The main objective of this study is to compare overall survival at five years between patients with SCD who received an allogeneic HCT from an HLA- matched or mismatched relative or HLA-adult matched unrelated donor and those with SCD who met eligibility criteria for allogeneic HCT but are receiving standard of care.

Secondary objectives are limited to patients who received allogeneic HCT and include the following and will be reported for the entire cohort and by donor type:

- Neutrophil and platelet recovery
- 1- and 2-year graft failure
- Day 100 grade II-IV and III-IV acute GVHD
- 1-, 2- and 5-year chronic GVHD
- 5-year disease-free survival

Additionally, the primary outcome, overall survival will be reported by donor type

5.2 Accrual

The study will target accrual of 200 patients receiving allogeneic HCT. In 2014 and 2015, the annual number of allogeneic HCTs done in the United States for those aged 16 years and older is 62 and 54, respectively. Based on the experience with myelodysplastic syndromes, we expect the number of HCTs to increase with activation of this CED study. Therefore, our conservative estimate of accruing 50 per year over 4 years from activation of this CED study is feasible.

5.3 Sample size and power calculation

Preliminary estimates provided by the 4 collaborating institutions indicate that a sample size of approximately 1000 patients will be available to form the non- HCT contemporary controls. We assume ~50% (n=500) of these patients have already met or will meet eligibility criteria for allogeneic HCT to serve as controls during the prospective period of accrual for patients undergoing allogeneic HCT (cases). Controls will be selected based on the following criteria:

- Stroke
- Neurologic deficit lasting > 24 hours
- Recurrent pain crisis
- Recurrent episodes of ACS
- RBC transfusions to prevent vaso-occlusive crisis
- High TRJV.

Cases will be matched to 1-3 controls based on age (within the same decade) and time of onset of the indication for allogeneic HCT (within the same calendar year). Each potential control can be matched to multiple cases, as comparisons will be performed only within the matched sets. We have chosen to use an IIT approach for our primary endpoint, comparison of overall survival between cases and controls. It is assumed that among the contemporary controls (non-HCT group), some may cross over into the allogeneic HCT group (case) during the study. In the event a “control patient” crossover to the allogeneic HCT group, this “control patient” is now eligible to acquire 1-3 controls and will remain in the study both as a control for the cases it was matched to, as well as a case. We assume 450 – 500 controls are available and that ~50% of cases will be matched to at least 2 controls.

The power calculations are based on the method of Lachin[37] for multiply matched case-control studies treating 5-year overall survival as a binary outcome. The goal is to

achieve 80% power at a two-sided 5% significance level to detect a 10% difference between the 5-year overall survival of patients receiving HCT versus not receiving HCT. The power of study depends on the survival experience of the control group, and the number of controls per case.

The following table shows several scenarios with the desired power, with the most likely scenario that formed the basis of the calculations marked in bold.

5-year OS		Proportion of cases with			Total number of cases	Total number of controls*	Power
Without HCT	With HCT	1 control	2 controls	3 controls			
80%	90%	100%	0%	0%	200	200	90%
75%	85%	90%	10%	0%	200	220	80%
72%	**82%**	**50%**	**30%**	**20%**	**200**	**340**	**80%**
70%	80%	33%	33%	34%	200	402	80%
65%	75%	0%	0%	100%	200	600	80%

* A single patient serving as control to multiple cases is counted multiple times

5.4 Stopping rules for safety

A safety monitoring will be conducted to ensure that the early mortality in the HCT arm is not excessive. Specifically, we will consider stopping the study if there is sufficient evidence to indicate that the 100-day overall mortality of the HCT arm is above 10%. This outcome will be evaluated after every 50 cases, and stopping for excess toxicity will be recommended if 10 or more out of the first 50 patients die within 100 days of the transplant (10/50), or 16/100, or 22/150, or 28/200. The operating characteristics of this boundary are shown in the following table.

Underlying 100- day mortality	Probability of stopping the trial	Expected number of cases treated
10%	7.3%	192.5
12%	24%	176.2
14%	50%	149.8
16%	75%	120.8
18%	90%	96.7
20%	97%	79.7

5.5 Analysis plan

5.5.1 Analysis of the primary endpoint

The primary outcome of the study is survival at five years after transplant.

The primary analyses will be performed using inverse probability of censoring weights to estimate the average treatment effect among treated (ATT) for 5-year overall survival.[38,39] The estimated survival difference at other time-points will also be computed and presented graphically with pointwise 95% confidence intervals. This analysis will be conducted when all cases have reached 5 years of follow-up, which is expected to happen at 9 calendar years after the start of the study.

5.5.2 Analysis of secondary endpoints

Secondary objectives are limited to patients who received allogeneic HCT. The time to event for all outcomes in the following analyses starts at the time of transplant. Kaplan-Meier curves will be used to present estimates of overall and disease-free survival overall and by donor type.[40] The cumulative incidence of chronic and acute GVHD will be estimated using the Nelson-Aalen estimator. The outcomes at specific time-points will be compared using the pseudo-value approach.[41]

5.5.3 Interim analyses

No interim efficacy analyses will be performed due to the nature of the primary outcome – 5-year overall survival. Unlike in studies with overall survival as primary outcome, patients with longer follow-up do not contribute additional precision to the estimate of the effect. Thus, information accumulates at a slower rate, and an interim analysis would be substantially less powerful.

6.1 Relevance to CMS Beneficiary Population and Adherence to Guidelines for CED Studies

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.

The principal purpose of the study is described in Chapter 2.

The primary objective of the study is to compare overall survival at 5 years of patients receiving HCT versus standard of care.

Secondary objectives are limited to HCT recipients. We will describe transplant-outcomes for the entire cohort and by donor type: neutrophil and platelet recovery, graft failure, acute and chronic GVHD and disease-free survival. In addition, we will describe overall survival by donor type.

b. The rationale for the study is well supported by available scientific and medical evidence.

The rationale for the study is described in Chapter 1.

Severe SCD is associated with higher mortality rates than the general population, estimated to be 4.4 deaths per 100 person years. Several published reports have shown allogeneic HCT is curative yet this treatment is associated with complications related to the transplant procedure that can potentially result in death.

Therefore, we hypothesize that HCT recipients will experience mortality that may exert an early impact on survival but that rate will plateau by 2 years. On the other hand, those receiving standard of care will not be susceptible to early death, but will gradually succumb to the cumulative effects of their disease with a mortality rate much higher than in the general population. Therefore, the goal of this study is to establish that 5-year overall survival after HCT is higher by at least 10% compared to standard of care.

c. The study results are not anticipated to unjustifiably duplicate existing knowledge.

Existing knowledge is summarized in Chapter 1. There is a CMS approved clinical trial that is accruing patients. This trial has a similar objective in that it compares survival after HCT (*from* HLA-matched sibling or HLA-matched unrelated donor and using intensive pretransplant conditioning regimen) to standard of care. This proposal will complement the findings of that clinical trial in that patients not eligible for the clinical trial may be offered an HCT on this study, thereby providing CMS with data on a broader spectrum of patients and HCT approaches. Such examples include patients who are unable meet the trial specified inclusion criteria or tolerate the trial prescribed intensive transplant conditioning regimen, those without an HLA-matched related or unrelated donor and those who are not geographically close to a center with that trial open. The current study will provide access to a rigorously designed trial to most patients who meet CMS's eligibility criteria for reimbursement under CED.

d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research questions being asked in the National Coverage Determination.

The methodology, including statistical power, is detailed throughout this study plan. The design is similar to a recently approved CED plan for evaluating transplantation in patients with myelofibrosis.

e. The study is sponsored by an organization or individual capable of completing it successfully.

The CIBMTR is responsible for the conduct of this study. The CIBMTR has performed hundreds of studies with accompanying peer-reviewed publications in its over 40 years of existence as a scientific organization dedicated to advancing HCT worldwide. The CIBMTR consists of a voluntary network of over 400 transplant centers worldwide. The CIBMTR's research database includes information on >440,000 transplant recipients

and received information for about 15,000 new transplants annually. CIBMTR data, statistical and scientific expertise have resulted in over 1000 peer-reviewed publications (www.cibmtr.org/ReferenceCenter/PubList/index.html). In 2010, the CIBMTR launched the CMS-approved study "Assessment of Stem Cell Transplantation in Medicare Beneficiaries with Myelodysplastic Syndrome and Related Disorders." In 2017, it launched the CMS approved study entitled "Prospective Assessment of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis" and in collaboration with the Blood and Marrow Transplant Clinical Trials Network (BMTCTN 1503; NCT# 02766465), a prospective clinical trial for adolescents and adults with severe SCD evaluating use of HLA matched related and unrelated donors with intensive pretransplant conditioning.

As of December 2007, all US transplant centers are required to report data on their related and unrelated donor transplants to the CIBMTR. The CIBMTR's data collection is described in Chapter 4.0. Data are verified using computerized checks for errors, review of submitted data by physicians, and on-site audits of participating centers to monitor data quality. Follow-up of HCT recipients is rigorous and completeness rates for 1 through 5 years is greater than 90%. CIBMTR data collection forms are found on the CIBMTR's website (http://www.cibmtr.org/DATA/Data_Mgmt_Forms/index.html). The CIBMTR will utilize its existing network and data collection infrastructure to obtain HCT-related data and through its partnership with 3 other academic institutions (Johns Hopkins Medical Institute, Case Western Reserve University, Oakland Children's Hospital) and the Medical College of Wisconsin (home to CIBMTR) have a population of adolescents and adults with SCD who will serve as the control population.

The investigators and their corresponding institutions are listed below and their curriculum vitae enclosed:

- Javier Bolanos- Meade, MD (Co-investigator; Johns Hopkins Medical Institute)
- Mary Eapen MBBS, MS (Principal investigator; Medical College of Wisconsin)
- Joshua Field, MD (Co-investigator; Medical College of Wisconsin)
- Carolyn Hoppe, MD (Co-investigator; UCSF Benioff Children's Hospital, Oakland)
- Sophie Lanzkron, MD (Co-investigator; Johns Hopkins Medical Institute)
- Jane Little, MD (Co-investigator; Case Western Reserve University)
- Aniko Sabzo, PhD (Statistician; Medical College of Wisconsin)

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46 and all aspects of the study are conducted according to appropriate standards of scientific integrity.

The CIBMTR is committed to scientific integrity and high ethical standards for research. The Study Protocol will be reviewed for compliance with all applicable Federal regulations concerning the protection of human subjects as detailed in 45 CFR Part 46

and for scientific integrity by a central IRB, using the IRB supported by the National Marrow Donor Program.

Data collection for HCT recipients is approved by the IRB for the National Marrow Donor Program.

Data collection for non-HCT recipients (standard of care) is approved by the IRB for the Johns Hopkins Medical Institute.

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.

Stopping rules are described in Chapter 5.

Stopping guidelines for patients assigned to the donor arm: Patients will be monitored for death by day-100. The stopping rule for unacceptable day-100 mortality considers all patients together and we will consider stopping the study if the mortality at day-100 exceeds 10%. This will be evaluated after every 50 cases and stopping for excess mortality is recommended if 10 or more out of the first 50 patients die within 100 days of the transplant (10/50 or 16/100 or 22/150 or 28/200).

Stopping guidelines for patients assigned to the no donor arm: None; patients are receiving standard of care as prescribed by their treating physician.

h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.

See Chapters 2, 3 and 5 of Study Protocol.

The primary objective of the study is to compare overall survival at 5 years of patients receiving HCT versus standard of care.

i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy subjects.

Not applicable

j. This study is registered at Clinical Trials.gov:

Pending (Application submitted)

k. Method and timing of public release of all pre-specified outcomes to be measured.

Regardless of the outcomes, the results of this study will be incorporated into a primary manuscript and submitted to a peer-reviewed journal within 12 months of receiving within 12 months of final analysis. Final analysis will be conducted when all patients enrolled in this study have been followed for a minimum of 5-years from date of enrollment (i.e., date of transplant). In addition, results will be made public via abstracts submitted to the American Society of Hematology meetings or a similar appropriate meeting.

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally under underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why criteria are necessary.

Our study will be an accurate reflection of the population of adolescents and adults receiving allogeneic HCT for SCD in the US along with appropriately matched controls receiving standard of care therapies. As described in the study protocol all patients with SCD who meet study eligibility are enrolled. None are excluded based on gender, race and ethnicity. Inclusion and exclusion criteria are described in Chapter 2:

- Gender: women and men with SCD are eligible
- Minorities: the study benefits patients with severe SCD the majority of whom are of African-American descent; in fact, the advantage of this protocol is its broad accessibility to a representative sample of US patients with SCD undergoing HCT
- Medicare beneficiaries: most patients will be Medicare beneficiaries
- Retention of study participants: Data on HCT recipients and non-HCT recipients are reported to established, well-supported databases. Reporting on HCT recipients is mandatory in accordance with the Stem Cell Therapeutic Outcomes Database mandated through Congressional legislation and retention of patients is high. Non-HCT recipients are followed at 4 sickle cell centers in the US with demonstrated commitment to long-term studies in SCD.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicare eligibility.

The study design targets a young adult population with SCD with significant complications that predict a future with significant morbidity and early mortality. Many will already have disabilities that qualify them for Medicare; information regarding insurance payer is collected on standardized CIBMTR data collection forms. If the hypothesis that transplantation extends a survival benefit in this population is established by the study, then a beneficiary subpopulation would be established that mimics the eligibility criteria employed in the study.

7.0 List of Appendices

Appendix A. CIBMTR Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries, NCT01166009)

Appendix B. Variables collected on supplemental form to determine indication for HCT.

Appendix C. CIBMTR procedures governing human subjects research, HIPPA compliance and consent Form

Appendix D. Data collection template for non-HCT cohort

Appendix E. Johns Hopkins IRB approval of SCD database and consent Form

Appendix F. Biosketches for study team members

8.0 References

1. Walters MC, Patience M, Leisenring W, et al: Bone marrow transplantation for sickle cell disease. N Engl J Med 335:369-76, 1996

2. Bernaudin F, Socie G, Kuentz M, et al: Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood 110:2749-56, 2007

3. Ware RE, Davis BR, Schultz WH, et al: Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicenter, open-label, phase 3, non-inferiority trial. Lancet 387:661-70, 2016

4. Le PQ, Gulbis B, Dedeken L, et al: Survival among children and adults with sickle cell disease in Belgium: Benefit from hydroxyurea treatment. Pediatr Blood Cancer 62:1956-61, 2015

5. Lobo CL, Pinto JF, Nascimento EM, et al: The effect of hydroxycarbamide therapy on survival of children with sickle cell disease. Br J Haematol 161:852-60, 2013

6. Gladwin MT: Cardiovascular complications and risk of death in sickle-cell disease. Lancet 387:2565-74, 2016

7. Steinberg MH, McCarthy WF, Castro O, et al: The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5-year follow-up. Am J Hematol 85:403-8, 2010

8. Gladwin MT, Sachdev V, Jison ML, et al: Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 350:886-95, 2004

9. Gladwin MT, Barst RJ, Gibbs JS, et al: Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PLoS One 9: e99489, 2014

10. Elmariah H, Garrett ME, De Castro LM, et al: Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol 89:530-5, 2014

11. Machado RF, Barst RJ, Yovetich NA, et al: Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood 118:855-64, 2011

12. Klings ES, Machado RF, Barst RJ, et al: An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med 189:727-40, 2014

13. Kassim AA, Galadanci NA, Pruthi S, et al: How I treat and manage strokes in sickle cell disease. Blood 125:3401-10, 2015

14. McClellan AC, Luthi JC, Lynch JR, et al: High one year mortality in adults with sickle cell disease and end-stage renal disease. Br J Haematol 159:360-7, 2012

15. Smith WR, Penberthy LT, Bovbjerg VE, et al: Daily assessment of pain in adults with sickle cell disease. Ann Intern Med 148:94-101, 2008

16. Steinberg MH, Barton F, Castro O, et al: Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 289:1645-51, 2003

17. Powars DR, Chan LS, Hiti A, et al: Outcome of sickle cell anemia: a 4- decade observational study of 1056 patients. Medicine (Baltimore) 84:363-76, 2005

18. Darbari DS, Kple-Faget P, Kwagyan J, et al: Circumstances of death in adult sickle cell disease patients. Am J Hematol 81:858-63, 2006

19. Fitzhugh CD, Lauder N, Jonassaint JC, et al: Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. Am J Hematol 85:36-40, 2010

20. Lanzkron S, Carroll CP, Haywood C, Jr.: Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep 128:110-6, 2013

21. Platt OS, Brambilla DJ, Rosse WF, et al: Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 330:1639-44, 1994

22. Gluckman E, Cappelli B, Bernaudin F, et al: Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 129:1548-1556, 2017

23. Bolanos-Meade J, Fuchs EJ, Luznik L, et al: HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood 120:4285-91, 2012

24. Ruggeri A, Eapen M, Scaravadou A, et al: Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant 17:1375-82, 2011

25. Kamani NR, Walters MC, Carter S, et al: Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Biol Blood Marrow Transplant 18:1265-72, 2012

26. Shenoy S, Eapen M, Panepinto JA, et al: A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood 128:2561-2567, 2016

27. Vaughn JE, Storer BE, Armand P, et al: Design and Validation of an Augmented Hematopoietic Cell Transplantation-Comorbidity Index Comprising Pretransplant Ferritin, Albumin, and Platelet Count for Prediction of Outcomes after Allogeneic Transplantation. Biol Blood Marrow Transplant 21:1418-24, 2015

28. Spellman S, Bray R, Rosen-Bronson S, et al: The detection of donor- directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood 115:2704-8, 2010

29. Gladstone DE, Zachary AA, Fuchs EJ, et al: Partially mismatched transplantation and human leukocyte antigen donor-specific antibodies. Biol Blood Marrow Transplant 19:647-52, 2013

30. Gragert L, Eapen M, Williams E, et al: HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med 371:339-48, 2014

31. Locatelli F, Kabbara N, Ruggeri A, et al: Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood 122:1072-8, 2013

32. Krishnamurti L, Sullivan, K. M., Kamani, N. R., Waller, E. K., Abraham, A., Campigotto, F., Zhang, W., Smith, S., Hassell, K. L., Decastro, L., Wu, C. J., Neuberg,

D. S., & Walters, M. C.: Results of a Multicenter Pilot Investigation of Bone Marrow Transplantation in Adults with Sickle Cell Disease (STRIDE). Blood 126:543, 2015

33. McCurdy SR, Kanakry JA, Showel MM, et al: Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. Blood 125:3024-31, 2015

34. Nathalie Dhedin JdlF, Francoise Bernaudin, Mathieu Kuentz, Leena Karnik, Tatsuki Koyama, Robert A. Brodsky, Michael DeBaun, Adetola A. Kassim: Haploidentical Bone Marrow Transplant with Post-Transplant Cytoxan Plus Thiotepa Improves Donor Engraftment in Patients with Sickle Cell Anemia: Results of an International Multicenter Learning Collaborative. Blood 128, 2016

35. Socie G, Stone JV, Wingard JR, et al: Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med 341:14-21, 1999

36. Wingard JR, Majhail NS, Brazauskas R, et al: Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol 29:2230-9, 2011

37. Lachin JM: Sample size evaluation for a multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. Stat Med 27:2509-23, 2008

38. Li Y, Schaubel DE, He K: Matching methods for obtaining survival functions to estimate the effect of a time-dependent treatment. Stat Biosci 6:105-126, 2014

39. Zhang X, Zhang MJ, Fine J: A Mass Redistribution Algorithm for Right Censored and Left Truncated Time to Event Data. J Stat Plan Inference 139:3329-3339, 2009

40. Kaplan E, & Meier, P. (Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association 53:457-481, 1958

41. Logan BR, Zhang MJ, Klein JP: Marginal models for clustered time-to- event data with competing risks using pseudovalues. Biometrics 67:1-7, 2011