PROTOCOL FULL TITLE

A multi-centre open randomised controlled trial to assess the effect of related haplo-donor haematopoietic stem cell transplantation versus standard of care (no transplant) on treatment failure at 24 month in adults with severe sickle cell disease

Protocol Short Title

REElated haplo-DonoR haematopoietic stEm cell transplantation for adults with Severe Sickle cell disease (REDRESS).

REDRESS

Trial Identifiers

ISRCTN:	ISRCTN90484310		
REC Number:	22/LO/0702		
IRAS Number:	312212		
NIHR Reference:	NIHR130674		
Protocol Version Number:	3.0	Date:	01 November 2023

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1. STUDY SYNOPSIS

TITLE OF CLINICAL TRIAL:	**RElated haplo-DonoR haematopoietic stEm cell transplantation for adults with Severe Sickle cell disease**
Protocol Short Title/ Acronym:	REDRESS
Study Phase:	III
Sponsor Name(s):	King's College Hospital NHS Foundation Trust
Chief Investigator(s):	Dr Victoria Potter
IRAS Number:	312212
REC Number:	22/LO/0702
Medical Condition Or Disease Under Investigation:	Sickle Cell Disease
Purpose Of Clinical Trial:	To evaluate the clinical and cost effectiveness of Haploidentical Stem Cell Transplantation (SCT) for adults with severe sickle cell disease (SCD), who have failed other therapies or are intolerant of existing therapies or require chronic transfusions to prevent on-going complications of SCD.
Primary Objective:	To assess clinical effectiveness of Haploidentical SCT when compared to the standard of care for severe sickle disease.
Secondary Objectives:	To determine the cost effectiveness of Haploidentical SCT. To evaluate the complications of Haploidentical SCT when compared to on-going complications of those participants with SCD who continue to receive standard of care. To contrast the Haploidentical SCT and standard of care groups on quality of life indices. To determine overall treatment success of the Haploidentical SCT procedure in terms of sustained engraftment and cure of the SCD phenotype. To describe the clinical characteristics of the transplant participants from transplant to 24 months post-randomisation.
Trial Design:	A multicentre, phase 3, open label, randomised controlled trial.

Sample Size:	120 participants.
Summary Of Eligibility Criteria:	Adults with severe SCD phenotype who are at high risk for morbidity and mortality with a confirmed haploidentical donor. Participants must be fit to proceed to stem cell transplantation and capable of providing written informed consent.
Intervention (Description, frequency, details of delivery)	Participants receiving Haploidentical Stem Cell Transplantation will receive the transplant conditioning regimen as per the standard transplant protocol.
Comparator Intervention:	The comparator arm is standard medical care for this patient population. Standard medical care may include all currently available non-trial therapies for SCD.
Version And Date Of Final Protocol:	V3.0, 01 November 2023

1.1 PROTOCOL AUTHORISATION

Chief Investigator:

Signature ..... Victoria Potter (Mar 23, 2024 08:09 GMT) Date 03/23/24 .....

Statistician:

Ben Carter
Signature ..... Ben Carter (Mar 25 2024 09:12 GMT) Date 03/25/24 .....

Health Economist:

Paul Tappenden
Signature ..... Paul Tappenden (Mar 25 2024 18:03 GMT) Date 03/26/24 .....

1.2 REVISION HISTORY

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date
1.0	Not applicable, first version	19 May 2022
1.1	Administrative changes and update to participant timeline (Section 5.4).	18 July 2022
2.0	Section 3.4 – clarified that informed consent required from donor. Section 4.5 – updated to include how participant care will be managed in the event of an incidental finding. Section 11.2.4 – clearer explanation of how pregnancy outcome data will be collected.	31 October 2022

3.0	Section 3.1 – amended to remove the need for screened patients to be discussed at the national haemoglobinopathy panel (NHP). Section 3.3 – removal of the need for end organ damage to be ratified by NHP as part of inclusion criteria. Section 4.2 – confirmation that Total Body Irradiation is included as part of pre-transplant conditioning protocol and description of example TBI protocol added. Update to the transplant protocol diagram. Section 5.3 – addition of secondary outcome measure to collect employment status of participants. Section 5.4 – update to participant timeline to include collection of employment status. Section 10.3 – revision of internal pilot (statistical) to clarify Go/No Go criteria. Section 11.2.1 – clarification that the expedited SAE reporting exemption for hospital admission for standard post-operative/post-transplant management also includes infectious complications such as viral, bacterial and fungal complications.	01 November 2023

1.3 GLOSSARY OF TERMS

ACS	Acute Chest Syndrome
AE/AR	Adverse event/Adverse Reaction
ATG	Thymoglobulin
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
BSA	Body Surface Area
BSBMTCT	British Society of Blood and Marrow Transplantation and Cellular Therapy
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
CMV	Cytomegalovirus
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Data Clarification Request
DLCO	Diffusing Capacity Of The Lungs For Carbon Monoxide
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EBV	Epstein-Barr Virus
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group score
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture system
EDTA GFR	Glomerular Filtration Rate Measured by 51 Cr-EDTA Clearance
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	Standardised Measure Of Health-Related Quality Of Life Developed By The Euroqol Group
EFS	Event Free Survival
FEV_1	Forced Expiry Volume
FVC	Forced Vital Capacity
GGT	Gamma-Glutamyl Transferase
GP	General Practitioner
GCP	Good Clinical Practice
GvHD	Graft versus Host Disease
Hb	Haemoglobin
HbS%	Sickle Cell Haemoglobin percentage
HC	Hydroxycarbamide
HCC	Haemoglobinopathy Coordinating Centres
HIV	Human Immunodeficiency Virus
HTLV	Human T-Lymphotropic Virus
HLA	Human Leucocyte Antigens
HRQoL	Health-Related Quality of Life
HSCT	Haematopoietic Stem Cell Transplantation
HTA	Human Tissue Act
ICF	Informed Consent Form
IME	Important Medical Event
ISF	Investigator Site File
ITT	Intention to Treat
JACIE	Joint Accreditation Committee ISCT-Europe & EBMT
KCL	King's College London
KCTU	King's Clinical Trials Unit
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MDT	Multi-disciplinary Team
mITT	Modified Intention to Treat
MMF	Mycophenolate Mofetil
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NIH	National Institute of Health
NIHR	National Institute for Health Research
NHP	National Haemoglobinopathy Panel
NHS	National Health Service
NHSE	NHS England
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PCP	Pneumocystis Pneumonia
PEFR	Peak Expiratory Flow Rate
PI	Principal Investigator at each recruiting site
PIN	Participant Identification Number
PIS	Participant Information Sheet
PP	Per Protocol
PPP	Per Protocol Population
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
REC	Research Ethics Committee
RN	Research Nurse
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SCT	Stem Cell Transplantation
SDW	Source Data Worksheets
SDV	Source Data Verification
SOC	Standard of Care
SS	Senior Statistician
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Total Body Irradiation
TDS	Three times a day
TLCO	Transfer Factor for Carbon Monoxide
TM	Trial Manager
TMA	Thrombotic Microangiopathy
TMF	Trial Master File
TMG	Trial Management Group
TRM	Transplant Related Mortality
TRV	Tricuspid Regurgitation Velocity
TS	Trial Statistician
TSC	Trial Steering Committee
ULN	Upper Limit of Normal (Hepatic Function)
UK	United Kingdom
UK NHP	UK National Haemoglobinopathy Panel
VC	Vital Capacity
VOC	Vaso-occlusive Crisis
VOD	Veno-Occlusive Disease
WOCBP	Women of Child-Bearing Potential

1.4 Protocol Contents

2. INTRODUCTION

2.1 BACKGROUND AND RATIONALE

Sickle cell disease (SCD) is inherited abnormality of haemoglobin, resulting in recurrent acute pain crises and severe chronic health issues affecting neurological, cardiorespiratory, hepatic and renal systems. SCD mostly affects those from African or Afro-Caribbean backgrounds. Life expectancy is shortened compared to the general UK population and many patients continue to suffer health problems despite treatment [1,2]. The only currently available and licensed therapies for adults with SCD are transfusions and hydroxycarbamide (HC). Both are inadequate, with many patients showing only partial response or being intolerant of treatment.

Societal and caregiver burden is high. Significant health care costs are accrued for the NHS and Quality of Life (QoL) is impaired even compared to other chronic diseases, impacting adversely on educational, employment and social outcomes which worsen with age. The only available curative therapy is haematopoietic stem cell transplantation (HSCT). Stem Cell Transplantation (SCT) typically involves a combination of chemotherapy and immune suppressive drugs prior to the infusion of haematopoietic stem cells. Engraftment of the stem cells with subsequent production of a new haematopoietic system results in red blood cell production that does not have the sickle phenotype effectively curing severe SCD.

SCT for sickle cell disease is well established globally to treat and cure those with a severe disease phenotype [3-10]. The two largest prospective data sets to date for adults [7,10] demonstrate excellent sickle free survival (85-87%) in 152 recipients of sibling SCT. Reductions occurred in hospital admissions, transfusions, haemolysis, iron overload and opiate use. No mortality due to the SCT procedure occurred (transplant related mortality also known as TRM). Rates of graft versus host disease (GvHD) were low and fertility was preserved. This protocol use in this trial showed benefit in QoL [8] and at 1 year, improvements were demonstrated in pain, vitality, general health and social functioning. Differences in SCD symptoms were detected early post-SCT and continued to improve with time. A recent European analysis of sibling SCT also demonstrated excellent long-term event free survival (EFS) of 81% in 154 adults [9]. This data supported the NHS England (NHSE) decision to routinely commission sibling HSCT. However, >70% of this 'in need population' will not have a suitable sibling donor [6,7]. Due to the low numbers of appropriately matched unrelated donor options on international donor registries for the ethnic groups most affected alternate donors such as haploidentical donors are required for patients with severe SCD. Haploidentical donors (half matched family donors) are nearly universally available hence rapidly expanding the donor pool. This allows the curative potential of SCT to be extended to almost all fit patients with severe SCD.

Within the UK paediatric practice, haploidentical stem cell transplants are routinely commissioned, and safety and efficacy data are very encouraging. Novel transplant protocols have allowed the utilisation of Haploidentical SCT donors for adult patients with increasingly encouraging results in later SCT studies [11-16]. For severe SCD, haploidentical SCT would be considered throughout North America and mainland Europe, for patients without a fully matched sibling donor.

This study will examine not only the efficacy of the haploidentical donor approach, but also investigate the cost effectiveness and quality of life outcome from these procedures, and add to the efficacy data, we anticipate potential cost savings for the NHS as the recurrent costs of repeated hospital admissions, pain management, and blood transfusions are offset by the one-off non-recurrent cost of SCT. For example, 6077 hospitalisations in 2010-11 with SCD as the primary diagnosis cost

NHS commissioners £18,798,255. This equates to approximately £3093 per hospital admission and underestimates the true cost of caring for this group of patients as it does not include the cost of chronic transfusion therapy, iron chelation, hydroxycarbamide, painful crisis and routine outpatient appointments. Furthermore, additional costs such as those incurred by patients and society due to loss of employment and adverse effects on quality of life are not captured by these studies. Therefore, there is data confirming the proof of principle of a haploidentical approach in adults with severe SCD.

If shown to be as efficacious and safe as preliminary published data, it would provide those most in need patients with a donor option, having a major impact on the quality and length of life for those with severe SCD.

2.2 Summary of known and potential risks of Intervention

The haploidentical SCT has both immediate and long-term risks associated, although the probability of these risks are low.

These include:

- Graft vs Host Disease (GvHD),
- Graft Rejection
- Transplant Related Mortality (TRM)
- Infection
- Veno-Occlusive Disease (VOD)
- Side effects related to immunosuppressive medication

2.3 Objectives

2.3.1 Primary Objective

The primary objective is to determine the clinical effectiveness of Haploidentical SCT for adults with severe SCD. The primary outcome measure is treatment failure at 24 months. Treatment failure is defined as occurrence of vaso-occlusive crisis (VOC), or transfusion from 6 months post-randomisation.

2.3.2 Secondary Objectives

a. To determine the cost-effectiveness of Haploidentical SCT.

b. To evaluate the complications of Haploidentical SCT when compared to the on-going complications of those participants with SCD who continue to receive standard of care.

c. To contrast the Haploidentical SCT and standard of care groups on quality of life indices.

d. To determine overall treatment success of the Haploidentical SCT procedure in terms of sustained engraftment and cure of the SCD phenotype.

2.4 TRIAL DESIGN

This is a multicentre, phase 3, open label randomised controlled trial designed to evaluate the clinical and cost-effectiveness of Haploidentical SCT when compared to standard of care for adult participants with severe sickle cell disease in the UK.

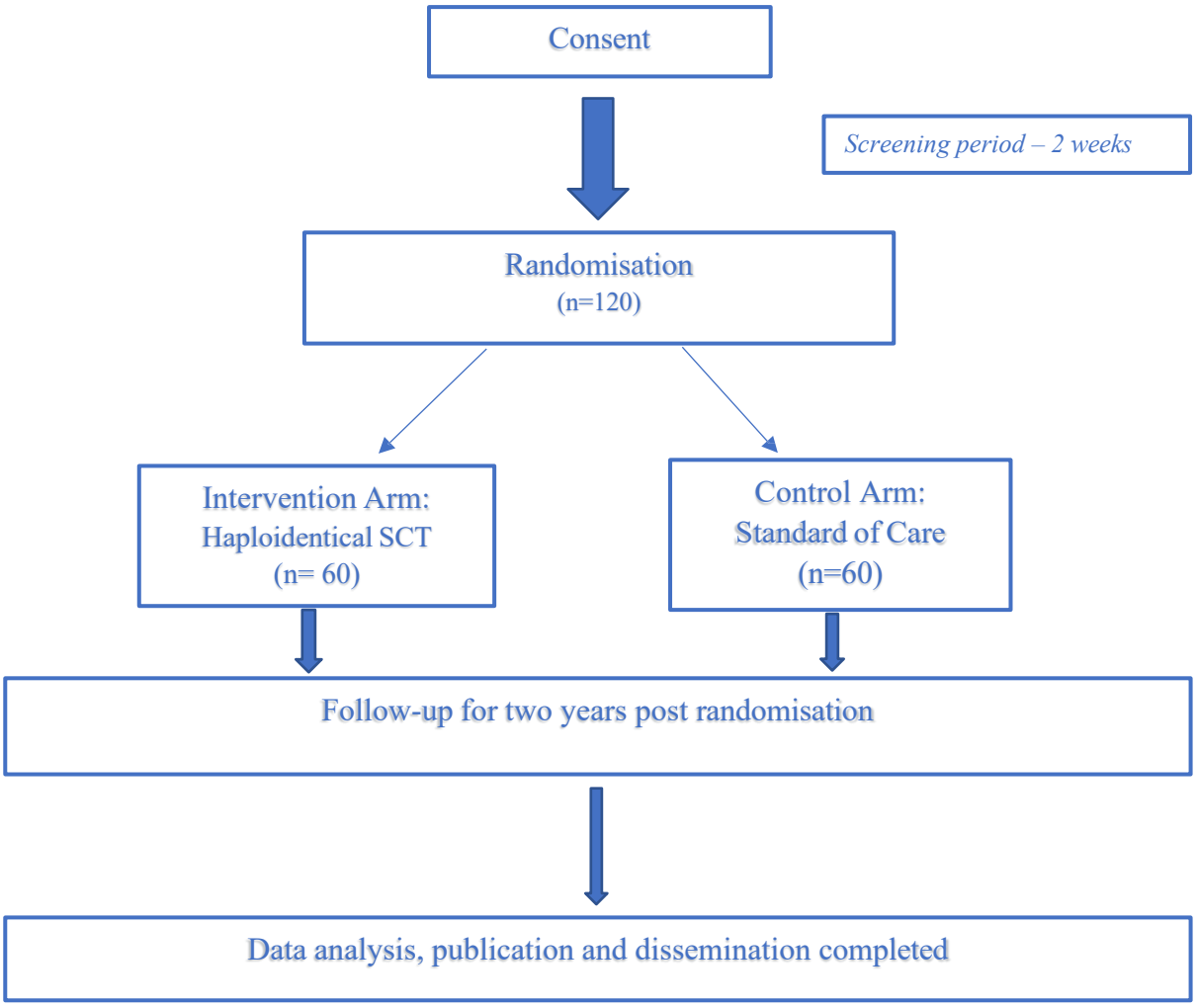

Figure 1: Trial design flow chart.

3. PARTICIPANTS

3.1 STUDY SETTING & RECRUITMENT

Participants will be recruited through haemoglobinopathy clinics within accredited haemoglobinopathy specialist centres/haemoglobinopathy coordinating centres (HCC).

Eligible patients for Recruitment:
To deliver this study an NHS wide network of transplant centres either co-located, or in partnership with a designated red cell centre (HCC) has been established.

Further study sites will be considered if they have suitable SCD patient populations, suitable transplant and sickle cell disease expertise and fulfil the site selection parameters. A balance of London and Regional Centres to ensure equity of access to this treatment nationally is required.

Transplant sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol.
- Data collection requirements.
- Must be a transplant centre accredited by the British Society of Blood and Marrow Transplantation and JACIE for undertaking allogeneic transplants in adults.
- Must have on site support by Sickle Physicians.

The centres include co-applicants on this proposal with, at present, 3,309 adults with SCD, of whom 525 are currently on long term transfusion. A similar number (or a higher number) will be treated with hydroxycarbamide (of whom 20-30% will be non-responders). This indicates a potentially eligible trial group of 630-682 patients. Assuming a very conservative acceptance by the eligible patient group of 30% (189-204 patients) we will meet the recruitment criteria defined in our study timeline with the currently available pool of patients.

In addition, there is a larger population of patients with sickle cell disease linked to the study sites through HCC local networks. The study will be widely disseminated through these local networks and patient groups to encourage referral from additional sites.

3.2 DONOR ELIGIBILITY

A haploidentical matched donor for each participant must be identified prior to randomisation. Matched donors will be identified and assessed as fit to donate as per local centre standard clinical protocol.

3.3 PARTICIPANT ELIGIBILITY CRITERIA

3.3.1 INCLUSION CRITERIA

a) Adult patients age ≥ 18 years

b) Confirmed haploidentical donor

c) Severe SCD phenotype who are at high risk for morbidity and mortality. Severe SCD is defined by at least one of the following:
   i. Clinically significant neurologic event (stroke) or deficit lasting > 24 hours.
   ii. History of ≥2 acute chest syndromes in a 2-year period preceding enrolment despite optimum treatment, e.g. with hydroxycarbamide (HC).
   iii. History of ≥3 severe pain crises per year in a 2-year period preceding enrolment despite the institution of supportive care measures (e.g. optimum treatment with HC).
   iv. Administration of regular transfusion therapy (=8 packed red blood transfusions per year for 1 year to prevent vaso-occlusive complications).
   v. Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion.
   vi. Patients requiring HC/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions.
   vii. Established end organ damage relating to SCD, including but not limited to progressive sickle vasculopathy and hepatopathy.
d) Patients must be fit to proceed to Haploidentical SCT as defined below:
   i. Karnofsky score ≥60
   ii. Cardiac function: LVEF ≥45% or shortening fraction ≥25%
   iii. Lung Function: FEV_1, FVC and TLCO ≥50%
   iv. Renal function: EDTA GFR ≥40 ml/min/1.73m^2
   v. Hepatic function: ALT <x3 ULN and bilirubin <x2 the upper limit of normal, those with hyperbilirubinemia due to sickle related haemolysis will not be excluded. No radiological evidence of cirrhosis.

e) Written informed consent.

3.3.2 EXCLUSION CRITERIA

a) Fully matched sibling donor.
b) Previous bone marrow transplant.
c) Pregnancy or breast feeding.
d) Participants able to conceive a child that are unprepared to use effective contraception.
e) Clinically significant donor specific HLA antibodies.
f) HIV infection or active Hepatitis B or C.
g) Uncontrolled infection including bacterial, fungal and viral.
h) Participation in another interventional trial in the last three months.
i) Pre-existing condition deemed to significantly increase the risk of Haploidentical SCT by the local Principal Investigator.

3.4 INFORMED CONSENT

It is the responsibility of the Investigator or delegate to obtain written informed consent for each participant and donor prior to performing any trial related procedure. A Participant Information Sheet (PIS) is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. The Investigator should also emphasise that the participant is completely free to refuse to take part or withdraw from the trial at any time. The participant should be given ample time (at least 24 hours) to read the PIS and to discuss their participation with others outside of the site research team. The participant must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial, they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator must then sign and date the form. A copy of the Informed Consent Form should be given to the participant, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial the participant's trial number should be entered on the Informed Consent Form maintained in the ISF.

Details of the informed consent discussions should be recorded in the participant's medical notes, this should include the date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial, the participant should have the opportunity to ask questions about the trial and any new information that may be relevant to the participant's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the participant in which case the process above should be followed and the participant's right to withdraw from the trial respected. Participants are permitted to re-consent at the same visit that new information is provided if they wish to do so.

Electronic copies of the PIS and ICF are available from the Trial Manager and should be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial should be recorded on the Participant Screening/Enrolment Log and, with the participant's prior consent, their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

4. INTERVENTIONS

4.1 EXPLANATION FOR THE CHOICE OF COMPARATORS

The comparator arm is standard medical care for this patient population. This will be the most ethical and applicable comparator for the study.

4.2 INTERVENTION AND COMPARATOR DESCRIPTION

4.2.1 INTERVENTION DESCRIPTION

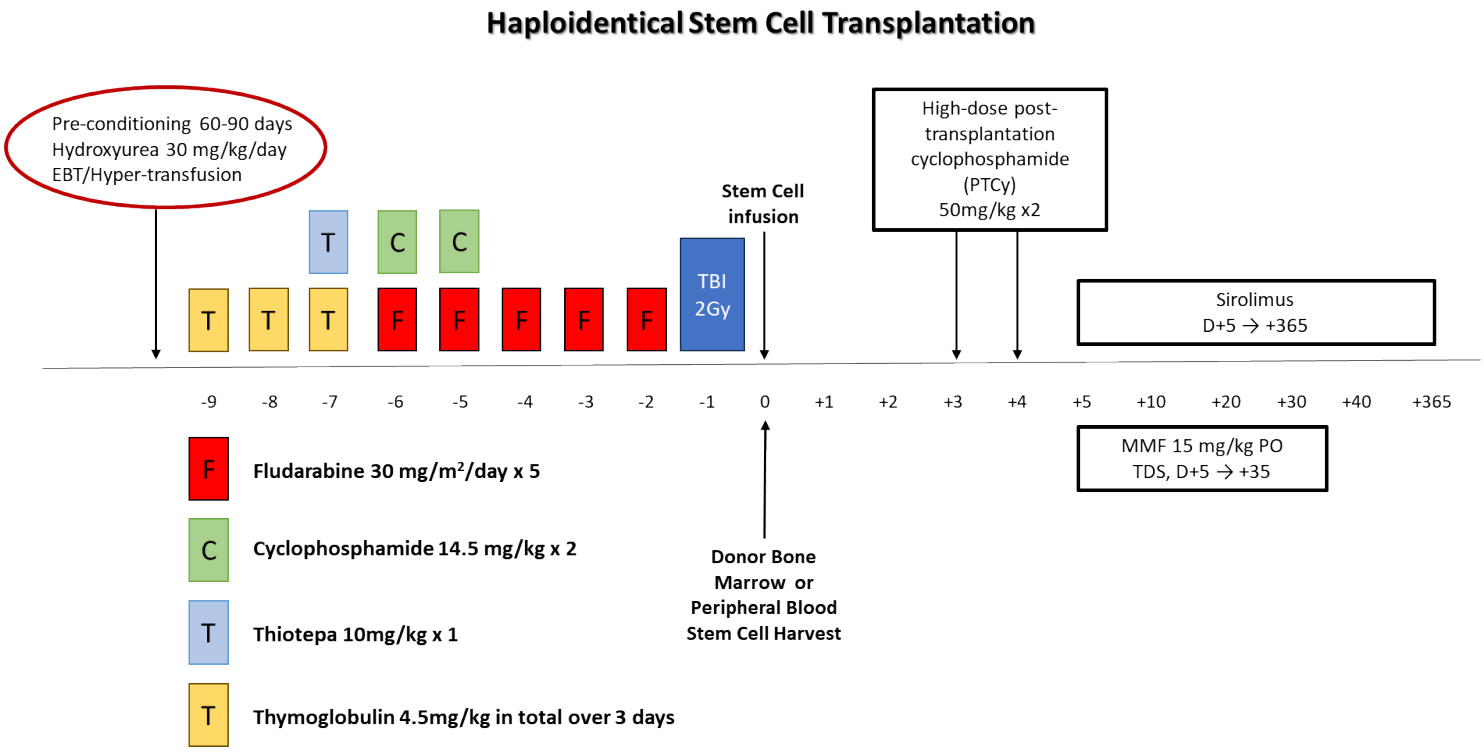

Figure 2: Haploidentical SCT procedure

Participants receiving Haploidentical SCT will be admitted to hospital to receive the transplant conditioning protocol: Thiotepa, Cyclophosphamide, Fludarabine, ATG (Thymoglobulin), Total Body Irradiation (TBI) as per the schedule set out above which is in accordance with local dosing protocols. The drugs used in the protocol are standard of care for transplant procedures and classed as non-investigational medicinal products.

Stem cells from a haploidentical donor will be infused on Day 0 according to standard institutional practices. Bone marrow is the preferred stem cell source however peripheral blood may be used as an alternative where required due to donor reasons. Stem cells may be collected and cryo-preserved prior to infusion. Donated stem cells will only be stored in Human Tissue Act (HTA) and JACIE accredited facilities for stem cell transplantation. If the samples are not infused to the participant, they will be disposed of in accordance with HTA regulations.

4.2.2 TOTAL BODY IRRADIATION (TBI)

Currently the UK standard of care haplo-identical protocol includes TBI. For this to be delivered, patients require a TBI planning CT, and confirmatory CT scan on the day of treatment. The treatment dose of 2Gy TBI will then be delivered as part of the transplant conditioning. As this study is taking a pragmatic approach to intervention delivery, variation to the TBI protocol in accordance with local procedures is expected and acceptable. Below is an example of the local TBI protocol for the lead site as reference:

- Total body irradiation (TBI) is a part of the conditioning protocol in this study. A single fraction of 2Gy (200cGy) is delivered on day -1. The technique used for delivery TBI will be centre dependent but must be able to reliably deliver a uniform dose distribution.

- Suitable radiotherapy techniques include an extended source-skin technique (SSD) with the patient treated in a lying, standing or semi recumbent position on a couch at an extended distance, approximately 4-5m from the source, allowing coverage of entire body by an open field.

- Treatment will be delivered using at least 2 opposing fields with the patient rotated 180 degrees between the opposing fields.

- A Perspex (or equivalent material) shield of 10-15mm thickness should be placed next to the couch. Measurements of separation should be taken along the length of the patient and based on these, a combination of bolus, tissue compensators and shielding should be used to achieve a homogenous dose distribution. Lung shielding and kidney shielding should be avoided unless required to improve dose homogeneity.

- A beam energy of 6-10 MV should be used and the treatment dose prescribed to mid plane.

- In vivo dosimetry with either diodes or thermoluminescent dosimetry should be used for verification and where possible a test dose should be delivered, typically <20 cGy ahead of the treatment. According to results from the test dose, adjustments can be made to the bolus, shielding and compensators and the number of monitor units correctly scaled. The variation in dose delivered should be less than 10% across the body [22].

- Alternatively, an optimised conformal technique can be used whereby the patient will undergo a planning CT and dosimetry performed using treatment planning software. Treatment will be delivered using either a 3D conformal or an intensity modulated technique, such as volumetric arc therapy or helical tomography, according to local protocol.

- For this the patient will undergo a planning CT scan in the treatment position. position. A thermoplastic shell or moulded vacbag may used for stability. The CT scan should include the entire body from vertex to feet. A slice thickness of 5mm is adequate in most cases. Intravenous contrast is not required.

- The clinical target volume (CTV) for TBI is the entire body. The CTV can be generated using an auto-contouring tool but must be verified manually by the clinician. The planning target volume (PTV) is the CTV clipped from the skin by 4-5mm. The only mandated organ at risk (OAR)is the lungs. Other OARs such as heart, kidneys, brain and eyes can be contoured at Clinician's discretion. Total marrow or total lymphoid irradiation should not be used for the purpose of this study.

- The plan produced by the planning software should achieve homogenous coverage of entire body with less than 10% variation and ensure a PTV D95 of >95% is achieved.

- Geometric verification and dosimetric quality assurance for optimised TBI will be according to local protocols and may include KV or cone beam CT imaging on the day of treatment.

4.2.3 COMPARATOR DESCRIPTION

Standard of Care Treatment Arm (no transplant)

Standard medical care may include any currently available therapies for SCD patients. These may or may not include regular elective transfusion therapy or medications such as hydroxycarbamide. Any treatments that become approved for use during the trial, or available to individual participants on a named-patient basis or via a compassionate access programme are permissible. The choice of standard of care treatment is made by the treating physician with no protocol restrictions. Participants in the SOC arm should not receive other investigational therapies.

4.3 Criteria for discontinuing or modifying allocated interventions

4.3.1 Treatment discontinuation

Treatment for those in the Haploidentical SCT arm will be discontinued if any of the following criteria is met:

a) The participant becomes irreversibly medically unfit for transplant
b) The donor becomes irreversibly medically unfit for donation

4.3.2 Modification of allocated intervention

Should there be any deviation from the standard SCT protocol, it is the responsibility of the Principal Investigator (or delegate) to inform the Chief Investigator (Dr Victoria Potter) immediately.

4.4 Relevant concomitant care permitted or prohibited during the trial

There are no restrictions to the medical management of participants in the standard of care arm or treatment arm.

4.5 Provisions for post-trial care and incidental findings

Participants in both arms will continue to be followed up in the specialist centres involved. Any unexpected incidental findings from investigations will be communicated to the participant by the clinician who requested the test. Any medical care required will be arranged by the treating clinician or the participant will be referred to the appropriate medical speciality.

5. Outcomes

5.1 Primary Outcome

The primary outcome measure is treatment failure or mortality by 24-month post-randomisation. Treatment failure is defined as occurrence of vaso-occlusive crisis, or transfusion from 6 months post-randomisation.

Vaso-occlusive crisis (VOC) [17] is defined as pain crisis (defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion) which requires therapy with oral or parenteral opioids or parenteral NSAID as well as other complicated crisis such as acute chest syndrome (ACS), priapism and hepatic or splenic sequestration.

For purposes of this study, the following detailed definitions will be used to identify each subtype of VOC event:

1. **Uncomplicated pain crisis** is defined as an acute episode of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; but is *not* classified as an acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism. The end of an uncomplicated pain crisis will be considered the resolution of acute pain, such that residual pain (or absence of any pain) is considered to be chronic, and the current pain medication regimen is considered to be for this chronic pain.

2. **Acute Chest Syndrome (ACS)** is defined on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with alveolar consolidation but excluding atelectasis (as indicated by chest X-ray). At least one of the following additional signs or symptoms needs to be present as well: chest pain, a temperature of more than 38.5°C, tachypnoea, wheezing or cough. ACS will be considered resolved when the subject is no longer hospitalised (unless form reason other than the ACS episode) and none of the additional signs or symptoms above are present.

3. **Priapism** is defined as an unwanted or painful penile erection lasting at least 30 minutes. The end of an acute priapism event will be when the unwanted erection has resolved for at least 2 hours.

4. **Hepatic sequestration** is defined on the basis of findings of right upper quadrant pain, an enlarged liver, and an acute decrease in haemoglobin concentration (e.g. a decrease in haemoglobin of ~ 2 g/dL). Acute hepatic sequestration will be considered resolved when right upper quadrant pain has returned to baseline (pre-event) levels and haemoglobin has been stable for 24 hours.

5. **Splenic sequestration** is defined on the basis of findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in haemoglobin concentration (e.g., a decrease in haemoglobin of ~ 2 g/dL). Acute splenic sequestration will be considered resolved when left upper quadrant pain has returned to baseline (pre-event) levels and haemoglobin has been stable for 24 hours.

VOCs as defined above, can be managed at home or by a healthcare visit:

- **Healthcare visit** is defined as any visit to a medical facility such as emergency room, hospital and/or office visit, which includes pain management of VOC in situ.

- **Managed at home** is defined as **no visit** to any medical facility and/or healthcare professional to receive treatment for VOC. Healthcare contact for medical advice is allowed.

Finally, in addition to VOCs leading to healthcare visit or managed at home, other types of events are of interest in this study:

- **Other acute pain crisis managed at home** is defined as pain crisis (defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion and which requires **therapy with enteral (oral, rectal and sublingual) analgesia,**

excluding opioids), but it does not require a visit to a medical facility and/or healthcare professional. Healthcare contact for medical advice is allowed.

5.2 SECONDARY OUTCOMES

a. Health related QoL as measured by EQ-5D-5L at 3, 6, 9, 12, 15, 18, 21 and 24 months.

b. Healthcare utilisation: Frequency of hospital admissions and opiate use in Haploidentical SCT and standard of care groups by 24 months.

c. Employment status of participants at 24 months.

d. All-cause mortality, defined as death from any cause by 24 months from randomisation.

e. Sickle Cell Disease-related mortality (excluding transplant related complications): defined as death due to any sickle cell disease related cause by 24 months.

f. Sickle type haemoglobin percentage (HbS%) as measured by haemoglobin electrophoresis at 6, 12 and 24 months.

g. SCD related complications (transfusion requirement, painful VOC, stroke, pulmonary hypertension) by 24 months.

h. Haemoglobin levels, Reticulocyte count, LDH, Bilirubin at 6, 12, and 24 months

i. Pulmonary function as measured by FEV_1 %, FEV_1/FVC ratio, TLCO % at 12 months and 24 months

j. Renal function as measured by urea, creatinine and eGFR at 6, 12 and 24 months

k. Iron overload as measured by Ferritin and FerriScan (R2-MRI) at 24 months

l. Cardiac function and pulmonary hypertension as measured by echocardiogram/TRV at 12 and 24 months

m. Cerebrovascular progression as measured by clinical stroke or evidence of progression on MRI/MRA at 24 months

n. Evidence of hepatic progression as measured by liver function (ALT, AST, ALP, GGT, Bilirubin) and FibroScan at 24 months.

o. Percentage of participants requiring opioid use for pain related to vaso-occlusive sickle related crisis at 12 months and 24 months.

5.3 CLINICAL CHARACTERISTICS OF THE TRANSPLANT PARTICIPANTS

The following characteristics will be described:

a. Time to neutrophil and platelet engraftment in the Haploidentical SCT arm as measured by neutrophil and platelet count.

b. Graft versus Host Disease: Grade 2-4 acute and moderate to severe chronic GvHD. GvHD to be assessed and graded as per NIH clinical criteria in the Haploidentical SCT arm.

c. Incidence of significant infectious complications (bacterial, viral, fungal) in the Haploidentical SCT arm.

d. Lineage specific chimerism: defined as % donor chimerism in unfractionated, T-cells and Myeloid Cells in the Haploidentical SCT arm.

e. Proportion of participants in the Haploidentical SCT group requiring immunosuppressive drugs at 24 months post-randomisation.

f. Transplant related mortality – the proportion of participants that die due to complications of the Haploidentical SCT.

5.4 PARTICIPANT TIMELINE

		Baseline	Randomisation	*Transplant	Month 3 post-randomisation (+/- 7 days)	Month 6 post-randomisation (+/- 14 days)	Month 9 post-randomisation (+/- 14 days)	Month 12 post-randomisation (+/- 14 days)	Month 15 post-randomisation (+/- 14 days)	Month 18 post-randomisation (+/- 14 days)	Month 21 post-randomisation (+/- 14 days)	Month 24 post-randomisation(+/- 7 days)	Ongoing	End of Study
1	Registration Form	x												
2	Patient Eligibility	x												
3	Donor characteristics	x												
4	Medical History	x												
5	Participant Baseline characteristics	x												
6	HCT-Comorbidity Index (HCT-CI)	x												
7	Randomisation Form		x											
8	Transplant form*			x										
9	Vaso-occlusive crisis Log (VOC)												x	
10	Transfusion log												x	
11	GvHD Assessment Log*												x	
12	EQ5D-5L	x			x	x	x	x	x	x	x	x		
13	Health Resource Use				x	x	x	x	x	x	x	x		
14	Haematology	x				x		x				x		
15	Biochemistry	x				x		x				x		
16	Virology	x				x*		x*				x*		
17	Urine	x				x		x				x		
18	Lineage specific chimerism log*												x	
19	Sickle type haemoglobin % (HbS%)	x				x		x				x		
20	MRI/MRA head	x										x		
21	FerriScan Liver Scan R2-MRI	x										x		
22	FibroScan	x										x		
23	Pulmonary Function Test	x						x				x		
24	Echocardiogram	x						x				x		
25	Employment status	x										x		
26	Concomitant Medications Log												x	
27	Adverse Events (inc. admissions)												x	
28	Withdrawal Form													x
29	PI Sign Off													x

Table 1. Schedule of events (=transplant arm only)*

Data	Description
Registration form	Participant registration to be completed in the Elsevier MACRO EDC system to obtain a study PIN
Patient eligibility & donor characteristics	Inclusion and exclusion criteria for the participants and donor characteristics to be completed. If there is a change of donor after data entry, the characteristics of the new doner should replace those of the previously planned donor
Medical history	Relevant medical history to be completed during screening; any new symptoms or diagnoses post-consent but pre-randomisation should be completed on this form
Baseline Characteristics	A physical examination including vital signs, weight, and ECOG performance status.
Haematopoietic Cell Transplantation – Comorbidity Index (HCT-CI)	Score derived from the HCT-CI calculator providing information on the overall and non-relapse mortality risk for a patient after undergoing haematopoietic cell transplantation.
Randomisation form	Participants are randomised as per section 6.3.2 and relevant information transcribed to the EDC system
Transplant form*	Transplant form is to be completed during hospital admission and updated subsequently as information becomes available
Vaso-occlusive crisis log	All episodes of VOC to be recorded, including dates and type of VOC
Transfusion log	All transfusions to be recorded, including any administered post-transplantation
GvHD Assessment Log*	If transplant recipients develop Graft versus Host Disease (GvHD) at any stage in the trial, details must be recorded in the EDC system.
EQ5D-5L	Validated quality of life assessment.
Health Resource Use	Questionnaire completed by participant enquiring about the type and frequency of health care services used during the assessment period.
Laboratory samples (local laboratories): Haematology Biochemistry Virology Urine sample Lineage specific chimerism log HbS%	All laboratory samples should be undertaken as per normal clinical practice requirements in both trial arms. Results to be transcribed to the EDC system at the timelines in table 1 are detailed below. If clinically significant abnormal results are detected on any tests, consider recording as an adverse event. Full blood count (FBC) (haemoglobin, white cell count, neutrophil count, platelet count) and reticulocyte count for timepoints above. Urea, creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and ferritin for timepoints above. Pre-emptive treatment for viral re-activation should be delivered as per local policy and recorded as concomitant medications. Pre-transplant virology to be transcribed to the EDC are Epstein-Barr Virus (EBV) (IgG), Cytomegalovirus (CMV) (IgG), Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Human T-lymphotropic virus (HTLV), Hepatitis B, Hepatitis C & Hepatitis E. Post-transplant virology to be transcribed to the EDC are EBC (PCR) and CMV (PCR) for timepoints above. Results to be transcribed to the EDC system are urine protein:creatinine ratio (PCR) only for timepoints above. Lineage specific chimerism (Unfractionated, CD3, CD15) in both whole blood and T-cell compartments should be performed as per normal clinical practice requirements in transplant recipients and all results transcribed to the EDC. At a minimum, results should be transcribed at months 6, 12 and 24. Sickle type haemoglobin percentage (HbS%) measurements
MRI/MRA head	MRI/MRA head is to be performed as per standard local procedures.
FerriScan Liver Scan R2-MRI	FerriScan liver scan R2-MRI is to be performed as per standard local procedures.
FibroScan	FibroScan liver performed as per local procedures.
Pulmonary Function Test	Pulmonary function test is to be performed as per local policy. Results should be transcribed for FEV_1 (%), FEV_1/FVC, and a Transfer Factor for Carbon Monoxide (TLCO %) corrected for Hb as per timeline above.
Echocardiogram	Echocardiogram is to be performed as per standard local procedures.
Employment status	Questionnaire to identify employment status of participants at 24 months.
Concomitant Medications Log	Concomitant medication may be given as medically indicated and all concomitant medication must be recorded in the EDC.

Data	Description
Adverse Events Log (inc. admissions)	Any new symptoms or diagnoses post-randomisation are considered adverse events. Issues related to uncomplicated surgical recovery are not considered adverse events and need not be recorded in the EDC. Serious adverse events will be submitted in an expedited manner. See section 11.2.
Withdrawal Form	To be completed in the event of withdrawal from all further data collection, including from medical notes only, or in the event of participant death.
PI Sign Off	To be completed prior to database lock by the site PI, to confirm the accuracy of the EDC data.

Table 2. Study procedures and data collection (=transplant arm only)*

5.5 PARTICIPANT FOLLOW UP

Participants will be followed-up for a 24-month post-randomisation visit according to the trial assessment schedule (section 5.4). Follow-up visits will occur at the transplant centre for those participants receiving Haploidentical SCT. Follow-up assessments for those participants receiving Standard of Care may be conducted at their local sickle cell centre. Follow-up assessments for the trial visits for Standard of Care participants may be conducted remotely by qualified trial personnel.

6. ASSIGNMENT OF INTERVENTIONS: ALLOCATION

6.1 SEQUENCE GENERATION

6.1.1 METHOD OF ALLOCATION SEQUENCE

The randomisation sequence will be generated using minimisation with stratification factors of sickle status at time of recruitment, recruitment site, and participant age. Participants will be randomised on a 1:1 basis between two treatment groups.

6.1.2 STRATIFICATION FACTORS

Name of stratification	Stratification groups
Sickle status at time of recruitment	01 | Predominantly VOC 02 | Predominantly transfusion
Recruitment Site	All active recruitment sites
Participant Age	01 | Below 30 years 02 | 30 years and above

Table 3. Stratification factors

6.2 CONCEALMENT MECHANISM

Minimisation will incorporate a random component to assure allocation concealment.

6.3 IMPLEMENTATION

6.3.1 ASSIGNMENT OF PARTICIPANTS TO INTERVENTIONS

A web-based randomisation system will be implemented, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Following consent, confirmation of eligibility and collection of baseline data, participants will be randomised.

6.3.2 RANDOMISATION PROCEDURE

- Prior to randomisation but after consent, obtain a unique Participant Identification Number (PIN) from the Elsevier MACRO EDC system.
- Ensure the initials, age at consent and stratification information above for the participant are available.
- Log on to the website: go to www.ctu.co.uk, click 'randomisation' and select "REDRESS"
- Enter your username and password
- Click on the Randomisation tab at the top of the page and choose *Randomisation Request*
- The study site selection will open. Choose the relevant site and click on **Randomise.**
- Under Profile Details, enter the:
  - Participant Identification Number (PIN). This is a 6-digit number which is obtained from MACRO.
  - Participants initials. This will consist of 2 or 3 letters. Enter in upper case. Do not put a dash between the letters.
  - Participant's age at consent.
- Under Data Collection, answer the question with a 'Yes' or 'No'. To answer the question, click on Edit, choose the appropriate response, and then save. Once the question is answered click on submit.
- You will receive a randomisation notification by email. This will provide details of the treatment arm assigned to the participant.
- Print a copy and file in the Investigator Site File.

6.4 BLINDING STATUS OF RESEARCHERS

The planned blinding of the research team and committees is detailed in table 4 below.

Individual blinding status	Blinded	Unblinded
Chief Investigator		**X**
Principal Investigators at site		**X**
Trial Manager/monitor		**X**
Senior Statistician	**X**	
Junior Statistician		**X**
Senior Health Economist	**X**	
Junior Health Economist		**X**
Trial Participants		**X**
Outcome Assessors/Research Nurses		**X**
Treating clinicians		**X**
Trial Steering Committee (TSC)	**X**	

Individual blinding status	Blinded	Unblinded
Data Monitoring Committee (DMC)		X

Table 4. Blinding status of research team

6.5 PROCEDURE FOR UNBLINDING IF NEEDED

No unblinding procedure is required as this is an open-label trial.

7. LABORATORY TESTS

Time points for laboratory tests for the purposes trial are described in the schedule of events. See details in section 5.4, tables 1 and 2. All laboratory tests are to be completed as per standard practice at local sites.

8. WITHDRAWAL & TREATMENT DISCONTINUATION

8.1 PARTICIPANT WITHDRAWAL

A trial participant has the liberty to withdraw their consent for further data collection at any time and for any reason, without penalty or loss of benefits to which the individual would otherwise be entitled. Participants who withdraw consent for further data collection will discontinue their future participation in the trial. Where possible, withdrawal should be avoided by requesting notes-based data collection only.

The Investigator will make every reasonable effort to keep each participant in the trial. However, if the Investigator removes a participant from the trial treatment or if the participant declines treatment they should be followed-up according to the trial schedule unless they withdraw specific consent.

In the event of a participant's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the participant wishes to withdraw and record the details on the appropriate eCRF. All efforts will be made by the Investigator to report the reason for withdrawal as thoroughly as possible. All information collected up until point of withdrawal will be retained and analysed.

8.2 TREATMENT DISCONTINUATION

If a participant randomised to the Haploidentical SCT arm does not receive the transplant, the reasons will be recorded and reported. Data collection will continue until 24-months as per the study schedule.

9. DATA COLLECTION AND MANAGEMENT

9.1 PLANS FOR ASSESSMENT AND COLLECTION OF OUTCOMES

9.1.1 SOURCE DATA WORKSHEETS

Source data worksheets will be supplied to all recruiting sites by the Trial Manager. These will be prepared after the database specification is finalised and database testing is complete.

9.2 PLANS TO PROMOTE PARTICIPANT RETENTION AND COMPLETE FOLLOW-UP

If a participant wishes to withdraw from the study, the research team will offer the participant the opportunity to discontinue trial treatment with no further attendance at trial visits but may ask permission of the participant to continue collecting follow up data from medical notes. The participant will not be required to attend trial visits or contacted for data in person or over the phone. It is anticipated that this will enable participants to complete follow up without active participation and for primary outcome data to be collected.

9.3 DATA MANAGEMENT

There are two datasets in the trial; the KCTU randomisation dataset and the KCTU Elsevier MACRO EDC system dataset. The CI will act as custodian for the trial data.

9.3.1 DATA ENTRY

Randomisation data will be entered as per section 6.3.2.

Study site staff will be delegated by the site PI to access the eCRF and randomisation systems via a Study Site Delegation Log. The request for user access must go to the Trial Manager, who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Authorised staff at sites will transcribe baseline and follow up data from the source data worksheets (SDWs) by going to www.ctu.co.uk and clicking the link to access MACRO. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Training videos for data entry staff, study site monitors and Trial Managers are available at www.ctu.co.uk under the 'Training' section. Users can self-register and should select the MACRO related training videos.

9.3.2 SECURITY (EDC)

The CI delegate (e.g. Trial Manager) will request usernames and passwords from KCTU on behalf of recruiting sites. Systems access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participant initials and age at consent will be entered into the systems. Hospital number, email address, participant names and addresses, and full postcodes will not be entered into the EDC system. Trial sites will maintain a master participant log linking participant identifiers to study numbers. No data will be entered unless a participant has signed a consent form to participate in the trial.

9.3.3 DATA QUALITY PROCESSES

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, where appropriate for the purpose of data cleaning and will request amendments to the MACRO EDC system data as required. No data will be amended independently of the study site responsible for entering the data.

No data can be amended in the randomisation system, however CI or delegate (e.g. Trial Manager) may request King's Clinical Trials Unit to add notes against individual participant entries to clarify data entry errors. Any errors should be reported by site staff to the Trial Manager as soon as possible once they are detected. The Trial Manager will onward report errors to KCTU and retain records in the TMF.

The KCTU will provide the Trial Manager with Data Management Plans for both the Elsevier MACRO EDC system and the randomisation system once the systems are made live. Those documents will be filed in the Trial Master File.

The Trial Manager will raise Data Clarification Requests (DCRs) with sites in the EDC system. Study sites will periodically review raised DCRs and respond to the queries raised.

Site monitoring visits will be conducted by the Trial Manager. KCTU will create a study specific monitoring plan for the study outlining the monitoring activities to be undertaken.

9.3.4 Database Lock

At the end of the trial, the site PI's will review all the data for each participant in the MACRO EDC system and provide electronic sign-off to verify that all the data are complete and correct.

The Trial Manager will confirm all checks are complete and all monitors queries have been resolved prior to database lock. At this point, with the agreement of the senior statistician, all data can be formally locked for analysis.

When the final data extract is requested, KCTU will remove all data entry user access prior to data extract and will retain only 'monitor' access for site PI's and other relevant individuals.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that all user access is removed from the MACRO EDC system. A copy of the database is to be stored in the TMF.

9.4 End of Trial

The end of trial will be the last participant's last follow-up visit (i.e. the 24 month visit). The Trial Manager will notify the ethics committee that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

9.5 Confidentiality

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and the Data Protection Act (2018). With the participant's consent, their initials and age at consent will be collected at trial entry. Participants will be identified using only their unique trial number, initials and age at consent on the

CRF and correspondence between the Trial Manager and the participating site. A screening log will be maintained by the site Investigator and will not leave the NHS site.

The study site will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. laboratory staff). Representatives of the REDRESS trial team may be required to have access to the participant's medical notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

10. STATISTICAL METHODS

In addition to this protocol, a Statistical Analysis Plan (SAP) will be drafted by the Senior Statistician who will remain fully blinded throughout the trial.

10.1 SAMPLE SIZE JUSTIFICATION

Using historical control data, we estimate a 24-month treatment failure rate of at least 88% [18,19] which will be reduced to 60% in those randomised to the transplant group (e.g. a success rate of 40%). To detect this difference in proportions using a 5% significance level, with 90% power we will need to analyse 100 participants (50:50). Assuming a dropout rate of 15%, we will inflate this to 120 participants.

10.2 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

10.2.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

Using a modified Intention to Treat (mITT) population, we will analyse the 24-month binary outcome as treatment failure using a mixed-effects multivariable logistic regression. Site will be fitted as a random effect. The analysis will be adjusted for participant: age; sex; sickle status at baseline.

10.2.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

We will apply a similar analysis to the primary outcome methodology to the secondary outcomes. Continuous outcomes will be analysed using a multivariable regression, fitting site as random effects with consistent fixed effects. Outcomes will multiple time-points will also include participant as a random effect.

Overall and disease related mortality will be analysed using a Cox's proportional baseline hazards regression fitted with a shared-frailty effect of site and participant, adjusted for consistent confounders. The proportional hazards will be assessed visually using a log-log plot. If the assumption was not reasonable, this will be analysed as a binary outcome in a method consistent with the primary outcome.

10.3 Internal Pilot (statistical)

No formal assessment is planned for efficacy.

At the end of one year after the first site being opened to recruitment, we will determine the feasibility of continuing the trial using the following Go/No Go criteria:

Criteria	Red (80%)	Amber (81%-99%)	Green (100%)
To have opened at least 6 sites	< 5	5	6 or more
Randomised at least 1 participant per site open	< 5	5	6 or more
To have randomised 30 participants across all sites	< 24	24 to 29	30 or more
An average recruitment rate/ site/ per quarter for each open site	< 1.6	1.6 to 1.9	2 or more

Table 5: Internal Pilot Go/No Go criteria

10.4 Methods for additional analyses (e.g. subgroup analyses)

The following Subgroup analyses will be fitted:

- Sex
- Age Group
- Sickle status at time of recruitment (VOC or transfusion)

10.5 Methods to handle missing data

Missing outcome data will be explored by pattern missingness. Any patterns found will be reported.

10.6 Populations under investigation

10.6.1 Modified Intention to Treat (mITT)

The primary population for analysis will be the mITT population. This will be defined as all participants randomised and providing at least one post-baseline measure at 6 months, 12 months, 18 months and 24 months of the primary outcome. Participants who experience transplant failure and withdraw from the study without any post-baseline data will be recoded as treatment failure.

10.6.2 Per protocol population (PPP)

Participants with recorded protocol violations (PV) will be excluded from the PPP. A protocol violation is defined as an event which is substantially important and the action may impact on the study findings. A protocol deviation (PD) is defined as an event or activity that deviates from the protocol which is unlikely to impact on the study findings. For example, a measurement outside of a visit window.

10.7 METHODS TO HANDLE COMPLIANCE

- Participants randomised to the transplant and receiving the transplant within 5 months will be considered compliant.

- Participants randomised to standard of care who receive a transplant within 24 months will be considered non-compliant.

10.8 SENSITIVITY ANALYSIS

Any sensitivity analysis required will defined in the SAP.

10.9 PLANS FOR ACCESS TO THE PROTOCOL

It is anticipated that the full protocol, SAP and all results will be available as open access publications according to the rules of the funding body.

10.9.1 ASSESSMENT OF THE ANALYSIS ASSUMPTIONS

Assessment of logistic regression
If there are no events (or all participants are an event) in either treatment group for the primary (or secondary) outcomes, the analysis will revert to a Fisher's exact test at 24 months.

Assessment of linear regression
The residuals will be assessed for normality, a constant variance and having a zero mean and distributed from an identical, independent distribution. If this is not appropriate, the outcome will be transformed.

Assessment of Cox – proportional baseline hazards
The baseline hazards will be assessed with log-log residuals. If this is not found to be reasonable, the analysis will be replaced with a mixed effects logistic regression consistent with the other secondary outcomes. Any changes to the planned analysis will be revised by a fully blinded analyst and approved by the oversight committees.

Any additional changes needed will be outlined by the senior statistician who will be blinded to the allocation. All amendments will be approved by the Trial Steering Committee.

10.10 HEALTH ECONOMIC ANALYSIS

We will undertake a model-based health economic analysis to compare SCT for haploidentical donors versus current standard non-curative therapies for the treatment of severe SCD. The analysis will provide important information for decision-makers to determine whether the use of Haploidentical SCT for patients with severe SCD represents good value for money for the NHS. The economic analysis will be undertaken from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Cost-effectiveness will be assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Health outcomes and costs will be discounted at a rate of 3.5% per annum. Costs will be valued at current prices. The economic analysis will characterise trade-offs between potential improvements in longer term outcomes (e.g.

survival and health-related quality of life [HRQoL]) and the potential for adverse effects with Haploidentical SCT.

We anticipate that the economic analysis will most likely adopt a state transition modelling approach, with three discrete health states reflecting whether participants have:

a) not yet failed treatment

b) failed treatment or

c) died.

Model parameters will be informed by the trial as well as other external sources. Estimates of time to treatment failure and adverse effects will be estimated directly using data on primary and secondary outcomes collected within the trial. Longer-term event rates may be explored through statistical analyses of clinical follow-up of participants with severe sickle cell disease through the European Society for Blood and Marrow Transplantation (EBMT) and British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) patient registries.

The impact of clinical events on participants' HRQoL will be informed by the collection of EQ-5D-5L data at 3-monthly intervals from participants over the course of the trial; depending on guidance from UK decision-making bodies at the time of the final economic analysis, it is likely that these data will be mapped to the EQ-5D-3L using the algorithm reported by Van Hout *et al* [20]. Resource use associated with the disease and its management will be estimated from data collected within the trial, including information on routine and unscheduled hospitalisations, transfusions, concomitant medications, standard care drug treatments (e.g. hydroxycarbamide).

The costs of Haploidentical SCT will be based on NHSE tariff values; other Haploidentical SCT-related costs incurred after 3 months (e.g. those relating to infection-related events) will be estimated separately. Costs will be valued at current prices using routine reference cost sources (NHS Reference Costs, the Personal Social Services Research Unit annual unit cost report, and the British National Formulary) and other literature, where appropriate.

Uncertainty will be assessed using deterministic and probabilistic methods. Deterministic analyses will include one-way sensitivity analyses and scenario analyses to identify key drivers of the cost-effectiveness of Haploidentical SCT. Probabilistic sensitivity analysis will be undertaken to estimate the likelihood that Haploidentical SCT is cost-effective relative to current standard non-curative therapies. Uncertainty will be represented using cost-effectiveness planes and cost-effectiveness acceptability curves. Value of information analysis will be undertaken to inform the prioritisation and design of future research. The analysis will be reported in line with the updated CHEERS economic evaluation publication guidelines [21].

11. OVERSIGHT AND MONITORING

11.1 COMPOSITION OF THE COORDINATING CENTRE AND TRIAL STEERING COMMITTEE

11.1.1 SPONSOR

The trial is sponsored by Kings College Hospital NHS Foundation Trust.

11.1.2 Coordinating Centre

The trial is being conducted under the auspices of the King's College Trials Unit (KCTU), Kings College London, according to their local procedures.

11.1.3 Trial Management Group

Title	Name*	Role
Chief Investigator	Dr Victoria Potter	Chair
KCTU Operations Director	Caroline Murphy	Member
KCTU Head of Clinical Trial Operations	Joanna Kelly	Member
KCTU Senior Statistician	Prof Ben Carter	Member
KCTU Junior Statistician	Rose Tinch-Taylor	Member
KCTU Senior Trial Manager	Daryl Hagan	Member
Health Economist	Dr Paul Tappenden	Member
Clinical Co-applicant	Dr Ben Carpenter	Member
Clinical Co-applicant	Dr Rachel Kesse-Adu	Member

**The protocol will not be formally amended to replace individuals who leave the project after ethics approval, unless an amendment is submitted for other reasons*

Table 6. TMG membership

The TMG is responsible for the study co-ordination, data quality and budget management. The TMG members listed in table 6 above will meet at least monthly throughout the trial. The CI will chair the TMG. Minutes will be taken by the Trial Manager and retained in the TMF. The TMG will review recruitment to the study across all study sites and will take appropriate action in the event the study recruitment rate is lower than anticipated.

11.1.4 Trial Steering Committee (TSC)

The TSC is an executive committee, reporting to the funder (NIHR) and the Sponsor. Independent members will be independent of both the Sponsor organisations and of any recruiting study sites.

Terms of reference of the TSC will be agreed at the first meeting, prior to start of recruitment. Meetings will be scheduled approximately 2 weeks after each Data Monitoring Committee (DMC) meeting. Minutes will be taken by the Trial Manager and retained in the TMF. The Trial Manager will prepare reports to the TSC.

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the recommendation of the Trial Steering Committee.

11.1.5 Data Monitoring Committee (DMC)

The DMC will be composed of three independent members: a statistician and two clinicians. The DMC is an advisory committee, reporting to the Trial Steering Committee. They will receive a report of recruitment, serious and non-serious adverse events, and a summary of accumulated clinical data from the Trial Statistician and will meet in person or by teleconference. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC will work to the DAMOCLES guidance and a DMC charter will be agreed at the first meeting outlining responsibilities, reporting, meeting frequency, documentation, and other matters. The Trial Statistician will prepare reports to the DMC.

11.2 Adverse Event Reporting and Harms

Adverse Event definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant.
- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to the Haploidentical SCT.
- **Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
  - results in death
  - is life-threatening
  - required hospitalisation or prolongation of existing hospitalisation
  - results in persistent or significant disability or incapacity
  - consists of a congenital anomaly or birth defect.
- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious:
  - Development of haematological malignancy
  - Grade III/IV acute GvHD or moderate to severe chronic GvHD.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

11.2.1 Expedited Serious Adverse Event Reporting Exceptions

The following events are exceptions and should not be reported in an expedited manner as a Serious Adverse Event:

- Hospital admission for protocol defined treatment (including admission for transplant).
- Hospital admission for pre-planned elective procedures unless the condition worsens and results in unplanned prolonged hospitalisation.
- Hospital admission for standard post-operative/post-transplant management. This includes infectious complications such as viral, bacterial and fungal complications that are routinely

recognised post-transplant. These will be recorded as per Section 5.3, Clinical Characteristics of the Transplant Population.

These data should be recorded on the transplant form or adverse event log as appropriate.

11.2.2 Evaluating AEs and SAEs.

Assessment of Intensity
The Investigator will assess intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** An event, which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality
The Investigator is obligated to assess the relationship between the intervention and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the intervention will be considered and investigated.

The causal relationship to the Haploidentical SCT assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

- **Not Related:** In the Investigator's opinion, there is not a causal relationship between the Haploidentical SCT and the AE.
- **Remote:** The temporal association between the AE and intervention is such that the Haploidentical SCT is not likely to have any reasonable association with the AE.
- **Possible**: The AE could have been caused by the study Participant's clinical state or the Haploidentical SCT
- **Probable**: The AE follows a reasonable temporal sequence from the time of Haploidentical SCT and cannot be reasonably explained by the known characteristics of the study Participant's clinical state.
- **Definitely:** The AE follows a reasonable temporal sequence from the time of Haploidentical SCT.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event prior to transmission of the SAE form to the Sponsor. The Investigator may change their opinion of causality considering follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Expectedness
A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

- **Expected:** An adverse reaction, the nature or severity of which is consistent with the applicable information for the study intervention.
- **Unexpected:** An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document.

11.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up each participant and provide further information to the Sponsor on the participant's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed up until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE/SAE CRF(s) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the Investigator. The updated SAE form should be re-sent to KCTU.

11.2.4 Pregnancy

Any pregnancy that occurs during study participation must be reported using a serious adverse event form. To ensure participant safety, each pregnancy must be reported to the Sponsor within 24 hours of learning of its occurrence. For male participants, the outcome of any reported pregnancies will be documented. For female participants, the pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the Sponsor. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the participant has completed the study and considered by the Investigator as possibly related to the intervention, must be promptly reported to the Sponsor.

11.2.5 Adverse Event Reporting Responsibilities

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24 hours) by the Investigator to KCTU via email to ctu@kcl.ac.uk.

The Chief Investigator will report relevant SAE's to the ethics committee and Data Monitoring Committee.

11.3 Plan Frequency and Plan for Auditing Trial Conduct

Monitoring of this trial to ensure compliance with Good Clinical Practice will be managed by the Trial Manager at the KCTU, King's College London.

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. participants' case sheets, blood results, imaging reports, trial protocol, statistical code, and etc).

KCTU will prepare a monitoring plan for approval by the TMG. Recruiting study sites will have a Site Initiation Visit prior to recruitment of the first participant and regular site visits thereafter to verify the data.

11.4 Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

The Trial Manager will be responsible for preparing and submitting protocol amendments to the ethics committee and the HRA, and circulating updated document versions to recruiting study sites, co-applicants, the TMG, TSC and DMC and (where relevant) the funder. Site Investigators will be responsible for communicating relevant information to study participants.

11.5 Quality Management

11.5.1 Site Set-up and Initiation

The Trial Manager will visit each study site prior to the start of recruitment, with the sponsor monitor, to ensure study site staff are aware of their responsibilities and are trained in key trial processes and procedures and will undertake remote monitoring and data cleaning activities. Any issues arising during remote or on-site monitoring will be escalated by the Trial Manager or sponsor monitor to the CI and/or TMG. Site Principal Investigators will supervise conduct within the recruiting sites.

11.5.2 On-site Monitoring

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the Trial Manager at KCTU. KCTU will create a study specific Risk-based Monitoring Plan that will detail the monitoring processes.

11.5.3 Central Monitoring

KCTU will conduct day-to-day central monitoring of the trial. KCTU staff will review data quality (e.g. errors of data entry, missing or inconsistent data, volume of data queries), timeliness of data entry, recruitment rates and any other site activities in accordance with risk-based monitoring plan to be developed by KCTU.

11.5.4 Audit and Inspection

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. participants' case sheets, blood test reports, X-ray reports, histology reports etc.).

11.5.5 Study Standard Operating Procedures (SOPs)

KCTU SOPs will be followed throughout.

12. Dissemination plans

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement and according to the publication policies of NIHR. Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of NIHR and KCTU.

13. Funding, data sharing, ethics, regulatory, insurance, archiving

13.1 Funding

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA). NIHR Reference number: NIHR130674. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Costs of transplant procedures are funded by National Health Service England (NHSE).

13.2 Availability of data and materials

Data will be available for sharing upon request for future scientific research, subject to the approval of the Chief Investigator.

13.3 Ethics/regulatory approval and consent to participate

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), and Research Ethics Committee (REC) for all required approvals.

13.4 Insurance and Indemnity

KCH (The Sponsor) will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its

employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office.

13.5 ARCHIVING

It is the responsibility of the Principal Investigator (PI) to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, participants' hospital notes, copies of CRFs etc) at their site are securely retained for at least 3 years after the end of the trial.

At the end of the trial, all trial data will be stored in line with Sponsor's archiving standard operation procedure. Recruiting sites will be responsible for archiving the source data and Investigator Site Files.

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15. APPENDICES

15.1 APPENDIX 1: PERIPHERAL BLOOD AND BONE MARROW TRANSPLANT – HAPLOIDENTICAL DONOR SICKLE VANDERBILT PROTOCOL

The Peripheral Blood and Bone Marrow Transplant – Haploidentical Donor Sickle Vanderbilt Protocol proforma is provided below from the next page.

Hospital No		Patient Name	

King's College Hospital NHS
NHS Foundation Trust

Peripheral Blood and Bone Marrow Transplant –Haploidentical Donor Sickle Vanderbilt Protocol

PATIENT:						
Hospital No:		**DOB:**		**Age:**		
Referring Hospital		**Referring Consultant**				
Clinical Trial		**Clinical Trials Number (if applicable)**				
Histological Diagnosis:		**Disease status at Dg:**		**Date:**		
Disease status at Transplant:				Date:		
Height:		**Weight:**				
Allergies:		**BSA:**				
Performance Status: (Karnofsky score)		**HCT-CI:**				
Blood Group:		**CMV Status:**				
Virology Date:	HBsAg:	HepBc:	HepB DNA:	Hep C:		
	Anti-HIV-1: Anti-HIV-2:	HTLV-1 &2:	EBV:Pos	Syphilis:		
Covid Swab:	Toxo IgG:	HEV:	Any change from baseline virology: Yes □ No □			

Donor:						
Donor Clearance date:		**Donor cleared by:**				
Hospital No:		**DOB:**		**Age:**		
Height:		**Weight:**		**Sex:**		
Blood Group:		**CMV Status:**		**HbS status:**		
Cell Dose / Harvest Date:		**Source:**	HPC-A / HPC-M			
Virology:	HBsAg:	HepBc:	HepB DNA:	Hep C:		
Date:_	Anti-HIV-1: Anti-HIV-2:	HTLV-1 &2:	EBV:Pos	Syphilis:		
	Toxo IgG:	HEV:	Covid Swab:			

HLA Type:	**HLA-A:**	**HLA-B:**	**HLA-Cw:**	**HLA-DRB1:**	**HLA-DQB1:**
Recipient:					
Donor:					

Haploidentical

HLA antibody screen:

Hospital No		Patient Name	

Conditioning Protocol			
Date	**Day**	**Event**	**Comments**
	-9	**Thymoglobulin (ATG) 0.5.mg/kg/day**	**Pre- conditioning 60-90 days** Hydroxyurea 30mg/kg/day EBT to start three months prior to HSCT
	-8	**Thymoglobulin (ATG) 2.0.mg/kg/day** **Red cell exchange transfusion**	
	-7	**Thymoglobulin (ATG) 2.0.mg/kg/day** **Thiotepa 10 mg/kg**	**Viral Prophylaxis:** Aciclovir 400mg BD PO□ If CMV positive: Letermovir 480mg daily until D+100 **Toxo Prophylaxis:** Azithromycin 500mg OD from D0 **VOD Prophylaxis:** Ursodeoxycholic acid 600 mg OD until discharge. □ **Fungal Prophylaxis:** Posaconazole prophylaxis 300mg bd on D0 and then 300mg od from D+1 □ **Anti-emetic prophylaxis:** Aprepitant 125mg D-4 □ followed by 80mg daily until D+1. Then restart 125mg on D+3 followed by 80mg until 48 hours after Ciclophosphamide 50mg/kg
	-6	**Cyclophosphamide 14.5 mg/kg** **Fludarabine 30 mg/m^2**	
	-5	**Cyclophosphamide 14.5 mg/kg** **Fludarabine 30 mg/m^2**	
	-4	**Fludarabine 30 mg/m^2**	
	-3	**Fludarabine 30 mg/m^2**	
	-2	**Fludarabine 30 mg/m^2**	
	-1	**TBI 200 cGy**	
	0	**Cell Reinfusion**	BM is preferred stem cell source
	+1	**Rest day**	
	+2	**Rest Day**	
	+3	**Cyclophosphamide 50 mg/kg with MESNA**	
	+4	**Cyclophosphamide 50 mg/kg with MESNA**	
	+5	**Start Sirolimus 5mg daily** **MMF 15 mg/kg po tds**	Stop Sirolimus D+365 Stop MMF D+35 **Sirolimus levels and weaning protocol** 0-6 months aim 9-11 ng/ml 6-9 months 7-8 ng/ml 9-12 months 5-7 ng/ml Monitor Triglycerides, and consider treating with a statins if elevated

1.History				
2. Co-morbidities				
3. Radiology				
4. ECG / MUGA				
5. Lung Function Tests				
6. EDTA / Renal				
7. Bone Marrow				
8. Disease Markers				
9. Current Medication				
10. Consent				
Date:				
Authorised By:	**Print name & job title below**		**Signature**	**Date:**
Plan Written by:		BMT SpR		
		Consultant		
		SCL Manager/ designee		
Date:				
2nd Stage Consent	**Print name & job title below**		**Signature**	**Date:**
Consent & Plan as above agreed:		BMT SpR		
Comments:				

Hospital No		Patient Name	

Discussed with:	(Haematology Consultant)

For SCL Copy Only:

Date	**Delivered to HOP / Ward by: (Print name)**	**Designation**
Date	**Received on HOP / Ward by: (Print name)**	**Designation**

END OF DOCUMENT

REDRESS_Protocol_V3.0_01Nov2023

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Signature Date: 2024-03-26 - 18:03:55 GMT - Time Source: server- IP address: 143.167.138.195

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