

FUNDERS



A single centred feasibility study to evaluate and compare the implementation of an antigen-prioritising algorithm with standard care to arrange units for blood transfusion prior to selection by staff at NHSBT

IRAS Short title: Haem-Match Feasibility Study

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Sponsor Ref: [Insert number, if applicable]

1 PROTOCOL SIGNATURE PAGE

The undersigned confirms that the following protocol has been agreed and accepted and the Chief Investigator agrees to conduct the trial in compliance with the approved protocol. and will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research Version 3.3, and any subsequent amendments, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:
Signature:
..... Date: ...../...../.....

Name (please print): .....

Position: .....

Chief Investigator:
Signature: ..... Date: ...../...../.....

Name: (please print): .....SARA TROMPETER.....

Chief Investigator:
Signature: ..... Date: ...../...../.....

Name: (please print): ...NICHOLAS GLEADALL.....

Lead Statistician: [redacted]
Signature: ..... Date: ...../...../.....

Name: (please print): .....WILLIAM ASTLE.....

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3 KEY TRIAL CONTACTS

Table 1: Key Trial Contacts

Chief Investigators	Dr Sara Trompeter (Clinical CI) Consultant Haematologist NHSBT, UCLH and Clinical Academic UCL Colindale Blood Donor Centre, Email: Sara.trompeter@nhs.net Alternative: sara.trompeter@nhsbt.nhs.uk Tel:02034567890 Dr Nicholas Gleadall (Computational CI) Assistant Professor, NHS Blood and Transplant and University of Cambridge Cambridge Blood Donor Centre, Long Road, Cambridge, CB2 0PT Email: ng384@cam.ac.uk Alternative: nicholas.gleadall@nhsbt.nhs.uk Tel: 01223 588183
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Sponsor	NHSBT R&D Department R&D Office NHSBT North Bristol Parkway, Filton, Bristol BS34 7HQ Email: research.office@nhsbt.nhs.uk Tel: 0300 123 23 23
Funder(s)	Department of Health and Social Care (previously under NIHR AI grant) NHS Blood and Transplant UCLH Biomedical Research Centre
Other Support	NHSBT ● Genomics Programme Board: Research infrastructure ● Red Cell Immunohaematology – staff time and expertise ● Clinical Trials Unit (CTU) team ● Hospital Services Team ● Quality team ● Data, Digital, Technology and Security (DDTS) Team Health Service Laboratories ● Transfusion and other laboratory support University College London Hospital ● Data support from SAFEHR Team

Clinical Trials team	uclh.haem-match@nhs.net 02034567890
Statistician	Dr William Astle Email: wja24@cam.ac.uk
Central Laboratories (UCLH/HSL)	Dr Samah Alimam E-mail: gen3@nhs.net
Central Laboratories (Pathology, NHSBT)	Name: Professor David Roberts E-mail: david.roberts@nhsbt.nhs.uk
Committees	1. BloodMatcher MDT: a. Purpose: To maintain BloodMatcher and act on any device issues and report where indicated; to apply bloodMatcher to the blood order on receipt from Haem-Match MDT; to transmit the output of bloodMatcher to the Haem-Match MDT 2. Haem-Match MDT a. Purpose: To check the blood order meets national standards/patient requirements; to check the output of BloodMatcher meets national standards/patient requirements and report to PI if any issues; to ensure that this information is passed to the bloodMatcher MDT; to ensure that output of BloodMatcher is presented to Hospital Services for unit allocation; to coordinate move to routine blood ordering practice in the event of a device failure. 3. Trial Management Group (TMG) 4. Trial Steering Committee (TSG) 5. Data Monitoring Committee (DMC)
Other relevant study personnel	Hospital services team NHSBT Transfusion Laboratory Team UCLH Clinical Team Cancer Services UCLH Sickle Cell and Thalassaemia Alliance for Research (STAR) team UCLH

4 ABBREVIATIONS AND GLOSSARY

AE	Adverse event
AR	Adverse reaction
ASADE	Anticipated Serious Adverse Device Event
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DD	Device Deficiency
DDRF	Device Deficiency Reporting Form
DHSC	Department of Health and Social Care
DM	Data Manager
DMC	Data Monitoring Committee
eDDRF	Electronic Device Deficiency Reporting Form
EDGE	EDGE research management system (https://edgeclinical.com/)
EHRS	Electronic Healthcare Record System
eSAERF	Electronic Serious Adverse Events Reporting Form
GCP	Good Clinical Practice
GP	General Practitioner
G+S	Blood Group and Antibody Screen
HRA	Health Research Authority
HSL	Hospital Services Laboratories
IBHO	Improving Black Health Outcomes
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IRAS	Integrated Research Application System
ISF	Investigator Site File (This forms part of the TMF)
MDT	Multi-disciplinary Team
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
NIHR BioResource	National Institute for Health Research BioResource
NIMP	Non-Investigational Medicinal Product
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research and Development
RCI	Red Cell Immunohaematology
REC	Research Ethics Committee
SABRE	Serious Adverse Blood Reactions and Events
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAERF	Serious Adverse Events Reporting Form

SAFEHR	Secure or Anonymised Framework for Electronic Health Records
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disorder
SHOT	Serious Hazards of Transfusion
SOP	Standard Operating Procedure
SRCP	Secure Computing Research Platform
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACO	Transfusion Associated Circulatory Overload
TAD	Transfusion Associated Dyspnoea
TRALI	Transfusion Associated Acute Lung Injury
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust
UoC	University of Cambridge
UoO	University of Oxford
USADE	Unanticipated Serious Adverse Device Events

5 TRIAL SYNOPSIS

Table 2: Trial Synopsis

Title of clinical trial	A single-centred feasibility study to evaluate and compare the implementation of an antigen-prioritising algorithm with standard of care to arrange units for blood transfusion prior to selection by staff at NHSBT
Protocol Short Title	Haem-Match Feasibility Study
Study Design	A prospective cohort study with comparison to retrospective data.
Study Aim	To evaluate the feasibility and safety of the implementation of an algorithm (bloodMatcher) that includes antigen matching information, and to compare the new algorithm with the current algorithm (standard of care), which arranges units principally according to storage age, prior to their selection by staff at NHSBT.
Trial Participants	NA. The algorithm evaluates units of blood for selection prior to transfusion in adult patients with sickle cell disorder
Planned Sample Size	Up to 3 selection episodes of units for transfusion in up to 40 patients
Treatment duration	Three retrospective selection episodes, three prospective selection episodes
Follow up duration	The last visit will occur a maximum of 8 weeks following the third prospective selection episode
Planned Trial Period	Jan 2026 – Jan 2027(12 Months)
Health Condition(s) or Problem(s) Studied	Mismatching of donor to recipient blood groups resulting in the risk of alloimmunisation.
Setting	Single-Site NHSBT: one NHS Blood and Transplant stock holding unit (SHU; Colindale, London)
Interventions to be compared	Units of blood will be proposed for selection to NHSBT Hospital Services staff by applying one of: Intervention 1: the bloodMatcher algorithm, which principally prioritises antigen matching information (prospectively), Intervention 2: the current algorithm that principally uses storage age (retrospectively).

Patients	Patients will be approached, consented and enrolled into a prospective-retrospective cohort study to evaluate an algorithm (bloodMatcher) for use by NHSBT staff when arranging units of RBCs for transfusion that prioritises antigen matching information, and to compare the algorithm with its present equivalent, which organises units principally according to age. Participants will also be invited to be co-recruited into the NIHR BioResource Improving Black Health Outcomes (IBHO) study REC 22/EE/0230. Participation in the NIHR BioResource is entirely voluntary and is not required for participation in this study.	
	Objectives	Outcome Measures
Primary	To evaluate the implementation of a principally antigen-prioritised algorithm (bloodMatcher) vs. the current principally age-prioritised algorithm used to arrange units for blood transfusion prior to selection by staff at NHSBT at a single SHU	We will consider two primary outcomes: ● Whether the 'Haem-Match MDT' approves/rejects each unit suggested for transfusion by bloodMatcher and the reason for any rejection (categorical) ● Whether the units ultimately selected by NHSBT are made available for timely transfusion when required, defined as a composite of delay to transfusion (categorical and quantitative), postponement or cancellation of transfusion (binary)
Secondary	To compare the degree of matching of blood groups achieved by bloodMatcher with that achieved by its present equivalent (standard of care), which organises units principally according to age	For each blood unit transfused and each blood group antigen (see list Table), we will record these events: ● Antigen mismatch (positive → negative): when an antigen positive unit is transfused to an antigen negative recipient (binary) ● Antigen mismatch (negative → positive): When an antigen negative unit is transfused to an antigen positive recipient (binary)
Tertiary	To inform the design of future multicentred studies of bloodMatcher, including the capabilities for electronic capture of relevant outcome and transfusion data	

6 FUNDING AND SUPPORT IN KIND

Table 3: Funding

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Department of Health and Social Care (previously under NIHR AI grant)	Salary costs
NHS Blood and Transplant	Salary Costs
UCLH Biomedical Research Centre	Salary costs

7 ROLES AND RESPONSIBILITIES

7.1 Trial sponsor and Funder

Sponsor: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

Funder: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

7.2 Trial Management Committees / Groups & Individuals

7.2.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly, at least once per month.
The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC.

7.2.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the (Independent) Data Monitoring Committee (if applicable) and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.

7.2.3 Data Monitoring Committee (DMC)

The role of the DMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held once per year to review interim analyses or as necessary to address any issues. The DMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

7.2.4 Chief Investigator (CI)

The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site. The CI role is to complete and to ensure that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards. The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC and JRO of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and sponsor.

7.2.5 Principal Investigator (PI)

Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

7.3 Protocol Development Group

Table 4: Protocol Development Group

Name	Affiliation	Authors' Contributions
Sara Trompeter	NHSBT, UCL, UCLH	Conceived of the study, initiated and developed study design, grant holder.
Nicholas Gleadall	NHSBT, UoC, UCLH	Conceived of the study, initiated and developed study design, grant holder.
Simon Stanworth	NHSBT, UoO and BTRU data-enabled transfusion practice	Initiated and developed study design, grant holder.
William Astle	NHSBT, UoC, UCLH	Conceived of the study, initiated study design, provided statistical expertise in clinical trial design and will conduct the primary statistical analysis, grant holder.
Kate Downes	NHSBT	Helped with implementation
David Roberts	NHSBT, UoO	Helped with implementation
Willem Ouwehand	NHSBT, UoC, UCLH	Initiated and developed study design.
Orod Razeghi	NHSBT, UoC, UCLH	Supported and developed study design.
Folarin Oyebolu	NHSBT, UoC, UCLH	Supported and developed study design.
Matthew Hazell	NHSBT	Helped with implementation & Supported and developed study design

Tom Bullock	NHSBT	Helped with implementation & Supported and developed study design
All authors contributed to refinement of the study protocol and approved the final version		

The Transfusion Practice Panel is run by the Cambridge Blood and Transplant Research Unit (BTRU). It is a Public and Patient Involvement and Engagement (PPIE) Group that is attended principally by people with SCD, most of whom are transfusion dependent as well as some people with other inherited blood disorders. The group meets regularly and has discussed all aspects of the study and protocol, the rationale, how the algorithm works and has provided crucial feedback and support through the design process. It is funded through the NIHR (now DHSC) grant.

8 KEY WORDS

Blood matching
Blood transfusion
Blood groups
Alloimmunisation
Sickle cell disorder

9 STUDY FLOW CHART

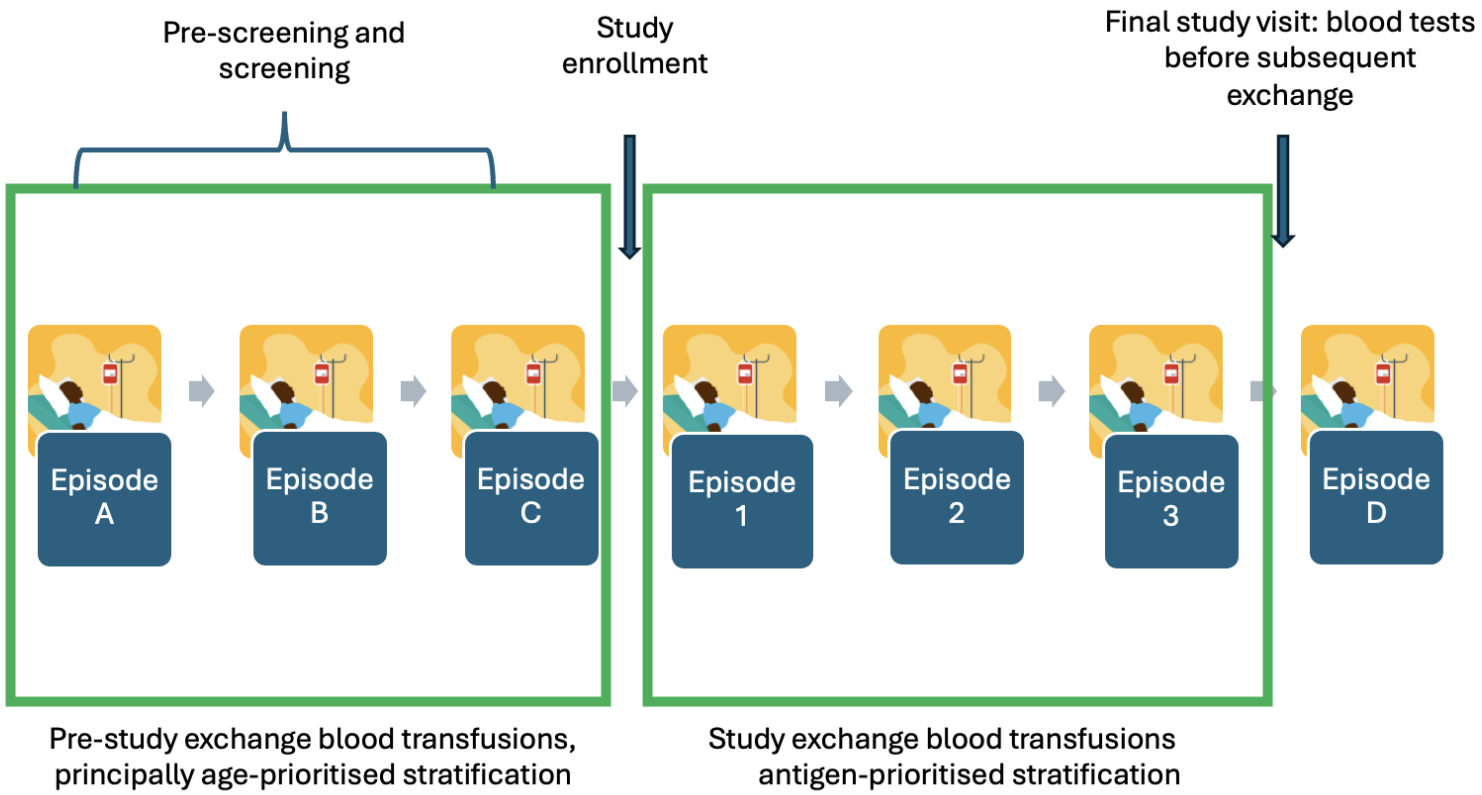


Figure 1: Study Flow Chart

10 STUDY SCHEDULE

Table 5: Study Schedule

Procedures	Visit number	1 Screening	2	3	4	5 Final visit
		Day –100 to Day -7	Episode 1*	Episode 2*	Episode 3*	Pre transfusion bloods Episode D and final visit*
Blood group antigen testing results, pregnancy test (if indicated)		x				
Scheduling of Transfusion		x	x	x	x	
Blood Order			x	x	x	
Patient attends for pre-exchange blood tests			x	x	x	x
Blood Order Review			x	x	x	
BloodMatcher Algorithm			x	x	x	
BloodMatcher Algorithm output review			x	x	x	
Unit Allocation			x	x	x	
Units prepared for transfusion			x	x	x	
Exchange Blood Transfusion			x	x	x	
Collation of data including adverse events			x	x	x	

*Window of flexibility: Patients will adhere to their routine transfusion cycles. These vary between 3-9 weekly and will be set by the clinical team. Blood tests can be performed up to 1 week before the transfusion, though more routinely are performed in the 72 hours prior.
Please see Appendices 1 and 2 for further details.

11 OVERVIEW

The aim of this feasibility study is to evaluate, both in terms of implementation and the degree of matching, the inclusion of antigen information in the algorithm used by NHSBT when arranging units of RBCs for transfusion prior to selection by NHSBT staff, and to compare the approach with the present algorithm, which arranges units principally according to age. The goal is to improve donor to patient antigen matching and thus reduce the risk of alloimmunisation and the risk of severe transfusion reactions for patients needing blood. By improving matching, we will de facto also reduce "waste", caused by giving valuable rare units to people who don't need them. We will also be collecting data to inform future multicentred studies of bloodMatcher.

NHSBT is the sole provider of blood products in England. Every day, the Hospital Services department at NHSBT is presented with thousands of orders for blood from hospitals. These orders are fulfilled by teams at NHSBT (known as "Hospital Services"). Current standard of care involves NHSBT hospital services (HS) staff selecting each unit of blood based on the requirements stipulated in the order e.g. 4 units of O positive blood, taking the older storage aged units of available blood units first, to minimise wastage. It is not practical given the numbers of units available and orders to fulfil, to consider further antigens other than what is specified (as minimum) in national standards. However, by not considering blood groups other than a limited number of key antigens (Davis *et al.*, 2017), there is a risk that there may be a mismatch between donor and recipient blood groups. This can cause the formation of a blood group antibody (alloimmunisation) and lead to clinically important transfusion reactions. These events can be immediately life threatening and can substantially limit the long-term treatment opportunities for patients, contributing to morbidity and mortality. The population cohort that most struggles with the complications of alloimmunisation is the study population of interest in this study — adults with sickle cell disorder (SCD) who are already recipients of regular exchange blood transfusions (EBT). It is also notable that by not considering the other blood groups we are sometimes transfusing rare complex blood to people who do not really need it — which is both inefficient and wasteful. Patients with SCD are already matched across a few more blood groups than the regular population, in recognition of this risk, however, there is substantial published data that this policy is still insufficient (Trompeter *et al.*, 2023). Given that an estimated 12,000 units of blood are issued each month for patients with SCD by NHSBT in England, and there are thousands of units in stock and hundreds of blood groups, extending the degree to which we match cannot be simply done by humans; we need a digital algorithm.

We have therefore developed a prototype algorithm to arrange units presented to NHSBT staff. This algorithm principally prioritises better matching of blood groups rather than the current system that principally prioritises on storage age of units. The impact of storage age has been evaluated in multiple clinical trials and is generally considered to be unimportant for clinical practice (McQuilten *et al.*, 2020, 2025, 2025) and has been removed from clinical guidance for almost all patient groups in the UK ('Joint Statement from NHS Blood and Transplant, National Blood Transfusion Committee, United Kingdom Thalassaemia Society and Sickle Cell Society.', 2023). The algorithm uses extended information on all blood groups for both the patient and the donor of the blood. Pilot testing of the algorithm, including

evaluation by experts in transfusion in NHSBT, suggests it improves the degree of matching of blood groups between donors and patients, opening up the possibility of a significant reduction in the likelihood of alloimmunisation (Oyebolu *et al.*, 2024). However, we now need to assess the use of the algorithm in real time.

Therefore, this protocol describes a feasibility study to evaluate the implementation of an antigen-prioritising algorithm of units presented to NHSBT staff for selection. Up to 40 adult patients with SCD, already well established on the exchange blood transfusion (EBT) programme, will be approached and consented to participate in the study. Each participant will receive red cell units picked by NHSBT staff as they would do as part of standard practice, ensuring the specific patient requirements are identified and met. However, the staff will have been presented with units in order suggested by an algorithm that uses antigen matching information in addition to unit age, which is all that is used by the current algorithm. Whilst all the routine checks that are in place will continue, we have added in an additional layer of checking – by senior clinical scientists in blood transfusion at NHSBT (Haem-Match MDT). The rest of the clinical care pathway will remain the same. The patients will act as their own internal controls, with information on up to three previous pre-study exchange episodes being compared to their study exchange episodes. 40 adult patients for three episodes was picked for pragmatic reasons, there are 140 patients on the programme, and it was felt that following patient choice and the inclusions and exclusion criteria, combined with the number of episodes, this would give the study group sufficient data to answer its aims and objectives as well as deliver the study within the funded timeframe.

12 RATIONALE

12.1 Overview

The aim of this feasibility study is to evaluate, both in terms of implementation and the degree of matching, the inclusion of antigen information in the algorithm used by NHSBT when arranging units of RBCs for transfusion prior to selection by NHSBT staff, and to compare the approach with the present algorithm, which arranges units principally according to age. The goal is to improve donor to patient antigen matching and thus reduce the risk of alloimmunisation and the risk of severe transfusion reactions for patients needing blood. By improving matching, we will de facto also reduce “waste”, caused by giving valuable rare units to people who don’t need them. We will also be collecting data to inform future multicentred studies of bloodMatcher.

Patients with SCD are frequently recipients of blood transfusions. Over 12,000 units of red blood cells per month are issued for patients with SCD by NHBST, the only blood supplier in England. There are over 15,000 patients nationally registered on the National Haemoglobinopathy Registry (NHR, 2024). But the current processes for matching blood for transfusion in patients with sickle cell disorders are sub-optimal. Many patients experience complications and adverse events due to blood for transfusion, in part because of difficulties providing antigen matched blood. We have developed an alternative principally antigen-prioritised algorithm (bloodMatcher) vs. the current principally age-prioritised algorithm used to arrange units for blood transfusion prior to selection by staff at NHSBT at a single stock

holding unit at NHSBT (SHU). Before embarking on larger studies, we first need to establish the feasibility of delivery and the safety of implementing such an algorithm in NHSBT systems.

12.2 The current problems of blood matching in sickle cell disorders

Red cells for transfusion have labels on their surface known as blood groups, of which over 300 blood groups of antigens are currently described. When there is a mismatch between a blood group of a donor and patient, there is a risk of blood group antibody formation, known as alloimmunisation. The impact of alloimmunisation can be significant, from a severe, even life threatening, transfusion reaction, delay in subsequent transfusion, to reduction in the available blood for transfusion, and sometimes, when particularly complex, an inability to source blood for transfusion.

For most red cell transfusion recipients, blood is sourced that is compatible with their ABO and D blood groups. To address the higher prevalence of antibodies in those with sickle cell disorder (SCD), the current standard of care in SCD is to match for blood that is compatible with the recipients ABO, RH (D CcEe) and Kell antigens (Davis *et al.*, 2017). However, despite this additional degree of matching, overall antibody prevalence in SCD patients is around 17% (Trompeter *et al.*, 2020). Our studies (Trompeter *et al.*, 2023), in line with other international data, have confirmed that many patients with SCD continue to develop new antibodies despite these additional matching requirements, suggesting that further matching is needed to mitigate this risk.

12.3 Our approach

We have developed a new algorithm to incorporate antigen matching when listing available units for selection of blood for transfusion by NHSBT in sickle cell disorder. This approach is required because of the complexities of current methods and scale of the demand - an estimated 12,000 units of blood per month are issued by NHSBT for patients with SCD in England. Current approaches to matching are largely manual, involving the evaluation of stocks by the NHSBT Hospital Services Team who pick units from a list of available units at NHSBT prioritised in order of storage age, and according to the order requirements. Further advances in matching cannot be achieved manually given the need to trade off the possible effects of mismatches of multiple antigens within and between patients and thousands of potential units available for allocation. It is not possible for a human to evaluate the relative benefits of all the possible allocations consistently, particularly since it will also often be necessary to allocate blood for multiple patients simultaneously, creating dependencies between patients. The complexities of matching are also magnified by the current concerns about limited blood supplies at a national level.

Alongside this development work on blood algorithms, have been advances in antigen typing of blood for transfusion. Our study group has developed a high throughput genetic testing array (Gleadall *et al.*, 2020) that has been adopted by the NHS for testing measuring the extended blood types of patients and in NHSBT for testing of donors (NHS England, 2023).

Therefore, given the complexities of current processes and in order to use knowledge around extended blood group typing efficiently, we have developed an alternative to the

current storage age-prioritising algorithm that arranges the blood units at NHSBT prior to selection by staff. This antigen-prioritising algorithm, known as bloodMatcher, arranges units for blood transfusion prior to selection by staff at NHSBT with the aim of reducing alloimmunisation. When arranging the units, the algorithm firstly ensures that current matching and selection guidance is met, and beyond this takes account the risk of alloimmunisation created by transfusing an antigen that is foreign to the patient, and the opportunity cost of making substitutions, that is of transfusing units that do not contain an antigen for which the recipient is positive. Older storage age units are prioritised for allocation to avoid wastage. Distance from the allocating SHU is also factored in. A redundancy is built into the algorithm such that very rare units are excluded, as these need to be retained for patients already alloimmunised. Mismatches are determined from the blood groups of patients and donors and are characterised by either a donor unit with a positive antigen being given to a patient who is negative for that antigen conferring a risk of alloimmunisation OR a donor unit with a negative antigen being given to a patient who is positive for that antigen conferring a waste of a valuable resource.

Estimates of the risk of alloimmunisation due to mismatches have been taken from published data, and for the current purposes only three additional antigens have been prioritised for matching. Following the feasibility study, it is anticipated this may be extended/improved in future studies. A simulation (internal data) making significant simplifying assumptions suggests that if applied nationally the algorithm has the potential to reduce the rate of alloimmunisation in sickle cell patients significantly – up to 98% if sufficient matched units were to be available (Oyebolu *et al.*, 2024). A complementary pilot test using one month of real-world supply and demand data was evaluated by experts in transfusion in NHSBT. The evaluation suggests improved matching of units for patients using the algorithm, opening up the possibility of a significant reduction in the likelihood of alloimmunisation as well as better use of antigen negative units for those who may benefit from them. However, this requires clinical evaluation which is the purpose of this study.

12.4 Single site study protocol

The Haem-Match feasibility study will be conducted to evaluate an antigen-prioritising algorithm to arrange available units of blood for selection by NHSBT staff at a single NHSBT site (Colindale, London), known as a stock holding unit (SHU) and compare it with the existing storage age-prioritising algorithm. The new algorithm will also account for the age of the blood as well as its location. The eventual recipients of the blood i.e. the trial participants, will be adults (16 years and over) with sickle cell disorder (SCD) on regular exchange blood transfusions (EBT) at UCLH. SCD participants are being chosen as they are the patient cohort who most often have issues with alloimmunisation. Those on EBT are already having regular multiple unit transfusions and thus are an ideal cohort for this innovation. We will not be including those who have very complex blood requirements, as defined as those whose cases are discussed routinely with the Red Cell Immunohaematology (RCI) team at NHSBT. This is because we are testing an algorithm to pick the appropriate units, and in this challenging cohort senior biomedical scientists (BMS) and Consultant Clinical Scientists (CCS) are routinely involved to pick the units. We are not including pregnant patients as pregnancy, independently from transfusion, is a risk factor for alloimmunisation. The recruited participants will have had three EBT already as part of

standard care prior to trial enrolment to assess reliability of attendance for transfusions and to ensure sufficient historical transfusion data is available for analysis.

We will collect data on the degree of matching and approved authorisation of antigen-prioritised units for blood transfusion prior to selection by staff at NHSBT and any impact on the care pathways or delays in transfusions as well as any adverse events. We will assess any impacts of national blood supplies, including use of sickle negative and Ro units (blood group Dce).

Dr Trompeter, CI, will use some of this data to contribute to her PhD thesis, registered at UCL (student ID 934574).

13 ASSESSMENT AND MANAGEMENT OF RISK

Risks associated with this study are already mitigated by the standard practices that will be maintained and that have been evaluated and monitored and as per normal clinical care. A full risk assessment has been written, supported by the NHSBT Quality team.

14 OBJECTIVE AND OUTCOME MEASURES/ENDPOINTS

14.1 Objectives

14.1.1 Primary objective

To evaluate the implementation of a principally antigen-prioritised algorithm (bloodMatcher) vs. its present equivalent (standard of care), the latter which organises units principally according to age prior to unit selection by staff at NHSBT at a single SHU

14.1.2 Secondary objective

To compare the degree of matching of blood groups achieved by bloodMatcher with that achieved by its present equivalent (standard of care), the latter which organises units principally according to age.

14.1.3 Tertiary objective

To inform the design of future multicentred studies of bloodMatcher, including the capabilities for electronic capture of relevant outcome and transfusion data.

14.2 Outcome measures/endpoints

14.2.1 Primary endpoint/outcome

We will consider two primary outcomes for each blood order:

- Whether the ‘Haem-Match MDT’ approves/rejects each unit suggested for transfusion by bloodMatcher and the reason for any rejection (categorical).
- Whether the units ultimately selected by NHSBT are made available for timely transfusion when required, defined as a composite of delay to transfusion (quantitative), postponement or cancellation of transfusion (binary).

14.2.2 Secondary endpoints/outcomes

For each blood transfusion and each blood group antigen (see list Table), we will record:

- Antigen mismatch (positive → negative): when an antigen positive unit is transfused to an antigen negative recipient (binary)
- Antigen mismatch (negative → positive): When an antigen negative unit is transfused to an antigen positive recipient (binary)

14.2.3 Tertiary endpoints/outcomes

The design of future multi-centred studies of bloodMatcher will be planned by protocol development.

14.3 Table of endpoints/outcomes

Table 6: Endpoints and Outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To evaluate the implementation of an antigen-prioritised algorithm (bloodMatcher) vs. its present equivalent (standard of care), which organises units principally according to age prior to selection by staff at NHSBT at a single SHU	● The number of times that the 'RCI senior scientist/Haem-Match MDT' approves/rejects the unit allocated for transfusion and the reason (categorical). ● Whether the allocated unit is made available for timely transfusion when required, defined as a composite of delay to transfusion (categorical and quantitative), postponement or cancellation of transfusion (binary)	For each transfusion order
Secondary Objective To compare the degree of matching of blood groups achieved between bloodMatcher and standard of care.	For each blood transfusion and each blood group antigen we will record: ● Mismatch: Whether an antigen positive unit has been transfused where the recipient is antigen negative (binary) ● Substitution: Whether a blood unit with a compatible (antigen negative) substitution has been transfused into an antigen positive recipient (binary) ● Waste: Whether a substitution has been made but a unit of equivalent overall match-compatibility carrying the relevant antigen is available (binary)	For each blood transfusion and each blood group antigen
Tertiary Objective To inform the design of future multicentred studies of bloodMatcher, including the capabilities for electronic	The design of future multi-centred studies of bloodMatcher will be planned by protocol development.	N/A

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
capture of relevant outcome and transfusion data		

15 TRIAL DESIGN

A retrospective-prospective cohort study to evaluate the inclusion of antigen matching information in the NHSBT algorithm that arranges units of RBCs for transfusion prior to selection by NHSBT staff, and to compare the approach its present equivalent (standard of care), which organises units principally according to age.

16 TRIAL SETTING

The study will be conducted at a single NHSBT site (Colindale) known as a stock holding unit – SHU). All staff involved in the study have contracts with NHSBT. The algorithm sits in the NHSBT computational space. NHSBT is the only procurer and distributor of blood products in England.

Ultimately the blood will be transfused to patients with SCD at a single hospital site (UCLH) as part of their scheduled routine clinical care which will be unaltered. Screening, consent and any study activity will be performed by people with NHSBT contracts.

17 PARTICIPANT ELIGIBILITY CRITERIA

17.1 Donor blood

Not all donor units will be included to ensure sufficient stock of particular specificity is available for those who may need it. The bloodMatcher algorithm excludes allocated or unavailable units from current stock, and also any units which possess an “extremely rare” blood type. For “moderately rare” units, 5% of issuable units are excluded, to allow for urgent requests for blood transfusion for those already alloimmunised to be met nationally as part of routine clinical practice. The blood types which constitute "extremely rare” and "moderately rare” units have been pre-defined and reviewed by NHSBT rare blood stock management teams.

17.2 Recipients (trial participants)

These will be selected for inclusion according to inclusion/exclusion criteria of the study by screening sickle cell EBT patient list.

Eligible consented participants will have three EBT episodes on the trial protocol and the data collated from these episodes compared with their three previous exchange transfusion episodes. The interval between episodes will be dictated by their usual clinical care, as will their transfusion parameters, blood tests, investigations and examination. There is no change to any aspect of their clinical care or any care in the hospital setting.

17.3 Participant Inclusion Criteria

- 16 years or older
- Sickle Cell Disorder (any genotype) on a regular EBT programme for at least three contiguous episodes
- Has a red cell genotype submitted for analysis on the Axiom array
-
- Willing and able to provide written informed consent.

17.4 Participant Exclusion Criteria

- Difficult to transfuse - defined as needing NHSBT Red Cell Immunohaematology (RCI) support for sourcing appropriate units or crossmatching units for transfusion OR episode of hyperhaemolysis in the past OR Delayed haemolytic transfusion reaction in last 4 months.
- Previous poor concordance or irregularity with transfusion regimen – defined as repeated changing appointment dates with little notice, or non-timely attendance for group and screen or for transfusion episodes (at discretion of PI)
- Current pregnancy or planning to become pregnant (a known risk factor for alloimmunisation)

18 TRIAL PROCEDURES

18.1 Recruitment

18.1.1 Participant identification

Adults with sickle cell disorder on the EBT programme are placed on the sickle cell EBT patient list on the EHRS. Members of the research team will identify eligible patients from this list by applying the inclusion and exclusion criteria. This information is all on the EHRS and there is no additional testing required to apply the inclusion/exclusion criteria. There are no planned additional visits as part of the study but should one occur, the participants would be paid reasonable travel expenses.

18.2 Screening

The following trial specific procedures will be carried out after consent to assess the participant's eligibility:

- Pregnancy test (serum or urine): for women of childbearing potential if appropriately timed.

All pre-treatment procedures will be carried out as specified in the Study Schedule (Table 5 and also Appendices 1 and 2).

18.3 Co-enrolment guideline

Involvement in other Clinical Trials of Investigational Products will be at the discretion of the CI. Patients will be provided with information about the NIHR BioResource Improving Black Health Outcomes study (REC 22/EE/0230) and invited to consider participation.

Participation in the NIHR BioResource is optional and not a condition of enrolment into the Haem-Match study.

18.4 Payment

Participants will not receive any payment for participating in this study as their only attendance will be for their routine clinical care (EBT).

18.5 Consent

The Investigator, or a person delegated by the Investigator will obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.
The person taking consent will be suitably qualified and experienced and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.
"Adequate time" will be given for consideration by the participant before taking part. Consent will be sought after being given the study documentation. It will be recorded in the patient medical notes (or electronic health record system) when the participant information sheet (PIS) has been given to the participant.
The informed consent process will involve:

- Discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the study
- The presentation of written material e.g. participant information sheet and consent form which will be REC approved and be in compliance with GCP, local regulatory requirements and legal requirements
- The opportunity for potential participants to ask questions
- Assessment of mental capacity: for consent to be ethical and valid in law, participants must be capable of giving consent for themselves. This includes:
    - Understanding the purpose and nature of the research, risks and benefits
    - Understanding the alternatives and being able to retain the information for long enough to make an effective decision.
    - If the participant loses capacity to consent for the study following consenting and during the study:
        - Where the participant gave specific consent to use samples and data following loss of capacity, these will be retained in identifiable form if this is necessary for the research.
        - The researcher will seek advice from a consultee about the participant's presumed wishes and feelings. The participant's samples and data must be withdrawn if the consultee so advises or if the participant indicates he/she wishes the research to be discontinued. We will ask for details of the consultee in the consent form
- The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason and without prejudicing his/her further treatment.
- Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this, this will be outlined in the consent form.

- Where a participant is required to re-consent or new information is required to be provided to a participant, the Investigator will ensure that this is done in a timely manner.
- No trial procedures, including the collection of identifiable participant data will be conducted prior to the participant giving consent by signing the Consent form.
- Consent will not denote enrolment into trial.
- A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy placed in the medical notes.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

18.6 Registration

18.6.1 Responsibilities

Participant registration will be undertaken by the research team using the EDGE research management system (https://edgeclinical.com/). Hosting for our system is provided by Microsoft Azure through Cancom UK. These data centres comply with key industry standards, such as ISO 27001:2013 and NIST SP 800-53, for security and reliability - EDGE UK – SSL Certification.

18.6.2 Documenting in EHRS (and EDGE)

- Study set up in the EHRS using IRAS and EDGE IDs.
- Patients screened by the research team.
- The Research Consultation Navigator in the EHRS will be used to document a potential participant's status in the study pathway. Their status will be allocated according to the table below; this will be updated as their status is changed

Table 7: EHRS documentation

Identified	Clinical or study team identified patient as potentially suitable to be recruited
Interested	Patient has expressed an interest in joining the study after having had it introduced and read the PIS
Ineligible – did not meet full criteria	Patient did not fulfil inclusion criteria, therefore could not be recruited to join study
Declined	Patient did not want to join the study
Waiting for consent	Appointment booked for patient to consent to join the study
Pre-screening	Pre-screening by clinical or study team for eligibility to join the study prior to being approached
Consented – in pre-screening	Consent signed, awaiting further screening before study activities
Consented – in screening	Consent signed, additional screening being undertaken prior to study treatments commencing

Enrolled – Recruited outside of Trust	Participant recruited outside of hospital, no study activities to occur at site.
Post consent screen fail	After signing consent form, did not meet all eligibility criteria and unable to continue on the study.
Enrolled – active on study	Consent signed and actively participating in study – treatments currently being undertaken
Enrolled – in follow up	All study related activities complete, follow up data still being collected
Completed	Study complete and participant no longer in follow up
Completed – Recruited outside of Trust	Study complete and participant no longer in follow up – recruited outside of hospital
Withdrawn	Participant or study team remove participant from study prior to completing – reason documented in comments.

Once consented, and confirmation of eligibility (see section18.2 for screening assessments), the following are recorded within the Research Consultation Navigator:

- Participant ID
- Study coordinator
- Study visit information added to the comments section using a smart phrase

Participant details sent to EDGE via data link in place as per other studies documented on EHRS.

Participants will be considered to be enrolled into the trial following: consent, pre-treatment assessments, confirmation of eligibility, completion of the registration process, allocation of the participant trial number and intervention by the central coordinating team/remote system.

18.7 Participant ID Allocation

Participant ID is allocated once participant has consented at coordinating site.
Number format
HM-ODS Code-XXX
e.g.: HM-RRV-001

Table 8: Participant ID Allocation

Participant ID	Surname	First Name	NHS Number
HM-RRV-001	Bloggs	Joe	1111 111 111
HM-RRV-002	Smith	Jane	2222 222 222

18.8 Baseline data

18.8.1 Baseline donor data

This donor baseline data collection is data that is routinely collected on blood donors. Its inclusion in the study will enable comprehensive analysis of the bloodMatcher algorithm's performance in optimising antigen matching based on the donor characteristics and blood group profiles available in the NHSBT donor population.

18.8.1.1 Demographic Information

- Donor identification number
- Sex
- Age (5-year band)
- Self-declared ethnicity

18.8.1.2 Transfusion results and Donation History

- Blood Group and Antigen Information
- Donation Centre
- Donation History

18.8.1.3 Donor Classification

18.8.2 Baseline recipient data

18.8.2.1 Demographic information

- Sex
- DOB
- Self-declared ethnicity
- Medical Record Number and/or NHS number

18.8.2.2 Details from three previous transfusion episodes

- Blood results performed as part of routine clinical care
- Observations

18.8.2.3 Healthcare history

- Comorbidities
- Haemoglobinopathy genotype

18.8.2.4 Transfusion History

- Transfusion adverse events
- Overall transfusion history

18.9 Trial Assessments

18.9.1 Overview

Assessments will be conducted according to the Schedule of Events (Table 5). The following subsections describe the primary, secondary, tertiary, and safety assessments in detail, aligned with the study objectives and regulatory requirements.

18.9.2 Primary Assessments

The primary objective is to evaluate the implementation of the antigen-prioritised algorithm (bloodMatcher) compared with current standard practice.

- Outcome measures:

    - The number of times the ‘RCI senior scientist/Haem-Match MDT’ approves or rejects the unit allocated for transfusion, and the recorded reason (categorical).
    - Timely transfusion of the allocated unit, defined as a composite of:
        - Delay to transfusion (quantitative).
        - Postponement or cancellation of transfusion (binary).
- **Timepoint of assessment:** Recorded for each transfusion order.

18.9.3 Secondary Assessments

The secondary objective is to compare the degree of blood group matching achieved between bloodMatcher and the standard of care.

- **Outcome measures:** For each blood transfusion and each blood group antigen:
    - *Mismatch*: transfusion of an antigen-positive unit to an antigen-negative recipient (binary).
    - *Substitution*: transfusion of a blood unit with a compatible (antigen negative) substitution into an antigen positive recipient (binary).
    - *Waste*: when a substitution is made but a unit of equivalent overall match-compatibility carrying the relevant antigen is available (binary).
    - *Substitution*: transfusion of a blood unit with a compatible substitution (binary).
- **Timepoint of assessment:** Recorded for each transfusion and each blood group antigen.

18.9.4 Tertiary Assessments

The tertiary objective is to inform the design of future multicentred studies of bloodMatcher, including evaluating the feasibility of electronic capture of relevant outcome and transfusion data.

- **Outcome measures:** Development of a protocol for a future multicentred study of bloodMatcher.
- Timepoint of assessment: Not applicable.

18.9.5 Safety Assessments

Please see section 20 Safety Reporting and Haemovigilance

18.9.6 Cross-reference to Schedule of Events

The timing of all assessments is summarised in the Schedule of Events (Table 5: Study Schedule). Deviations from the schedule may be permitted if operationally justified and will be documented in the trial master file.

18.10 Data Collection

18.10.1 Principles

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing, and disclosure of personal information, and will uphold the Act’s core principles. Data for the study will be collected and held within operational secure computing environments at NHSBT and UCLH.

The majority of data for the study will be stored at NHSBT using the NHSBT Secure Research Compute Platform (SRCP) which is ISO 27001 certified and is in routine use. The platform is hosted by the University of Cambridge Research Computing Services team and documentation is available here: https://docs.hpc.cam.ac.uk/srcp/index.html.

It is anticipated that almost all data would be electronic. In the event of any paper documentation, e.g. consent forms, these will be kept in a locked cupboard and will form part of the paper site file. Where part of individual care, they also will be uploaded to be part of the individual patient record.

Data will be stored for 30 years after the end of the study.

This patient data will be linked to the corresponding NHSBT data using secure pseudonymised identifiers to enable final analysis while maintaining patient confidentiality.

18.10.2 Core study data

18.10.2.1 Blood transfusion data

Core study data which will be collected and analysed within NHSBT infrastructure includes:

- **Blood order data**: e.g. antigen requirements, antibody requirements, standard patient demographics, patient NHSBT identifier, order type (i.e. Haem-Match order), required by date, number of units.
- **Blood unit sample tracking information and associated metadata:** e.g. donation identifiers (ISBT 128 compliant identifiers, https://www.isbt128.org), blood group antigen typing data, date bled, donor information.
- **Blood unit stock and logistics information**: e.g. issuable status of blood units, source donation clinic location, physical storage location, CMV status, quality flags.
- **BloodMatcher matching run data:** e.g. number of units available, number excluded, number of units requested, number of orders, overall allocation cost opportunity cost, computational logs, matching report outputs, results from automated tests which ensure current blood matching standards are met for each allocation.
- **Haem-Match MDT data:** e.g. outcome of MDT approvals including scientist notes if generated, reason for BloodMatcher suggestion rejection if rejected.
- **Blood unit allocation data:** e.g. allocation of unit to order, allocation date, delivery date.
- **NHSBT SRCP platform data:** e.g. user logins (including IP address, although UIS VPN is required for access), data access, computational operation logging, logged sending of reports to Haem-Match MDT.

18.10.2.2 Participant data

Participant data will be captured and initially stored at UCLH prior to deidentifying and transfer on NHS servers to NHSBT

- **Patient metadata**: e.g. demographics, weight, height, NHS number, hospital identifier, admission details, relevant medical history

- **Transfusion relevant parameters**: e.g. blood results, hospital held blood type data, hospital determined antibody status, crossmatch results, previous transfusion history, adverse reaction records
- **Blood allocation data**: e.g. units' arrival to blood bank, units allocated to patient, transfusion dates and times, pre- and post-transfusion monitoring data, clinical indication for transfusion, procedure details
- **Standard transfusion outcome data**: e.g. transfusion effectiveness measures, patient response indicators, discharge status, any transfusion-related complications or adverse events.

18.10.3 Data description in terms of how it meets study objectives

18.10.3.1 To investigate the impact of BloodMatcher on current hospital and NHSBT processes and blood stocks

- Time stamps of all interventions/events including individual order placement, MDT review duration for each case, allocation decisions per unit, and delivery confirmations
- Individual unit tracking: initial storage location, complete antigen profiles, unit identifiers (ISBT 128 compliant), SHU locations, expiry dates, CMV status, and quality flags for each unit
- Stock availability before and after allocation: inventory levels at unit level, antigen availability post-allocation, updated storage locations, and impact on future order fulfilment
- Competing demands on stock: other patient orders, emergency requests, planned surgical procedures, and unit location transfers
- Individual order and allocation data: patient-specific antigen/antibody requirements, demographics, NHSBT identifier, order type, required delivery dates, and specific unit-to-patient assignments
- Computational efficiency metrics: BloodMatcher processing time per matching run, matching algorithm performance, individual and total allocation costs and opportunity costs, immunisation risk calculations, units requested vs. units supplied/substituted.

18.10.3.2 To compare matching of blood groups achieved with the decision Support Algorithm (BloodMatcher) by comparison to standard of care

- Order specifics: comprehensive patient antigen and antibody profiles including rare antigens, detailed demographics and medical history, number of units ordered.
- Patient specifics: complete demographics and transfusion history, weight and height for dosage calculations, current blood parameters and coagulation studies, vital signs, previous transfusion reactions, relevant medications affecting coagulation, and history of immunisation.
- Matching quality metrics: degree of antigen matching/compatibility achieved, number and significance of antigen mismatches (expected zero due to automated checks), alloimmunization risk reduction assessment, crossmatch compatibility results, time to optimal match identification, and clinical appropriateness of decisions
- Comparative outcome measures: successful blood allocation and infusion, transfusion effectiveness indicators, adverse reaction rates, patient clinical response, length of hospital stay, additional/unexpected transfusion-related

complications, additional transfusion requirements, and additional post-transfusion haematology laboratory investigations required related to transfusion.

18.10.3.3 To inform the design of future multicentred studies of BloodMatcher, including the capabilities for electronic capture of relevant outcome and transfusion data

- Process evaluation: workflow assessment including ordering and decision-making processes, hospital laboratory integration including crossmatching and result reporting, NHSBT operational interfaces including stock management and delivery, inter-system digital communication protocols, identification of staff training requirements for beyond feasibility study rollout, and quality assurance mechanisms required for real implementation beyond feasibility study.
- Data collection capabilities assessment: electronic data capture infrastructure including recommendations for HIS/LIS/PULSE/HEMATOS integration, data quality and completeness metrics, automated versus manual data entry requirements, real-time reporting capabilities, data standardization across different systems, patient consent and governance frameworks, scalability for multi-site deployment, and comprehensive outcome data capture including transfusion effectiveness and laboratory follow-up results.

18.11 Subsequent Assessments and Procedures

Following the final EBT on the study, the participant will be, as part of standard care, scheduled for their next EBT. The blood tests taken, as part of standard care, in preparation for that transfusion will be recorded for the study. These are the same tests that were done previously prior to each exchange transfusion within the study. A schedule of all trial assessments and procedures is set out in the Study Schedule (Section 10).

18.11.1 Laboratory assessments

18.11.1.1 Local Laboratories

The following tests will be carried out at Local Laboratories for routine standard care (other than pregnancy test). This data, where the tests have been performed, will be collected:

Table 9: Laboratory Assessments in local laboratories

Laboratory test	Parameters
BLOOD	
Haematology	FBC, Haemoglobinopathy screen/Sickle percentage, reticulocytes
Serum chemistry	Renal and liver function and bone
Screening test	Serum or urine beta HCG (females only)
Blood transfusion	Group and Screen, Cross Match and unit allocation, Direct Antiglobulin Test, (where indicated)
URINE	
Urinalysis (dip stick)	Urine HCG

18.11.1.2 Central Laboratories: NHS Blood and Transplant

All these tests are part of routine standard care.

- Extended red cell genotype on Axiom array
- Investigation of blood transfusion reactions or new antibody formation (where indicated)

18.12 Long Term Follow-Up Assessments

None

18.13 Loss to Follow-Up

A participant will be deemed fully lost to follow up only in the (uncommon) circumstance where it is not possible to contact/locate the participant, and they have not withdrawn from the trial. Every effort will be made to collect primary and secondary outcome data. All data collected up to the point of withdrawal/lost to follow up will be used in the analysis of the study.

18.14 Withdrawal criteria

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.
It is always within the remit of the physician responsible for a patient to withdraw the patient from a trial (or certain aspects of the trial) for appropriate medical reasons, adverse events or new information gained about an intervention. Reasons for discontinuing the trial may include:

- Patient no longer on transfusion programme
- Patient withdrawing consent
- Persistent non-compliance to protocol requirements: i.e. not attending for exchange transfusions or pre transfusion blood samples as per standard care

The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes/electronic health record system. If a participant explicitly states that they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes. Any inclusion of collected data needs to be used in accordance with GDPR and HRA guidance.

18.15 Storage and analysis of clinical samples

There are no plans for additional samples to be collected other than those for standard clinical care.

18.16 End of trial

The expected duration of the trial is 12 months from recruitment of the first participant.
The end of trial is the date of the blood tests taken before the transfusion episode following the last transfusion episode on the study.

18.11 Co-enrolment guideline

19 TRIAL TREATMENTS NON- IMP

19.1 Name and description of intervention under investigation

An algorithm, known as bloodMatcher, will be used to arrange units of blood for planned exchange transfusions prior to selection by NHSBT staff for up to 40 consented participants, already on the exchange transfusion programme, for three transfusion episodes each. The algorithm will arrange available units of red blood cells for selection by NHSBT hospital services staff to minimise the risk of antibody formation, whilst meeting current blood matching standards. It will, as a minimum, select units according to current practice and guidance, that is, ABO, Rh CcEe D, Kell compatible, sickle negative, and negative for antigens to any clinically significant antibody as indicated in the blood order.

The purpose of the algorithm is to improve patient care by helping NHSBT to allocate blood units which minimise the risk to patients while also simplifying the logistical challenges of blood provision by considering all supply and demand for blood simultaneously. The core of the algorithm is a mathematical method called optimal transport, designed for rare resource allocation. By applying optimal transport principles, the algorithm manages this rare and critical resource more effectively, bringing benefits to patients which include better matching for patients in the form of reduced risk of alloimmunisation, fewer substitutions, fairer access to blood, reduced waste, improved matching and logistical efficiency, and better blood resource utilisation for all patients.

This study is designed to evaluate and compare the implementation of the algorithm known as bloodMatcher. This algorithm will, in addition to meeting current matching and blood allocation guidance, interrogate current blood stocks “on the day” to provide better matched blood for an additional limited number of antigens (S, Jk^a, Jk^b, Fy^a, Fy^b) . The algorithm ranks the units for each request according to compatibility (by comparing donor to recipient blood types), risk of antibody formation, geographical proximity and age of blood. That is, it makes sense if two units are of the same compatibility to request the unit that available in the local SHU (i.e. Colindale) rather than one located further away. Furthermore, it will incorporate the principle used to limit blood wastage where NHSBT issues the oldest units first. There are hard-coded software rules which prevent BloodMatcher from allocating incompatible units (e.g. it is not possible to arrange group A blood for selection to a group O recipient).

The blood order will specify a set number of units needed for the transfusion episode and this number of units at the top of the ranked list of available units will be scrutinised by a member of the Haem-Match MDT (consultant clinical scientists and senior clinical scientists (HSSTs)) who will assess if this meets current practice and guidance (as per above), and if so, pass the list onto Hospital Services at NHSBT, the team that is tasked with formally allocating the units to the order. The units will then be taken to the hospital and transfused to the recipient using standard processes.

There are several possibilities of this part of the process not meeting the requirements of the study, these can be any of adverse events, protocol deviation or contingency events and are described in the section 20: Safety reporting, haemovigilance, protocol deviation and contingency events and graphically in Appendix 3.

19.2 Concomitant treatment

There are no restrictions on any medicines that can be used before, during and after the study. Concomitant medications will be recorded by clinical teams as part of standard clinical care but not be part of the CRF or study dataset.

19.3 Treatment not permitted

There are no restrictions on any medicines/surgery/radiotherapy/procedures that can be used before, during and after the study.

19.4 Trial restrictions

Patients who are pregnant or planning to be pregnant during the study will be excluded (see inclusion/exclusion criteria). Females of childbearing potential must use effective contraception from the point of consent to + 4weeks after the last exchange transfusion. Effective forms of contraception acceptable for this trial are barrier e.g. condoms, pharmaceutical e.g. oral contraceptive pill or intrauterine contraceptive device (IUCD).

19.5 Assessment of compliance with treatment

Attendance for pre transfusion blood sampling and for transfusion sessions at allotted times/dates.

20 SAFETY REPORTING, HAEMOVIGILANCE, PROTOCOL DEVIATION AND CONTINGENCY EVENTS

20.1 Definitions and summary of processes

20.1.2 Adverse events

The definitions to be applied to adverse events recorded in this trial are given in Table 20a below. As this is a trial using an algorithm (bloodMatcher) to order units of blood prior to allocation for transfusion, events of interest are Device issues and those related to RBC transfusion. However, all other Serious Adverse Events occurring during the study period for each patient will be recorded for completeness. For grading of adverse events please refer to CTCAE version 5.0 dated November 27, 2017 (‘Common Terminology Criteria for Adverse Events (CTCAE)’, 2017).

If an adverse event has or may have occurred, the Haem-Match Research team should be alerted. They in turn will supply details of the event to the PI or the person with delegated responsibilities according to the delegation log. The PI will determine the seriousness of the event and then the Haem-Match Research team will complete the necessary paperwork and communicate this to the relevant teams and personnel according to the timeframes as described in this chapter. This may include CI, local R+D, TMG, DMC, TSG and REC.

Where SAEs are related or unexpected in relation to the trial procedure these should be reported to the REC by the CI or sponsor within 15 days of the CI becoming aware of the event. This should be on the SAE report form available on the HRA website. Sponsor should be notified but may just request a line listing every few months etc, rather than on individual basis. The safety reporting process will adhere to the HRA advice described here: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/ and here: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/safety-and-progress-reports-other-research-procedural-table/.

20.1.3 Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, for example it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time and must be reported to the Haem-Match Research Team. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

20.1.3.1 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:
a) the safety or physical or mental integrity of the participants of the trial; or
b) the scientific value of the trial
The site will inform the Haem-Match Research Team as soon as they are aware of a potential serious breach, so the Haem-Match Research Team can report the breach to the trial Sponsor. The Haem-Match Research Team and the Sponsor will discuss the breach and decide whether the breach is classified as serious. If the breach is serious, the Haem-Match Research Team will report to the REC within 7 days of becoming aware of the breach as per the UK regulatory requirements. The Haem-Match Research Team will notify the REC in writing of any serious breach of:
a) the conditions and principles of GCP in connection with that trial; or
b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

20.1.4 Contingency events

Contingency events are foreseen risks with a mitigation plan. These can disrupt the study and usually describe something operational or procedural that would not otherwise be classified as an adverse event. These do not need to be reported; however, data will be collected on these events. Examples include:

- Units approved by the Haem-Match MDT that are no longer available for allocation (e.g. if already allocated or needs to be allocated to another patient) ⇒ Hospital services to adopt standard practice, i.e. pick the units themselves according to standard guidance.
- Patient does not attend or attends too late for blood test or transfusion episode broken ⇒ Clinical team to determine whether transfusion can be delivered at another time, and

laboratory team to determine whether the allocated units can still be used or if not then the bloodMatcher process needs to be repeated

- Nursing team cannot deliver transfusion episode e.g. difficulty with venous access, apheresis machine broken ⇒ Clinical team to determine whether transfusion can be delivered at another time, and laboratory team to determine whether the allocated units can still be used or if not then the bloodMatcher process needs to be repeated

Table 10: Adverse event definitions, examples and safety reporting time frames

Term	Definition	Examples with suggested actions	Safety Reporting Timeframes
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a red cell component has been administered, including occurrences which are not necessarily caused by or related to that product.		No reporting required
Transfusion-Related Adverse Reaction or Event	Any untoward and unintended response in a participant to a transfused red cell component or relating to RBC transfusion.	e.g. antibody formation	Report to Sponsor up to 30 days post end of trial treatment
Adverse Device Event (ADE)	Any untoward medical occurrence in a participant to whom a medical device has been applied, regardless of whether it has a causal relationship with the device. It includes any undesirable sign, symptom, or disease (whether related or not) that occurs in a participant using the investigational device, the comparator, or during a procedure involving the device.		Report to TMG and sponsor within 5 working days
Serious Adverse Event (SAE)	Respectively any adverse event that does not necessarily have a causal relationship with the transfusion nor the device and: ● results in death ● is life-threatening* ● requires hospitalisation or prolongation of existing hospitalisation** ● results in persistent or significant disability or incapacity		Report to TMG and sponsor within 5 working days
Serious Transfusion related Adverse Reaction	Respectively any adverse event, adverse transfusion reaction or unexpected adverse transfusion reaction that are any of the below: ● results in death	e.g. delayed haemolytic transfusion reactions or hyperhaemolysis	Report to TMG and sponsor within 24 hours

Term	Definition	Examples with suggested actions	Safety Reporting Timeframes
	● is life-threatening* ● requires hospitalisation or prolongation of existing hospitalisation** ● results in persistent or significant disability or incapacity ● Is reportable under the SHOT haemovigilance scheme		
Unexpected Adverse Transfusion Reaction	An adverse reaction, the nature or severity of which is not consistent with the known reactions to transfusion of a red cell component (in the case of this study, red cells).		Report to TMG within 24 hours
Device Deficiency (DD)	A DD is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, user errors or inadequacy in information supplied by the manufacturer.	e.g. ● Haem-Match MDT does not authorise unit allocation due to guideline non-compliance → revert to standard of care for all participants. Root cause analysis undertaken by BloodMatcher MDT to identify fault and introduce safeguards ● Failure of bloodMatcher algorithm/IT preventing identification of suitable units → revert to standard of care	Report to TMG within 2 working days

Term		Definition	Examples with suggested actions	Safety Reporting Timeframes
Use Error		Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.		Report to TMG within 2 working days
Serious Adverse Device Events (SADEs)		A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. These can be divided into two categories:		
	Anticipated Serious Adverse Device effect (ASADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the current version of the Risk Assessment		Report to TMG and sponsor within 24 hours
	Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Risk Assessment		Report to TMG and sponsor within 24 hours

*The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

20.2 Reporting Timeframes

Safety monitoring will include both transfusion-related adverse events and device-related deficiencies and events.

All serious adverse events (SAEs), transfusion-related adverse reactions (ARs), transfusion-related Serious Adverse Reactions (SARs) will be recorded from Day 0 until 30 days post end of the study.

20.2.1 Expedited reporting (within 24-hours) is required for the following SARs

20.2.2 Serious Transfusion-Related Adverse Reactions. This includes, but not limited to, acute and delayed transfusion reactions to RBC blood components such as haemolytic transfusion reactions, transfusion-transmitted infections, severe allergic reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), any other suspected or definite transfusion-related SARs as described in Serious Hazards of Transfusion (SHOT) guidelines (*Serious Hazards of Transfusion (SHOT)*, 2025). Imputability must be assigned (see section 20.2.4 Blood transfusion reference safety information and assessing imputability)

- **Unexpected Adverse Transfusion Reactions** as defined in Section 20 (Safety reporting) and not listed in the Transfusion-Related SARs above Imputability must be assigned (see section 20.2.4 Blood transfusion reference safety information and assessing imputability).
- **Serious Adverse Device Events** an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Root cause analysis undertaken by BloodMatcher MDT to identify fault and introduce safeguards. TMG may consider pausing study until satisfied that safeguards are sufficient to recommence study. The Sponsor will assess causality and expectedness and report to REC within agreed timelines.

20.2.3 Events that require reporting to TMG within 2 working days

- **Device Deficiency.** Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, user errors or inadequacy in information supplied by the manufacturer.
- **Use Error** Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

20.2.4 SAEs that require reporting to sponsor/trial team within 5 working days

- **Serious Adverse Events.** Participants in this study have SCD and many have co-morbidities. Some of these patients will be expected to develop SAEs during the study, of which most will be unrelated to trial interventions. Due to the seriousness of the disease(s) the patients in this study are suffering from the following situations that fulfil the definition of an SAE are excluded from expedited notification within 24-hours but must be recorded on an SAE form (separate to the other CRFs) and reported to the Trial team within 5-days.

- Elective hospitalisation to evaluate the treatment management plan for the patient's disorder or for procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial involvement
- Admission to the intensive care unit
- Severe sepsis
- Major organ dysfunction (single or multi-organ) including chest syndrome, stroke, sickle hepatopathy
- Transient ischaemic attack, thromboembolic and ischaemic events (myocardial infarction, stroke, pulmonary embolus, DVT), biliary disease, pneumonia and chest infection
- Any other serious event related to the underlying disease or medication used to treat the disease

20.3 Blood transfusion reference safety information and assessing imputability

Blood components or products are not medicines, thus there is no SmPC or Investigator's brochure to refer to. Instead, the Serious Hazards of Transfusion (SHOT) haemovigilance scheme assigns "imputability" to blood component related adverse reactions. Refer to table 11 below for imputability in relation to red blood cells. Other reportable events do not need imputability assigned.

Table 11: Definitions of imputability assigned by SHOT

	Relationship to red cell transfusion	Description
N / A	Not Assessable	When there is insufficient data for imputability assessment
0	Excluded or unlikely	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to causes other than the blood or blood components, or where the evidence is clearly in favour of alternative causes
1	Possible	When the evidence is indeterminate for attributing the adverse reaction either to the blood, or blood component, or where there may be alternative causes.
2	Likely / probable	When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component
3	Certain	When there is conclusive evidence beyond reasonable doubt

20.4 Investigator Responsibilities and process

The Chief Investigator(s) (CI) has overall responsibility for the conduct of the trial. As this is a single site trial, the PI has responsibility for the research at their local site and is responsible for informing the Trial team of all reportable serious adverse events that occur at their site following the guidelines below.

20.5 Investigator Responsibilities

20.5.1 Investigator Assessment of Device Deficiencies and Use Errors

All DDs and use errors, as defined in Appendix 3, should be recorded via the Device Deficiency Reporting form (DDRF) and will be collected by the Trial team for investigation by the Computational PI. If the eDDRF is unavailable for any reason, a paper version of the form should be completed, scanned and emailed to uclh.haem-match@nhs.net.

It is the responsibility of the Computational Principal Investigator (PI) to ensure that all DDs and user errors are recorded as soon as possible after becoming aware of the event but not later than within 2 working days after the occurrence of the event.

Examples of device deficiencies warranting reporting include the following:

- Any situation where the device fails to perform as it is specified in the study protocol
- Other situations in which the device fails to meet expectations

20.5.2 Investigator assessment of SADEs

The Computational PI is responsible for the reporting and assessment of SADEs. All SADEs should be put on the Device Adverse Event log, reported on an SAE reporting form (SAERF) within 24 hours to the TMG and sponsor. If the eSAERF is unavailable for any reason, a paper version of the form should be completed, scanned and emailed to research.office@nhsbt.nhs.uk and uclh.haem-match@nhs.net.

20.5.3 Investigator Assessment of SAEs

When an SAE occurs (not including Serious Transfusion-Related Adverse Events nor Serious Adverse Device Events), the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definitions in Section 20.1 (Definitions and summary of processes). If the event is serious and is on the list of expected events in section 20.1, then the details must be recorded on the SAERF and transmitted to the TMG within 5-days. If the event does not fit any of the exempted categories, it must be recorded on an SAE form and be e-mailed to the TMG within 24-hours of becoming aware of it.

20.5.4 Investigator Assessment of Transfusion Reactions

Any transfusion reactions that occur must have their imputability assessed using the definitions described in table 20.2.4: "Blood transfusion reference safety information and assessing imputability". Two clinicians sitting on the TSG will independently review this data at the end of the study.

20.5.5 Investigator Notification

For all events that requires expedited reporting as defined in Section 20.2 (Reporting Timeframes), the TMG should be notified within 24-hours of the Investigator being notified. The initial notification to Trial team should be an email containing the participant's trial registration number, the time and date of the event, and the name of the event. A report detailing the SAE details should be completed, either on the online database or on a paper SAE form and emailed to the TMG and the PI, within 24-hours. AEs Reports are to be sent to the following email addresses: research.office@nhsbt.nhs.uk and uclh.haem-match@nhs.net.

The SAE and Transfusion SAE form (if applicable) must be completed by the Investigator (the consultant named on the delegation of responsibilities log who is responsible for the patient's care). In the absence of the Investigator, the form should be completed and signed by a member of the site trial team. The responsible Investigator should subsequently check, annotate and sign the form and email (or upload onto the database) to the Trial team as soon as possible. The initial report must be followed by detailed written reports as appropriate.

The Investigator or their delegate must record all expected SAEs that occur during the study period on an SAE form and notify them to the Trial team within 5-days.
The investigator or their delegate must follow-up all reported SAEs until resolution, or the event is considered stable.

Investigators or their delegate must supply the Trial team and any regulatory authorities with any supplementary information they request.

20.6 Sponsor Responsibilities

- The Trial team (Sponsor) will forward all red cell transfusion reactions received to the Chief Investigator (or a medically qualified delegate) for review.
- The Trial team will review all expedited SAE reports and forward them to the DMC for review, as often as instructed by them, and provide them as listings for review at DMC meetings. These will be copied to the Chief Investigator for review.

- The Trial team will agree the planned content of the DMC reports with DMC members prior to the inclusion of the first trial participant.
- The Trial team is undertaking the duties of trial sponsor and is responsible for the reporting of any unexpected Serious Transfusion-Related Adverse Red Blood Cell reactions or Serious Device Events to the research ethics committee (REC), should any occur, and for preparing annual safety reports to the REC.

20.7 Statutory Reporting

Hospital staff remain responsible for reporting all transfusion-related adverse events/reactions to SHOT/SABRE according to standard procedures, as required under the regulations of the EU Blood Directive. Staff at the institution are also responsible for notifying their local R&D department of SAE and SADEs (as per the institutions' standard local procedure).

20.8 Pregnancy Reporting

Pregnancy reporting is required within 7 days of notification for any female patient on the trial. All pregnancies within the trial should be reported to the Chief Investigator and the Sponsor using the pregnancy reporting form. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

21 STATISTICS AND DATA ANALYSIS

21.1 Sample size calculation

We intend to collect data on 3 retrospective and 3 prospective transfusion episodes on each of 40 participants. This sample size has been determined to maximise the amount of information available to address the primary objective. We are confident that we can recruit 40 patients as the unit treats 140 adult patients with SCD on regular exchange blood transfusion, most of whom will meet the inclusion criteria. If the collection of data is spread uniformly over twelve months, then at any time we expect to be collecting data from 10 patients, which we believe to be achievable given the support staff available.

We decided to collect data from three transfusion episodes per patient, because there is a significant fixed cost associated with the enrolment of a patient due to the need to obtain consent. There is therefore a trade-off between the cost of enrolling a new patient and the benefit gained from the extra independent information. Because there is no need to test a quantitative hypothesis to address the primary objective, we have not conducted a formal power analysis.

21.2 Planned recruitment rate

There are 140 adult patients with SCD on regular exchange transfusion, the majority of whom will meet the inclusion criteria. These patients are well known to the department and investigators. We aim to have pre-screened/screened/recruited most if not all 40 participants

prior to the first transfusion episode of the study, any remaining patients will be recruited during the first three months of the study. For the first month of the study we intend to allow one patient to enter observation as a recipient of matched blood each week. Assuming there are no operational difficulties, we then intend to increase the rate to at least two per week. In the worst-case scenario if we are unable to increase the rate and the patients enter the study uniformly across the study period, we will nevertheless have time to observe 3 transfusions on each of 40 patients within one year.

21.3 Statistical analysis plan

Because this is a feasibility study and the sample size is limited, we plan to perform a purely descriptive analysis. Our approach will be to present the data to the reader rather than perform any formal inferential analyses. Consequently, except in limited cases, we do not intend to perform estimation or uncertainty quantification. As described in more detail below, we intend to summarise certain results across all transfusions ('in total'), by intended recipient, and by transfusion episode. The stratifications are intended to illustrate whether certain individuals might contribute disproportionately to the total counts, perhaps due to their blood types. Although we will not have the power to make inferences about this.

21.3.1 Summary of baseline data and flow of patients

We will summarise the distribution of the following variables over the study participants:

- (biological) sex,
- self-reported ethnicity

using frequency tables.

Further, we will summarise the distribution of the following variables over the study participants:

- age
- recorded RBC antibodies
- recorded RBC antigens (presence and absence)

at the time of each of the first transfusions considered for which:

- the standard of care algorithm is used to arrange blood,
- the bloodMatcher algorithm is used to arrange blood.

We will summarise the distribution of age graphically, by reporting the mean (and its standard error), the median, the standard deviation and the inter-quartile range and summarise the recorded RBC antibodies and antigens using frequency tables.

21.3.2 Primary outcome analysis

We will summarise the number of approvals/rejections by the Haem-Match MDT of units suggested for transfusion by bloodMatcher, by counting the numbers of approvals/rejections in total and by reporting the distributions of the number of approvals/rejections for each intended recipient and planned transfusion episode and for each intended recipient over the course of the study. We will summarise, in a frequency table, the reasons for the MDT rejecting units suggested for transfusion by bloodMatcher.

We will define transfusion as being ‘timely’ if units of blood suitable for the patient are available in the local fridge at the time of the patient appointment and such units are transfused. In the intervention arm, such units may not necessarily be those selected for the patient by bloodMatcher. We will define a transfusion that is not timely as being a ‘delayed’ transfusion.

We will summarise the number of timely/delayed transfusions following:

- the suggestion of blood for a recipient by the standard of care algorithm,
- the suggestion of blood for a recipient by bloodMatcher,

by counting the number of timely transfusions/delayed transfusions in total and by reporting in tabular form the distribution of the number of timely/delayed transfusions by recipient.

We will classify delayed transfusions according to whether the transfusion needs to be rescheduled.

We will summarise the types of delayed transfusions following:

- the suggestion of blood for a recipient by the standard of care algorithm,
- the suggestion of blood for a recipient by bloodMatcher

by counting, in total and by recipient, the occasions upon which the delay does and does not require the transfusion to be rescheduled.

We will summarise the distribution of the time delay to transfusion (in hours) following:

- the suggestion of blood for a recipient by the standard of care algorithm,
- the suggestion of blood for a recipient by bloodMatcher,

graphically and by computing the mean (and its standard error), the median, the standard deviation and the inter-quartile range in each group. We will stratify this analysis by the type of delay (transfusion rescheduled/not rescheduled).

21.3.3 Secondary outcome analysis

For each blood group antigen, we will summarise the number of blood type discordances following:

- the suggestion of blood for a recipient by the standard of care algorithm,
- the suggestion of blood for a recipient by bloodMatcher,

by:

- counting the number of transfused units that are:
    - substitutions for the antigen (recipient is antigen positive but unit is antigen negative),
    - waste, that is substitutions where an antigen positive unit of equivalent match compatibility is available,
    - a mismatch with the recipient (recipient is antigen negative but unit is antigen positive)

  in total, for each recipient and planned transfusion episode and for each recipient over the course of the study, summarising the count distribution over recipients and transfusion episodes graphically.
- counting the number of transfusion episodes in which at least one transfused unit is:
    - a substitution for the antigen,

- a mismatch with the recipient

in total and by recipient summarising the count distribution over patients graphically.

Throughout the report of our analysis, we will take care to explain that our analyses are intended to be descriptive rather than inferential and that consequently, except in limited specified cases, we have chosen to present the data rather than attempt to estimate parameters and compute associated uncertainties.

21.3.4 Sub-group analyses

Because this is a feasibility study, we plan to perform a purely descriptive statistical analysis of the full dataset. We do not intend to perform any inferential analysis of subgroups.

21.3.5 Interim analysis and criteria for stopping the trial.

Because this is a feasibility study, we plan to perform a purely descriptive analysis of the full dataset. We do not intend to perform any interim inferential analyses. Should there be a device deficiency that cannot be fixed to the satisfaction of the computational PI within the timeframe of the study then the study may be paused until such a time it can be rectified. The TSG, DMC, Research Ethics Committee (REC) and the sponsor retain the right to suspend or terminate the study at any time if continuing it would place participants at undue risk, if significant new safety information emerges (e.g., from SADEs or other findings), or if the scientific or ethical justification for the study is no longer valid. Such decisions are typically made following a safety review, data monitoring assessment, or notification of serious adverse events that alter the trial's risk–benefit balance.

21.4 Participant population

The participant population will consist of patients aged 16 years or older with sickle cell disorder who have participated for at least six months in a chronic exchange blood transfusion programme.

Participants will be offered information about the NIHR BioResource Research Tissue Bank Improving Health Outcomes (IBHO) study (REC 22/EE/0230) and invited to consider participation.However, participation in the NIHR BioResource is entirely optional and not a requirement for inclusion in the Haem-Match study.

21.5 Procedure(s) to account for missing or spurious data

bloodMatcher accounts for missing antigen information for blood types on donors that must be matched according to the clinical guidelines by assuming the patient is negative and the donor is positive for the antigen. The outcome data are fully recorded in hospital electronic records as part of standard clinical management, so we do not anticipate any missing outcome data.

If a patient drops out at any stage we will record that fact. When presenting the summary analyses (as described in section 21.3) we will take care to indicate the number of transfusion episodes contributing to each statistic.

22 DATA MANAGEMENT

1.1 22.1 Data collection tools and source document identification

Data will be collected from sites on trial specific case report forms (CRFs) or data collection tools such as electronic CRFs. Source data are contained in source documents and must be accurately transcribed onto the eCRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.
A source document list will be implemented prior to the start of the trial to identify:

- which data is to be recorded directly onto the CRF
- which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF and
- which data is not to be recorded in the CRF but only recorded in source documents, e.g. participant questionnaires.

The methods used to maximise completeness of data should be described (e.g. telephoning participants who have not returned postal questionnaires).
It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

1.2 22.2 Completing Case Report Forms

All case report forms will be electronic (eCRF). Sites will be granted access to the eCRFs following approval. Sites must adhere to the instructions and submission schedule outlined in the protocol. The CI/PI is responsible for the accuracy of all data reported in the eCRF.

1.3 22.3 Data handling and record keeping

The Principal Investigator has overall responsibility for data collection at Site. Participant data will be entered onto the trial database directly. All case report forms will be electronic. Sites will be granted access to the EDC system following approval of all site registration documentation and completion of training. The trial team will be in regular contact with local site personnel to check on progress and to help with any queries that may arise. Incoming electronic forms will be checked for completeness, consistency, timelines and compliance with the protocol.

1.4 22.4 Access to Data

Direct access to the data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections, in line with participant consent.

1.5 22.5 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report.
NHSBT and the participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the Trial Master File, The Principal Investigator at the participating site agrees to archive his/her respective site's study

documents in line with all relevant legal and statutory requirements. Study documents will be archived for 25 years from the study end.

The Trial Master File will be archived at NHSBT, in accordance with the NHSBT Retentions Schedule. It will be archived for 25 years from the study end to be in line with new regulations requiring sponsors to ensure that the TMF is accessible, available and legible for at least 25 years (plus another 2 years if the data generated by the trial is being used to support an application for a UK marketing authorization).

Destruction of essential documents will require authorisation from the Sponsor.

23 MONITORING, AUDIT & INSPECTION

A trial-specific oversight and monitoring plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment, which may include on site monitoring. This will be dependent on a documented risk assessment of the trial. The trial will be monitored in accordance with the agreed plan. The degree of monitoring will be proportionate to the risks associated with the trial. Risk will be assessed on an ongoing basis by the Chief Investigator, and adjustments made accordingly (in conjunction with the Sponsor).

The Chief Investigator will be responsible for the day-to-day monitoring and management of the study. The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

24 ETHICAL AND REGULATORY CONSIDERATIONS

24.1 Research Ethics Committee (REC) Review & Reports

The Sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

Within 90 days after the end of the trial, the CI will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

24.2 Peer review

Peer review was completed as part of the grant application process through NIHR.

24.3 Public and Patient Involvement

We established a PPIE Panel in 'Transfusion Practice' for Haem-Match in 2020. The panel is co-chaired by Dr Shari Spencer, a trainee haematologist and patient with SCD and Dr Rachel Kesse-Adu, a consultant haematologist and the education lead for the UK Forum on Haemoglobin Disorders. The panel is coordinated by Anne Forde of the University of Cambridge. We have been fortunate to recruit a core group of thirty highly motivated, informed, and collaborative patient volunteers with transfusion-dependent anaemias. They are a highly invested group of patients, because of the serious symptoms of their diseases and their limited treatment options. Some have simple transfusion requirements; some are complicated by alloimmunisation and some are 'un-transfusable'. The distribution of ethnicities in the group is representative of the patient cohort. However, the composition of the group is socioeconomically, educationally, and geographically diverse. We have a balanced representation of volunteers across both sexes and ages. Like the patient cohort they represent, the volunteers have varied experiences of transfusion.

The panel meets online approximately six times a year for between sixty and ninety minutes. Our initial ambition was to have some meetings face-to-face, but the volunteers — many of whom face significant health difficulties — preferred to meet by video conference. Generally, each session begins with a short informal presentation from a project team member. This is followed by a group discussion on the presentation topic, sometimes including pre-prepared questions for the panel to elicit feedback on a particular aspect of the research and its implications for NHS operations or patient care. Topics have included:

- The content of NHSBT patient information leaflets,
- Decision support algorithm for blood matching and its use in a feasibility study
- The storage and transfer of patient data and samples
- Clinical trials
- Data security and the framework required to combine diverse patient information into a single database.
- The feasibility trial

We plan to consult the PPIE panel further regarding the dissemination of the study findings.

24.4 Regulatory Compliance

The trial will not commence until Favourable REC opinion is obtained.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with the sites (R&D department at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm ongoing Capacity and Capability for the study.

24.5 Protocol compliance

Protocol non-compliances are departures from the approved protocol.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. For example, it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

24.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.
The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

24.7 Complaints from Research Participants

In the first instance, research participant complaints (patients or health volunteers) will be reported to the CI/PI to investigate, as documented in the patient information sheet(s), and to the Sponsor via research.office@nhsbt.nhs.uk. For participants who are NHS patients, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures were undertaken. Complaints from NHS patients are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

24. 8 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the UK Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the regulations' core principles. The confidentiality standards will be maintained by coding each patient enrolled in the trial through assignment of a unique participant identification number. Only pseudo-anonymous data will be entered into the trial database.

Consent will be obtained via the participant to collect these data items. Identifiable information will not be retained for the analysis. The required data will be transferred directly to the trial database with access limited only to the trial team The trial statistician(s) will ensure that any onward data transfer is performed securely and in agreement with the terms of the relevant Data Transfer Agreement.

Consent will be sought from participants to inform their General Practitioner (GP) of their enrolment in the trial.

Data generated by this trial must be available for inspection upon request by representatives of national and local health authorities, NHSBT representatives, and the REC for the trial site, as appropriate. The data controller for this study is NHSBT.

24.9 Finance and Supply of Equipment

The research costs for the study have been supported by
NHSBT: Salaries of team members (ongoing)
UCLH: Salary of team member (ongoing)
DHSC: Salaries of team members

24.10 Financial and other competing interests

At the time of writing the protocol, the Chief Investigators, Principal Investigators and all members of the trial committees had no competing interests that might influence trial design, conduct or reporting. Any potential disclosures arising during the trial will be notified to the Chief Investigators. These will include ownership interests that may be related to products, services or interventions that may be significantly affected by the trial, commercial ties (including pharmaceutical and/or technology company, or behaviour modification) and any non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).

24.11 Indemnity

NHSBT holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that NHSBT has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. NHSBT does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused

by participation in this clinical study without the need to prove negligence on the part of NHSBT or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.
Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to NHSBT upon request. Insurance for Clinical Trials sponsored and managed by NHSBT is covered by the NHS Resolution Schemes as follows:
• The Clinical Negligence Scheme for Trusts (CNST): for negligent harm. Any clinical negligence liabilities owed to a patient/participant arising out of or in connection with practical implementation of clinical trials sponsored by NHSBT are covered by the Scheme.
• The Liabilities for Third Parties Scheme (LTPS): covers employers' and public liability claims from NHS staff, patients and members of the public. These range from straightforward slips and trips to serious workplace manual handling, bullying and stress claims. LTPS covers claims arising from breaches of the Human Rights Act, the Data Protection Act and the Defective Premises Act, as well as defamation, unlawful detention and professional negligence claims.

24.12 Post-trial care

Following the study, participants will revert to standard care as the funding and support for delivery of the study will have ended. If the study is successful the team will apply for funding to deliver a multicentre study of the device, with MHRA support and involvement. Outputs from the study will be made available to the operational leads of NHSBT for their transformation of a research tool to direct patient care.

24.13 Access to the final trial dataset

The final data set will reside with NHSBT. The Chief Investigators will have access and can approve access for other members of the trial team to facilitate analysis or to cover for absences. Access to the final data set for additional analyses will be permitted under the agreement of the TSC and according to the trial dissemination policy (see below).

24.14 Intellectual Property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights. All intellectual property rights and know-how in the protocol, the study data and in the results arising directly from the study but excluding all improvements thereto or clinical procedures developed or used independently of the study by each participating site, shall belong to NHSBT. All intellectual property rights deriving or arising from the material or any derivations of the material provided to NHSBT by the participating site shall belong to NHSBT. Each participating site agrees that by giving approval to conduct the study at its respective site, it agrees hereby to effectively assign all such intellectual property rights ("IPR") to NHSBT and to disclose all such know-how to NHSBT.

Each participating site agrees to, at the request and expense of NHSBT, execute all such documents and do all acts necessary to fully vest the IPR in NHSBT. Nothing in this section

shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of NHSBT or its funder. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

25 DISSEMINATION POLICY

25.1 Publication Policy

All publications and presentations arising from this trial will follow a transparent and ethical process overseen by the Publication Committee (comprising the Chief Investigators and the lead trial statistician).
The final trial results will be submitted for publication in a peer-reviewed scientific journal. Reporting will adhere to the *Consolidated Standards of Reporting Trials (CONSORT 2010) Statement* (Schulz *et al.*, 2010) and relevant extensions (e.g., for cluster trials, pragmatic trials, or patient-reported outcomes, as applicable). The CONSORT checklist and participant flow diagram will be used to ensure comprehensive, accurate, and transparent reporting of the trial's design, conduct, analysis, and outcomes.

25.2 Authorship and Acknowledgement

Authorship eligibility will be determined in accordance with the criteria established by the *International Committee of Medical Journal Editors (ICMJE)*. Named authors must have made a substantial intellectual contribution to the trial, been involved in drafting or revising the manuscript, approved the final version, and accepted accountability for the integrity of the work. Group authorship may be applied where appropriate, with all investigators acknowledged for their contributions.
Professional medical writers may assist with manuscript preparation under the direction of the authors and the Publication Committee. Any such involvement, as well as the source of funding for professional writing support, will be fully disclosed in line with ICMJE and Good Publication Practice (GPP) recommendations.

25.3 Data Ownership, Analysis, and Reporting

The Sponsor is the legal owner of all data arising from the trial. On completion of the trial, the data will be cleaned, locked, analysed, and tabulated in accordance with the statistical analysis plan, and a Final Trial Report will be prepared. The Final Trial Report will be held by the Sponsor and, where required, submitted to regulatory authorities. Information on where and how the full trial report can be accessed will be provided (e.g., trial registry, sponsor website, or publication supplementary materials).

25.4 Trial Registries and Public Disclosure

In line with applicable regulatory requirements, summary results of the trial will be made publicly available on recognised clinical trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN) within mandated timelines, regardless of outcome.

25.5 Rights to Publish and Review Processes

Participating investigators may not publish trial data independently of the Sponsor but will have the opportunity to contribute as authors or collaborators on joint publications in line with authorship eligibility criteria. The Publication Committee will coordinate manuscripts, abstracts, and presentations to ensure accuracy, consistency, and compliance with authorship and reporting guidelines.
As the trial is supported and funded in part by external bodies, this support will be acknowledged in all publications. Any review or publication rights held by a funding or supporting body will be specified in advance and will not compromise the independence of the data analysis or interpretation.

25.6 Communication of Results to Participants

Where feasible, participants will be informed of the outcome of the trial once the Final Trial Report has been completed. This may be achieved by provision of the published article, a summary results leaflet, or a specifically designed newsletter, as appropriate. Participants may also request results from their Principal Investigator; such information will normally be made available after the Final Trial Report has been compiled and/or results have been published.

25.7 Data Sharing and Transparency

Plans for data sharing will follow recognised best practice. Where possible, the trial protocol, full trial report, anonymised participant-level dataset, and statistical code used to generate the published results will be made publicly available. The location (e.g., Sponsor's website, recognised data repository), timeframe for release (e.g., within 12 months of publication of the primary results), and any conditions for access (e.g., approved data-sharing requests, data use agreements) will be clearly specified.

26 PROTOCOL AMENDMENTS

All protocol amendments will be developed, evaluated, and formally authorised by the Sponsor and participating sites, and submitted to the Research Ethics Committee (REC) and relevant regulatory authorities as required, in compliance with applicable GCP, national regulations, and institutional procedures.

27 REFERENCES

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28 APPENDICES

28.1 Appendix 1 Table of Detailed Schedule for Pre-screening, Screening, Consent and Enrolment

Guidance:

- Routine practice (RP) or deviation from RP (DRP) – this is marked for each section. However, there are occasional sub-actions which may be DRP if the overall section is RP and vice versa. This will be noted clearly in the sub-action column
- The various teams are: Apheresis Team (AT), Haem-Match Research team (HRT), Blood Bank team (BB), Haem-Match MDT (H-MDT), bloodMatcher MDT (B-MDT), PIs (Principal Investigators), CH (consultant haematologists), any staff trained in phlebotomy (PHLEB), any staff trained in venous access (VEIN), any staff trained in taking observations (OBS), Hospital Services (HS)

No.	Routine practice (RP) or deviation from RP (DRP)	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams involved
1.	DRP	Pre-screening	Review of existing adult patients on the red cell exchange programme	Haem-Match Research team to meet with PI and apheresis team to develop a shortlist of those likely to meet inclusion criteria	HRT, AT
2.	DRP	Screening, consent and enrolment	Establish meets inclusion/exclusion criteria		HRT
			Patient approached and given information around study		HRT
			Patient agrees to be part of study		

			Pregnancy test negative (for selected patients)		HRT
			Information about NIHR BioResource provided and discussed (optional)		HRT
			Consent form signed		HRT
			Study Number allocated		HRT
			Information uploaded on to Research Navigator		HRT
			Information uploaded onto trials database		HRT
			Genomic blood group sent		PHLEB, HRT
			Haem-Match Research Team informs Haem-Match MDT and BloodMatcher MDT of patient recruitment		H-MDT B-MDT HRT

28.2 Appendix 2 Table of Detailed Schedule for each transfusion episode

Guidance:

- Routine practice (RP) or deviation from RP (DRP) – this is marked for each section. However, there are occasional sub-actions which may be DRP if the overall section is RP and vice versa. This will be noted clearly in the sub-action column
- The various teams are: Apheresis Team (AT), Haem-Match Research team (HRT), Blood Bank team (BB), Haem-Match MDT (H-MDT), bloodMatcher MDT (B-MDT), PIs (Principal Investigators), CH (consultant haematologists), any staff trained in phlebotomy (PHLEB), any staff trained in venous access (VEIN), any staff trained in taking observations (OBS), Hospital Services (HS)

No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
1.	RP	Scheduling of transfusion	Apheresis team decide date of transfusion episode and pre transfusion blood testing,	Appointment dates are placed on EHRS by a member of the apheresis team.	AT
				Apheresis team informs Haem-Match Research team via email	UA HRT
			Apheresis team communicates to BT lab	Apheresis Team email Blood Bank cc'ing PI and Haem-Match research team, using excel spreadsheet, noting which patient is for Haem-Match feasibility study	UA BB HRT
			Haem-Match Research team document key events on shared diary	Appointment dates and times for apheresis and pre-exchange blood sampling and when samples	UA
			Transfusion targets	Target Hb and either HbS% or number of units is dictated by consultant haematologist. Note this will have been done prior to the study as these patients are on the programme already but can be adjusted at any point in the clinical care pathway prior to starting a transfusion.	CH UA
			Transfusion prescription	This includes the blood tests, and additional prescription medication needed peri/post procedure, as well as fluids	CH UA
2.	RP	Blood Order	Ordering of blood units	Blood order placed by Blood Bank on Online Blood Ordering System (OBOS) using the specific Haem-Match order, with full patient identifiers included, specific blood requirements and number of units and when the order is needed by	B

No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
3.	RP	Patient attends for pre-exchange blood tests		Within 72 hrs of transfusion episode, unless by exception from a consultant haematologist	
				Blood samples taken and sent to laboratory	PHLEB / AT
4.	DRP	Blood Order		OBOS order generates a PULSE reference number	
5.	DRP	BloodMatcher Algorithm	Using the blood matcher algorithm to arrange the units	Download of PULSE and HEMATOS data to SRCP	B-MDT
				Member of bloodMatcher MDT runs bloodMatcher	B-MDT
				Units arranged: their G numbers as their identifier	
				G numbers emailed by bloodMatcher MDT to Haem-Match MDT and cc Haem-Match Research Team	B-MDT
6.	DRP	BloodMatcher Algorithm output Review			
				Allocated member for that day from the Haem-Match MDT Reviews order, and checks two things: 1. About the participant/order: it is a participant in the study who is due a transfusion, that the specific requirements stipulated for the patient meet national standards.	H-MDT

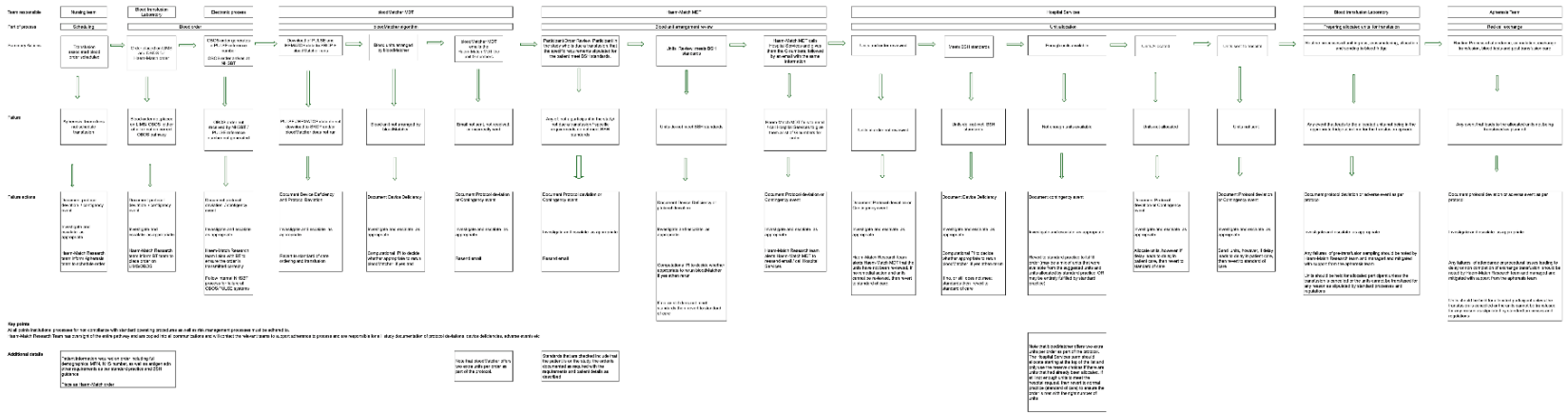
No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
				2. About the suggested units: does the specification of the units meet BSH standards and guidance	
				If either the participant/order OR suggested units do not meet criteria then: 1. Haem-Match MDT emails and calls Haem-Match Research Team 2. This information is also conveyed in an email cc'd to Haem-Match Research Team is cc'd PIs, and bloodMatcher MDT and Haem-Match Research Team	H-MDT
				If BOTH the patient and suggested units criteria are met then: 1. Haem-Match MDT emails and calls Hospital Services Supervisor and tells them of the G numbers of the units that should be allocated to the participant 2. This information is also conveyed in an email to Hospital Services and is cc'd to PIs, and bloodMatcher MDT and Haem-Match Research Team	H-MDT
				The Hospital Services Supervisor must send immediate confirmation this is being actioned by a reply all to the email above.	HS

No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
7.	RP	Unit Allocation		DRP [Hospital Services supervisor formally allocates units to the order] RP [Any qualified member of Hospital Services allocates units to the order] If insufficient units are available from the recommended G numbers then revert to standard practice to allocate units	HS
				Print order note	
				Operator locates required units	
				Operator validates required units	
				Units are stored in a reserved location until time of issue (units requested from other sites will be added to this location upon arrival)	
				Hospital Services team place the units in the box for transport to hospital	
				Operator issues units to UCH	
				Operator despatches units to Hospital ONLY once full order is complete	
				Units sent by NHSBT transport / courier	
				Haem-Match Research Team notes that units have been allocated on OBOS	HRT
8.	RP	Units prepared for transfusion		Electronic delivery note scanned	BT
				Each unit scanned in	
				For patient specific orders, print off screen shot of order	

No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
				Units placed in the fridge in blood bank	
				Allocated units on LIMS	
				Group and screen	
				Antibody identification	
				Cross match (EI or IAT)	
				Cross match successful	
				Issue units on LIMS	
				Label printed off and attached	
				Final tag check	
				Units placed in issue fridge	
				Move out in Bloodtrack™	
				Despatch units	
				Units arrive in clinical area	
				Courier logs on to fridge with their ID	
				Courier scans into Haemobank™ or apheresis fridge (Bloodtrack™)	
9.	RP	Exchange Blood Transfusion		Patient attends	A T
				Venous access achieved	
				Assessed as fit for procedure	
				Nurse checks blood available on Bloodtrack™	
				Nurse prints off pickup slip	
				Nurse logs on to fridge with their ID, takes out three at a time, each should be scanned individually.	
				Units transfused	

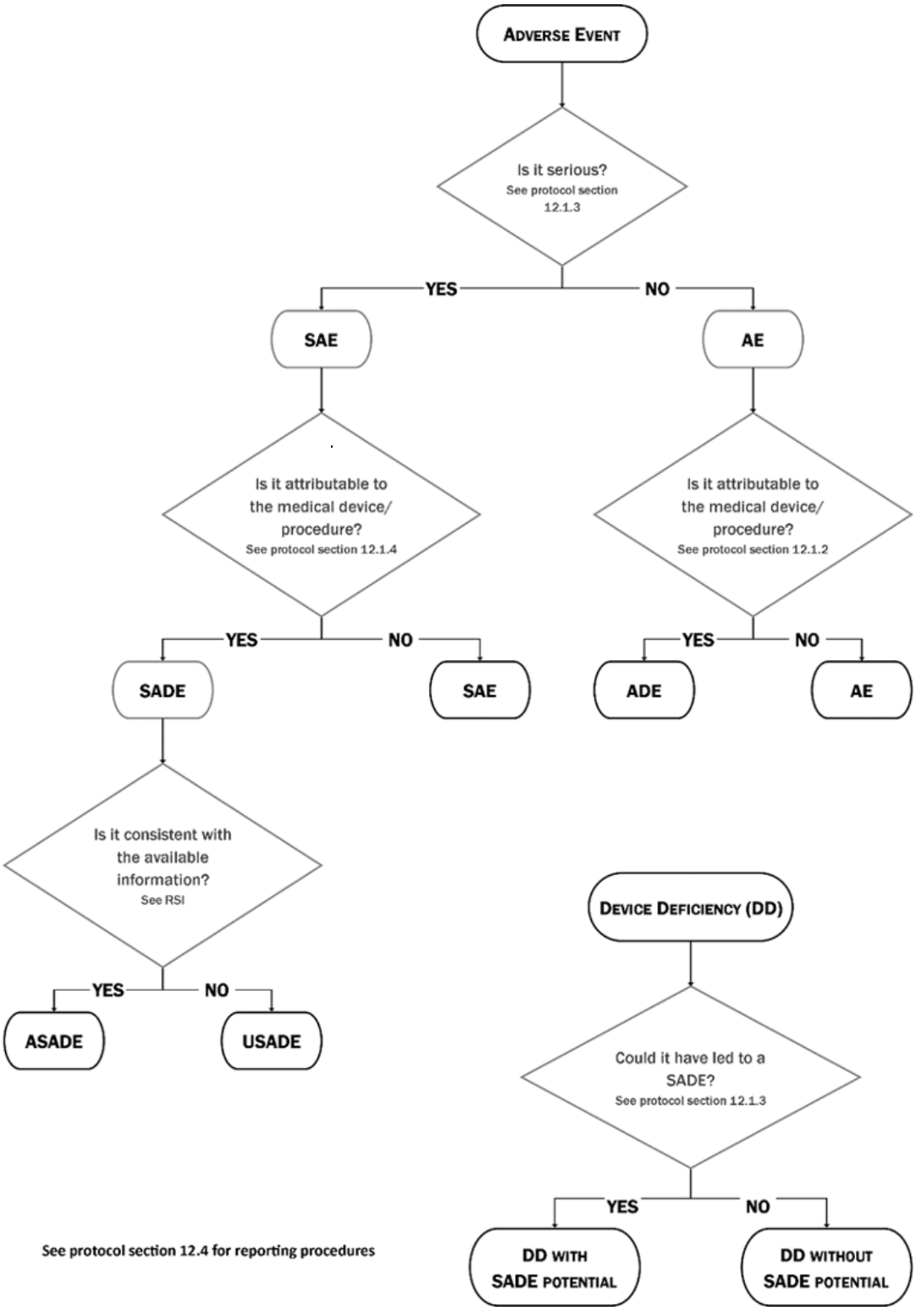
No.	RP/ DRP	Intervention and reference to any existing documentation	Detail	Sub-Actions	Teams leading activity
				Traceability tags placed in box	
				Patient infused saline	
				Patient has bloods taken	
				Next appointment given to patient by nurse	
				Nurse led discharge	
				MLAs pick up traceability tabs on a daily round and return to lab	BT
				Unused units returned to stock	
				Units are fated on LIMS	
10.	DRP	Collation of all data for transfusion episode	Patient data including adverse events	Information collated into CRF and entered into research database at UCLH, then deidentified and sent securely to B-MDT	HRT
			bloodMatcher and donor data - NHSBT including adverse events	Information collated into SRCP NHSBT	B-MDT

28.3 Appendix 3 Graphical representation of episodes with guidance regarding device deficiencies, adverse device events, protocol deviations and contingency events

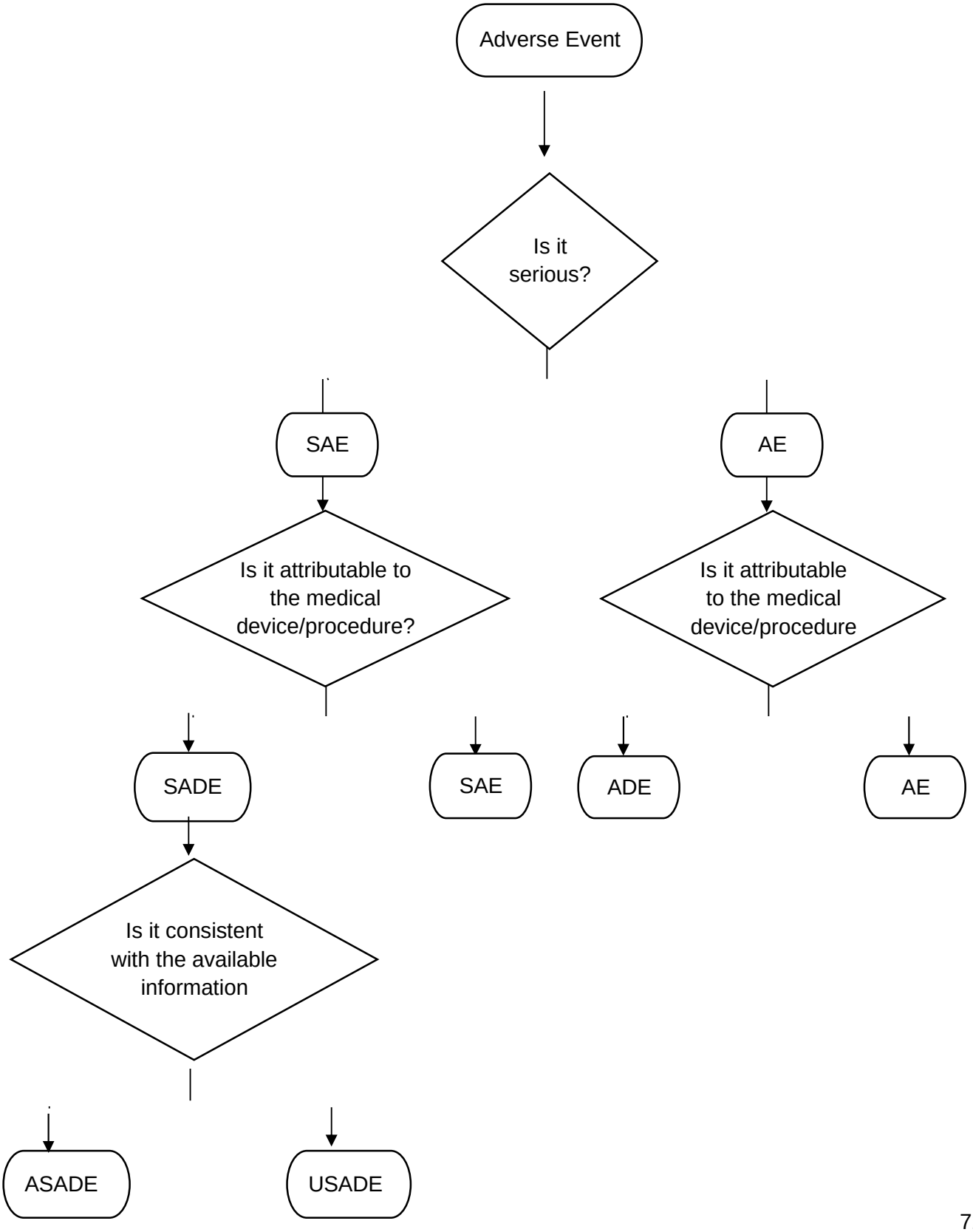


28.4 Appendix 4 Device Safety Reporting Flow Chart

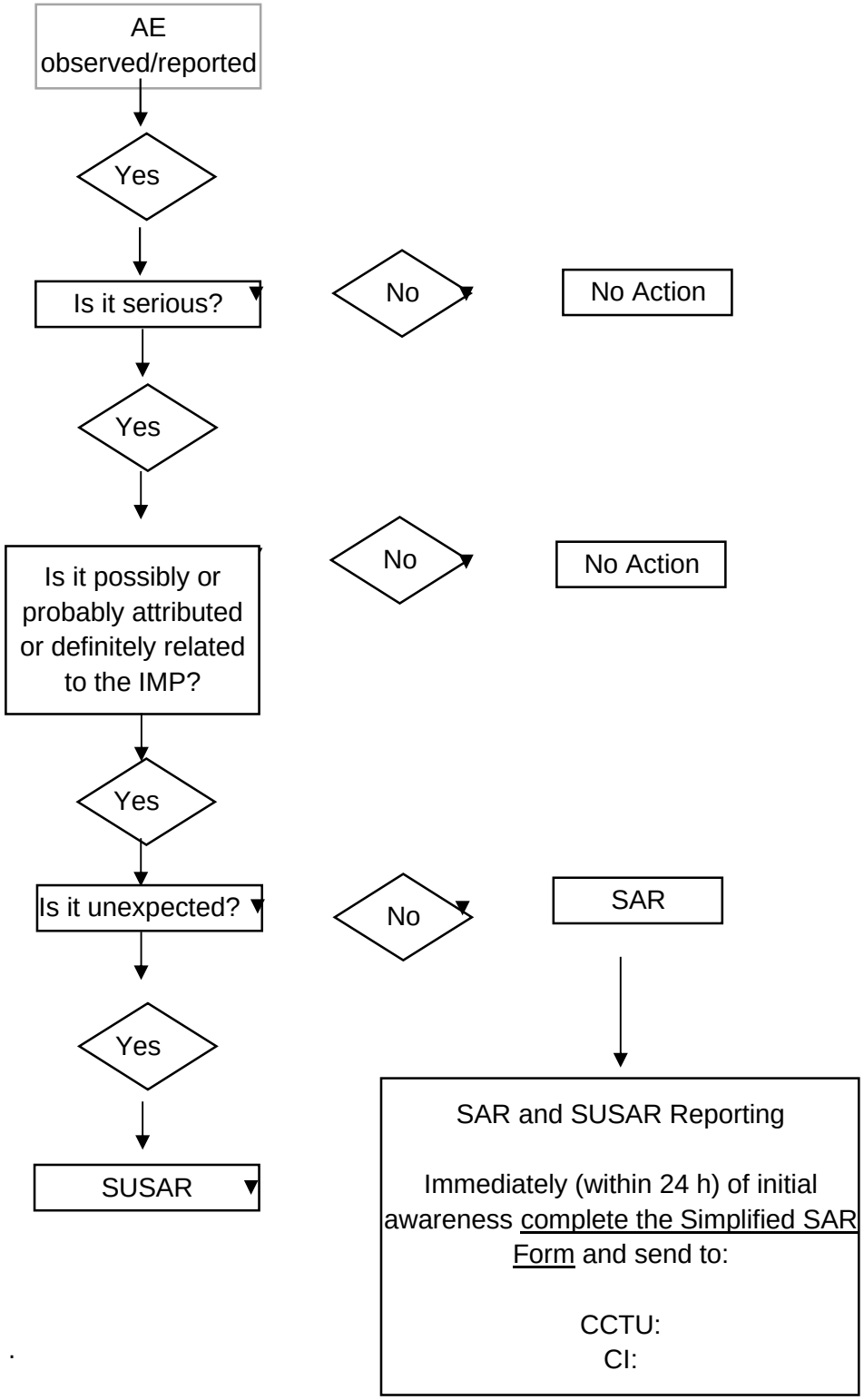
28.4.1 Device Deficiency (DD)



28.4.2 Adverse Device Events (SADE, ADE) and Adverse Events (AE/SAE)



28.5 Appendix 5 General Safety Reporting Flow Chart



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28.6 Appendix 6 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made