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Recovery and survival of stem cell originated red cells

Submission date 03/09/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 04/07/2019	**Overall study status** Ongoing	
Last Edited 01/04/2025	**Condition category** Other	

Plain English summary of protocol

Background and study aims
About 1.5 million red blood cell (RBC) donations are collected by NHS Blood and Transplant and transfused each year, but there are a small number of patients with rare blood group types for whom NHS Blood and Transplant cannot meet the transfusion requirements. New RBCs can be grown from human blood stem cells in the laboratory (manufactured red blood cells, mRBCs). It is hoped that this will provide a novel transfusion product for these patients in the future, some of whom require regular transfusions throughout life (e.g. for thalassemia or sickle cell disease). Researchers want to find out whether mRBCs are safe and last longer in the circulation in the body than standard donated RBCs (sRBCs). The mRBCs are all young whereas in standard donated blood the RBCs will be of varying ages, from young cells to those that are reaching the end of their life span. Studies have shown that younger RBCs stay in the circulation for longer once they have been transfused. If the mRBCs last longer than the sRBCs this could mean that such cells could eventually reduce how often transfusions are needed in patients who are dependent on transfusions.

Who can participate?
This study is a Phase 1 Trial in healthy volunteers with a unique recruitment process that requires pre-study matching for several blood groups and therefore is not open to the public domain.

What does the study involve?
The participants that are recruited will be given the information at the time of recruitment.

What are the possible benefits and risks of participating?
The participants that are recruited will be given the information at the time of recruitment.

Where is the study run from?
This trial is being managed by NHS Blood and Transplant Clinical Trials Unit in Cambridge (UK)

When is the study starting and how long is it expected to run for?
August 2018 to October 2025

Who is funding the study?
NHS Blood and Transplant and the National Institute of Health Research (NIHR) (UK)

Who is the main contact?
Restore.trial@nhsbt.nhs.uk
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Study website
https://www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/restore/

Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
2017-002178-38

IRAS number
229563

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS: 39643; IRAS: 229563

Study information

Scientific Title
A single centre, randomised, controlled, single-blind Phase I cross-over trial in healthy volunteers to assess the safety and survival of a mini-dose of red blood cells derived from CD34+ cells isolated from adult blood vs standard donated red blood cells

Acronym
RESTORE

Study objectives
Manufactured red blood cells (RBC) will have a longer survival in the circulation of the volunteers than the standard donated RBC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/11/2018, London-West London and GTAC Research Ethics Committee (Hammersmith Hospital, London, W12 0NN, UK; Tel: +44 (0)207 104 8007; Email: NRESCommittee.London-WestLondon@nhs.net), ref: 18/LO/1494

Study design
Randomized; Interventional; Design type: Treatment, Drug, Other

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Blood transfusion

Interventions
Setting:
1. Units of whole blood will be donated in the East Anglian region static or mobile donor clinics /sessions
2. Red cells will be produced from whole blood donations in licensed facilities at NHSBT Bristol (Filton)
3. Red cells will be radiolabelled with 51Cr in the Radiopharmacy Unit, Guy's Hospital, London
4. Recipients will receive infusions of radiolabelled RBCs in the Wellcome Trust/NIHR Clinical Research Facility at Addenbrooke's Hospital, and follow up blood samples will be taken at their home or place of work, according to their preference

Interventions to be compared:
Red blood cells manufactured from adult haematopoietic stem cells (mRBC)
Comparator: standard donated red blood cells (sRBC)

Selection of participants:
Potential donor participants born after 1st January 1996 with an extended blood group phenotype available were identified anonymously.
Potential recipients were sought from the Cambridge Bioresource (CBR) as part of the RESTORE-i feasibility trial. Potentially eligible members of the CBR were approached by the CBR team for their permission for the RESTORE study team to contact them to discuss their participation in this clinical trial.
To be potentially eligible for the trial, donors and recipients must be willing to participate, and also be blood group compatible with potential recipients or donors.
Once the panel of blood compatible Donors and Recipients has been identified as part of the RESTORE-i feasibility, groups of blood phenotype matched donors and recipients will be selected, with donors with the highest CD34+ (haematopoietic stem cell) counts selected as a preference. Each group will consist of a minimum of 1 donor and 2 recipients to ensure availability of recipients for the mRBC and avoid wastage.

Screening & consent
1) Donor Consent Visit (day -35 prior to the study intervention):
Donors will be sent a detailed information sheet and be given a minimum of 48 hours to decide if they are interested in participating, and if so a consent visit will be arranged with the study nurse. At the consent visit, the CI or delegated physician will explain in detail the exact nature, purpose, risks, requirements, implications and constraints of the study supported by written information. Donors will be given the opportunity to ask any questions they may have about the trial. If they agree, they will be asked to provide full written informed consent.

A whole blood sample is taken for standard screening for: sickle cell trait, pseudohyperkalaemia, G6PD deficiency, confirmation of blood group phenotype, virology (Hepatitis B, Hepatitis C, HIV), FBC/ferritin. A flag will also be placed on the NHSBT systems to prevent the Donor from being called for routine blood donations.

2) Recipient consent & screening visit:
At the consent visit, if potential recipients agree to participate in the trial and the study nurse

has re-confirmed their eligibility, they will be asked to provide written informed consent. Blood samples will also be taken to carry out cross-matches with the sRBC and mRBC prior to the infusions.
In the month prior to the study the potential recipient will undergo baseline medical investigations which will comprise:
I) Medical history (allergies, previous/planned surgery, ongoing investigations, heart disease, diabetes, gastrointestinal disease, respiratory disease, neurological problems, systemic illness, chronic infection, skin disorders, musculoskeletal disease, other illness, radioisotope exposure in the last 12 months)
II) Physical examination (BP, pulse, temperature, cardiovascular, respiratory, abdomen, CNS/PNS)
III) Clinical laboratory tests including full blood count, biochemistry and virology

The CI or delegate will review pre-study data to ascertain the potential recipient's continued eligibility for the trial which will be documented accordingly.
Once the study team is satisfied that the potential recipient is eligible following the additional screening tests, he or she will be allocated to a donor-recipient group Randomisation will be at the level of the donor-recipient group to which the individual is assigned.

Randomisation
It is envisaged that in total ten groups will be assigned to the intervention, n=5 will receive the standard red cells first, n=5 will receive the mRBC first. The randomisation will determine whether the recipients in a given group receive standard red cells or manufactured red cells first, to be followed by the alternate type of red cell, except that the recipients from the first 2 groups that go through the study will receive standard red cells first. The total number of recipients receiving standard red cells will be at least 15 of which only 10 recipients will go on to receive the mRBC.

Groups will be randomised by the independent statistician, determining which type of red cells will be received first for that group. The randomisation will also allocate each recipient an order within their group, to indicate which of the recipients should preferentially be transfused. In particular, this order will indicate which of the two recipients who received standard cells first should go on to receive manufactured red cells. In groups with more than one donor, donors will be ordered by descending CD34 count.

Study procedures:
1) Donors
Following screening, the blood donor will be called for a whole blood donation visit at a mutually agreed time. The donor will be required to meet all criteria for donation of blood for transfusion according to NHS Blood & Transplant Guidelines whereby they will donate one unit of whole blood. This unit of whole blood will be processed as follows:
- under GMP conditions in a licensed Blood Establishment into standard red cells (control arm) or
- by the Advanced Therapies Unit (ATU) within the Cellular & Molecular Therapies (CMT) facility at NHSBT Bristol, under its MHRA IMP Manufacturers' Authorisation to produce manufactured red cells (mRBC – intervention arm).

Routine tests on the samples accompanying the whole blood unit for HIV, HBV, HCV, HEV, Syphilis, ABO and Rh blood group will be performed. It is imperative for recipient safety, that recipients receive the correct unit of red cells that have been donated specifically for them and a full tracking system from donor to the recipient will be used.

Study Donors will attend at least two (and possibly additional) whole blood donation visits during the trial, each approximately 4 months apart.

2) Radiolabelling:
Prior to infusion, the cross-matching results will be checked. Bacteriology results will also be checked (sRBC and mRBC). On day 8-10 of red cell storage, the cells will be transferred to the Radiopharmacy Unit, Guy's Hospital where the cells will be radiolabelled with Cr51 according to the trial-specific Standard Operating Procedure. Haemolysis levels in the supernatant from the labelled cells will be checked prior to their release from the Radiopharmacy Unit for infusion into the volunteers.

3) Recipients (participants):
A medical history and assessment will be undertaken at the consent visit and reassessed on the day of infusion. Participants will attend the Addenbrooke's Clinical Research Facility for infusion of standard red cells and mRBCs at visits at least 4 months apart. Following each infusion, on the day of infusion blood samples will be taken at 5, 7.5, 10, 12.5, 15, 30 and 60 minutes. Further single blood samples will be taken at 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 75, 100 and 120 days post infusion in order to assess post-infusion survival of the red cells and to screen for red cell alloantibody formation.

Procedures post infusion:
1) EDTA blood samples (10 ml) will be taken for assessment of red cell survival at 5, 7.5, 10, 12.5, 15, 30 and 60 minutes post transfusion of the radiolabelled red cells. An additional sample will be taken at 24 hours and then on day 2, 3, 7, 14, 21, 28, 35, 42, 49 75, 100 and 120. Samples will be transferred to the Nuclear Medicine department where they will be subsequently analysed.
2) Basic observations for safety (pulse, temperature and blood pressure) will be recorded during the whole 6 hours spent by the recipients on the CRF and at each sampling done thereafter at the recipient's place of choice.
Additionally, participants will be counselled on the need to telephone for advice if they become unwell or experience any adverse reactions. Pharmacovigilance reporting will be undertaken as part of the trial.

Intervention Type
Biological/Vaccine

Phase
Phase I

Drug/device/biological/vaccine name(s)
Radiolabelled red blood cells, standard red blood cells (sRBC) and manufactured red blood cells (mRBC)

Primary outcome measure
Co-primary outcome measures:
1. Safety as assessed by:
1.1. Serological detection of new red cell alloantibodies against standard and/or manufactured red blood cells at 120 days after the first infusion of red blood cells and at up to 180 days after the second infusion of red blood cells.
1.2. Description of all serious adverse reactions that occur from day of infusion of RBCs until up to 180 days after the second infusion of red blood cells.
2. Survival of Red Blood Cells is measured as the time it takes for 50% of the radiolabelled RBCs to be cleared from the circulation (T50). Blood samples are taken at 5, 7.5, 10, 12.5, 15, 30 and 60 minutes post transfusion of the radiolabelled RBCs and then at 24 hours and then on days 2, 3, 7, 14, 21, 28, 35, 42, 49 75, 100 and 120.

Secondary outcome measures
Post-transfusion recovery of Red Blood Cells at 24 hours (PTR24) is measured by calculating the proportion of red blood cells infused that remain in the circulation at 24 hours following infusion

Overall study start date
01/08/2018

Completion date
31/10/2025

Eligibility

Key inclusion criteria
Participant Inclusion Criteria (blood donors)
Blood donors must satisfy all the following criteria to be eligible for the study:
1. Born after 1st January 1996
2. Able to donate whole blood
3. Fulfil all requirements to donate whole blood for transfusion according to UK Blood Services definition at the time of donation
4. Previous successful whole blood donation
5. Willing to consent to their blood donations being used for the trial, including scheduling donation appointments to suit the needs of the trial

Participant Inclusion Criteria (recipients)
The participants (recipients) must satisfy all the following criteria to be eligible for the study:
1. Over 18 years of age
2. In good general health
3. Female and of no child-bearing potential (sterilised, post-hysterectomy or post-menopausal) or male
4. Has a blood group profile that is compatible with one of the donors who will donate units of blood for the study
5. Willing to accept that participation in the trial will prevent them from becoming a blood donor or donating blood in the future, as is the case for individuals who have received a blood transfusion. Willing to accept that participation in the trial may affect their ability to donate organs or tissues in the future.
6. Able and willing to keep to the trial schedule
7. Able and willing to provide informed consent to participate
8. Female participants will need to have a negative pregnancy test on the day of infusion, even though they will have confirmed they have no child-bearing potential. Based on the dose of radiation received, there is no requirement for male participants to use contraception or for any recipients to avoid proximity with pregnant women

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
110 Years

Sex
Both

Target number of participants
Planned Sample Size: 15; UK Sample Size: 15

Key exclusion criteria
Current exclusion criteria as of 13/02/2024:
Participant Exclusion Criteria (blood donors)
Blood donors may not donate for the study if ANY of the following apply:
1. Confirmed positive for any microbiological tests performed on blood donors on a sample tested at the time of donation (Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis E (HEV), Human Immunodeficiency Virus (HIV), Human T-cell Lymphotropic Virus (HTLV), syphilis)
2. A positive direct antiglobulin test (DAT)
3. The presence of Sickle Cell Trait (HbAS), glucose-6-phosphate dehydrogenase (G6PD) deficiency, pseudohyperkalaemia
4. Have plans to travel in regions that would justify their deferral as a blood donor at the time of donation
5. Within 30 days of participating in another clinical trial, at the CI's discretion
6. Unable to use videoconferencing for study visits, at the CI's discretion

Participant Exclusion Criteria (recipients)
Potential participants (recipients) may not enter the study if ANY of the following apply:
screening tests.
2. Previous splenectomy.
3. Participation in another clinical trial within the last 30 days or currently participating in another clinical trial.
4. Receipt of radio-isotopes within the last 12 months, unless given as part of the RESTORE trial.
5. Past or present occupational exposure to radiation that necessitates or necessitated the wearing of a monitoring badge
6. Known allergy to Cr-51
7. Known allergies warranting the use of adrenaline (EpiPen)
8. Positive for clinically significant red cell alloantibodies, as detected by routine serological methods, including 3 cell screen.
9. Positive for any other cross-match reactivity on screening.
10. Positive pregnancy test
11. Females that are breastfeeding
12. Surgery planned for the period of study participation unless the CI/screening physician deems the risk of the participant experiencing substantial blood loss during that surgery as very low and unlikely to require a blood transfusion.
13. Subject to enhanced COVID-19 restrictions at the time of recruitment, due to clinical status, at the physician's discretion (e.g. "shielding" or "clinically vulnerable").
14. Unable to use videoconferencing for study visits, at the CI/trial physician's discretion.

Previous exclusion criteria:
Participant Exclusion Criteria (blood donors)
Blood donors may not donate for the study if ANY of the following apply:

1. Confirmed positive for any microbiological tests performed on blood donors on a sample tested at the time of donation (Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis E (HEV), Human Immunodeficiency Virus (HIV), Human T-cell Lymphotropic Virus (HTLV), syphilis)
2. A positive direct antiglobulin test (DAT)
3. The presence of Sickle Cell Trait (HbAS), glucose-6-phosphate dehydrogenase (G6PD) deficiency, pseudohyperkalaemia
4. Have plans to travel in regions that would justify their deferral as a blood donor at the time of donation
5. Within 30 days of participating in another clinical trial, at the CI's discretion

Participant Exclusion Criteria (recipients)
Potential participants (recipients) may not enter the study if ANY of the following apply:
1. Any clinically relevant abnormality on history, physical examination or laboratory screening tests
2. Previous splenectomy
3. Participation in another clinical trial within the last 30 days or currently participating in another clinical trial
4. Receipt of radio-isotopes within the last 12 months
5. Past or present occupational exposure to radiation that necessitates or necessitated wearing of a monitoring badge
6. Known allergy to Cr-51
7. Known allergies warranting the use of adrenaline (EpiPen)
8. Positive for red cell antibodies on screening.
9. Positive for any other cross-match reactivity on screening.
10. Positive pregnancy test
11. Females that are breastfeeding
12. Surgery planned for the period of study participation

Date of first enrolment
13/05/2021

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NHS Blood and Transplant, Cambridge Donor Centre (lead centre)
Cambridge Clinical Research Facility
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
NHS Blood and Transplant R&D Office

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Sponsor type
Hospital/treatment centre

Website
https://www.nhsbt.nhs.uk/

ROR
https://ror.org/0227qpa16

Funder(s)

Funder type
Government

Funder Name
NHS Blood and Transplant

Alternative Name(s)
National Health Service Blood and Transplant, UK National Health Service Blood and Transplant, NHSBT

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location

United Kingdom

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: BTRU-2015-10032

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/10/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the NHSBT Clinical Trials Unit after de-identification (text, tables, figures and appendices) 9 months after publication and ending 5 years following article publication. Data will be shared with investigators whose use of the data has been assessed and approved by an NHSBT review committee as a methodologically sound proposal.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No