Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Statins for Improving Organ Outcome in Transplantation (SIGNET)

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [x] Scotland
- [x] Wales
- [x] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

◉ Yes ○ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

◉ Yes ○ No

Approval may be required from CAG to access patient data without consent. Please check your response in Question 4.

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Statins for Improving Organ Outcome in Transplantation (SIGNET)

Please complete these details after you have booked the REC application for review.

REC Name:
London Queen Square

REC Reference Number:
21/LO/0412

Submission date:
07/05/2021

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Statins in Organ Donor Management
An evaluation of the benefits of a single dose of Simvastatin given to potential organ donors declared dead by neurological criteria on outcomes in organ recipients

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	John	Dark
Post	Professor of Cardiothoracic Surgery		
Qualifications	FRCS		
ORCID ID	0000 0002 4727 6085		
Employer	Newcastle University		
Work Address	Faculty of Medical Sciences Framlington Place Newcastle Upon Tyne		
Post Code	NE2 4HH		
Work E-mail	john.dark@newcastle.ac.uk		
* Personal E-mail	john.dark@newcastle.ac.uk		

Work Telephone	01912085851
* Personal Telephone/Mobile	07768400932
Fax	01912231152

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Miss	Amy	Evans
Address	NHSBT Clinical Trails Unit		
	Long Road		
	Cambridge		
Post Code	CB2 0PT		
E-mail	SIGNET@nhsbt.nhs.uk		
Telephone	01223588016		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	9691
Protocol Version:	1.0
Protocol Date:	12/04/2021
Funder's reference number (enter the reference number or state not applicable):	NIHR131124
Project website:	www.nhsbt.nhs.uk/SIGNET

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

We wish to investigate whether giving deceased organ donors a single dose of the commonly prescribed drug, Simvastatin, is beneficial for transplant recipients.

All donated organs have suffered some damage. As the brain dies chemicals are released which cause an "inflammation" of the body. Measurements of this "inflammation" link to how well the organs function after transplant. We know that statins have many benefits, including dampening down inflammation in the body and individual organs.

Doctors in Finland linked this information in a clinical study. Organ donors, donating their heart, were randomised to receive a statin. The recipients who received a heart from a donor who had statins had less heart damage. This was a small study but there was a small benefit for lung and liver recipients and no disadvantage in receiving any organ from a donor who had received the drug.

A significant number of organs offered for transplant are not used; for the heart, this figure is about 75%. The reason for being so selective is that poor function of the donor heart in the recipient is the most common cause of death after a transplant. Any step in the donor which might improve the transplanted heart, or other organ, could have a major benefit to the recipient.

We plan to enrol 650 adult brain dead donors across the UK per year in a randomised controlled trial. Half the donors will receive Simvastatin in addition to standard care, compared to standard care only. The drug will be given after the donor family have consented to both organ donation and involvement in research.

Half of the recipients will receive a heart from a donor given the drug. We will follow the results of transplant, using data already collected in the national transplant database. No extra data or blood samples will be needed.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

SIGNET will be the largest randomised controlled trial in organ donation, positioned perfectly to coordinate the unique strengths of the UK NHS organ donation infrastructure. It will evaluate the benefits of Simvastatin given to organ donors on outcomes in organ recipients.

Identification of participants: Organ donation is clinically delivered nationally by a pool of senior band 7 nurses (Specialist Nurse in Organ Donation (SNOD)) who move between hospitals to seek consent for and manage the organ donation process. These specialist nurses take responsibility for making an assessment of the medical history, ascertaining suitability for donation and communication with the retrieval team and recipient centres. Assessment for eligibility in this study is by comparison very straightforward, does not require any medical decisions and therefore we suggest eligibility assessment can be undertaken by this group of highly trained nurses. Eligibility will then be re-confirmed by a medic at the point of prescription.

Consent: The study will be enrolling organ donors, who have been declared brain stem dead by neurological criteria and therefore will not be able to provide consent. Family members will consent for their relatives to take part in the study. Potential organ donors will be identified and their next-of-kin consented by Specialist Nurses for Organ Donation (SNOD) for research according to the existing policies of the NHS Blood and Transplant(NHSBT)in line with the Human Tissue Act(2004) Legislation and subsequent guidelines. SNOD's have specialized training and experience in how to identify and approach families who may be open to participating in organ donation and related research

avoiding any unnecessary distress during the sensitive period of mourning. Research consent will be obtained immediately after families consent to organ donation. Special care will be taken to avoid upsetting the families during this process. Research consent is obtained prior to any research activities being performed. In order to minimise distress to the donor family, the consent will be documented on the current organ donation consent and authorisation form with a study specific sticker added. This is the current mechanism for consent in non-CTIMP organ donation studies. This will be scanned into the patient notes and a copy can be left for the local research team. As with the information sheet, this sticker will not be localised per site due to the large volume of study sites in order for this to form part of the organ donation pack that SNODs take to sites.

There are some situations, especially in the COVID pandemic, where family are not able to visit the ICU in person and consent for organ donation is taken over the phone. The existing organ donation and research consent form has a section to record where consent is taken via telephone or video with a space for a witness to sign. The conversation is recorded and the patient information can be emailed or posted to the family. In situations whereby the family provide consent for organ donation via phone/video we will also take study specific consent in this way.

This is a donor study and, as such, the donor families will be consented but we will not seek consent from organ recipients. We will however be providing a letter and information sheet to patients on the transplant waiting list to inform them of the national study and how we will use their data. This will be disseminated via the transplant centres, of which many will already be participating sites, and we will also be disseminating this information centrally through the various organ specific patient associations, national advisory groups, the UK Organ Donation and Transplantation Research Network (UKODTRN) and social media/study website. We do not anticipate risk to the recipients of organs treated with simvastatin; allergy is rare and the amount of drug that would be transferred with the organ would be very small. Currently 15% of organ donors are receiving statin therapy and this is not currently a reason to decline organs. This was presented to a PPIE group and feedback was that the group felt that allowing the recipient to decline an organ from a donor taking part in the study would put recipients at a disadvantage.

Randomisation: Following consent for organ donation and study specific consent, the SNODs will perform the randomisation using Sealed Envelope (a centralised web-based randomisation system). This will be accessed via their iPADs, using 3G to connect. There may be some areas in the hospital where there may be poor signal, however the person randomising can go outside to try and connect or contact SealedEnvelope or the central research team in order to connect and randomise the patient.

Administration of the Intervention: It is likely that the trial intervention will be more effective the earlier it is given following the diagnosis of death. Sites will therefore be asked to give the Simvastatin as soon as possible following consent. Simvastatin is a commonly prescribed drug and although there are some risks associated with Simvastatin; these are all seen at multiple doses and this will be a single dose. The Simvastatin will be administered via nasogastric (NG) tube. As part of the donor care bundle, this will be in place for most donors, but may need to be inserted. Sites will be told to insert and check placement of this, using their standard procedure.

Safety Reporting: We recognise that the intervention is very low risk and is given to a complex patient population. The standard definitions of a SAE (results in death, is life threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, consists of a congenital anomaly or defect") do not apply in a patient who is confirmed brain-stem dead. Therefore we will report SAEs that the PI assesses as related to the study and unexpected. SAEs will only be reported in donors because this is a donor study and safety in recipients can be assessed through the primary and secondary outcome analysis.

Data collection: Although this is a donor study we will be following up the organ outcomes in the recipients, through the UK Transplant Registry. This data is already collected on the UK Transplant Registry as part of standard procedure under article 6.1 (e) and 9 (j) of the UK General Data Protection Regulation and is held and stored by NHSBT and data will not be shared outside the trial team. The UK Transplant Registry donor ID will be used to link with the recipient data on the registry and this donor ID will be stored in a restricted area of the study database, only accessible by the study data managers. An independent NHSBT statistician, who already has access to the UK Transplant Registry, will link the donor and recipient data and provide this in a pseudoanonymised form, to the trial statisticians for analysis. Patients on the organ waiting list will be informed of the trial and how we will use their data if they receive an organ from a donor in the study. This was suggested to our PPI panel and they were supportive of this approach. Our Information Governance team have reviewed our data protection impact assessment and they are happy with the security measures in place.

Study Management: We will deliver SIGNET specific training to the SNODs through NHSBTs existing national training and quality assurance systems. GCP training for SNODs is commensurate with the SNOD trial delegated responsibilities and recognises the existing SNOD expertise in taking and establishing informed consent with families. For SNODs this training would be delivered as part of the trial specific training taking place through the existing national training program. This training will include an introduction to the principles of GCP, medical care of

trial subjects, compliance with the protocol, investigational product, randomisation and unblinding, informed consent, records and reports and safety reporting.

Training for the PI, associate PI and ITU research teams will be delivered virtually, covering all study related procedures including screening, consent, eligibility checks, prescribing and administration of the intervention, data collection and SAE reporting. It will be the PI/associate PI's responsibility to cascade this training to the local ICU team and ensure that they sign the training log to document this. Prescribers and ICU staff, other than the core research team, will not be on the delegation log. It will be the PI/Associate PI's responsibility to ensure the ICU staff are aware of the study and training is cascaded.

We've sought PPIE support and review of study design and practicalities for delivery of the study. They are supportive of the strategies used. We have also sought out advice from the MHRA and HRA in the form of an innovation office meeting. The outcome of the innovation office meeting was that SIGNET is not a CTIMP.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

Does treatment of potential organ donors with simvastatin during protocolised care after diagnosis of death using neurological criteria improve outcomes in patients undergoing transplantation?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

We will be looking at secondary outcomes in all organs, including organ utilisation rates, graft and patient survival at 30 days, 3 months and 12 months, length of hospital and ITU stay, 12m eGFR for kidney transplant recipients, 3m meal tolerance test stimulated C-peptide for pancreas islet recipients and other organ specific outcomes.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

All organs removed from donors have already suffered a degree of damage. As the brain dies (and all of these donors are brain-stem dead) chemicals are released which cause an "inflammation" of the whole body. Measurements of this "inflammation" link to how well the organs function in the recipient after transplant.

In parallel, we know the cholesterol-lowering drugs "statins" have benefits across a range of health problems which go beyond the direct benefits on cholesterol. In particular, statins damp down inflammation in the body and in individual organs. Statins protect the lungs and kidneys in a range of illnesses.

Recently, transplant doctors in Finland linked all this information in an innovative clinical study. Organ donors who were about to donate their heart were randomised to receive a dose of a statin. They randomised 84 donors so 42 received the drug. After the transplant, the recipients who received a heart from a donor who had statins had less heart damage. The numbers were modest, and no survival advantage could be demonstrated. There was a small benefit for lung and liver recipients, but importantly there was no disadvantage in receiving any organ from a donor who had received the drug.

A significant number of hearts and other organs offered for transplant by the donor family are not used; for the heart, this figure is about 75%. The reason for being so selective is that poor function of the donor heart in the recipient is by far the most common cause of death after a transplant. Any step in the donor which might improve the transplanted heart could have a major benefit to the recipient. The same principle applies to all the other organs transplanted.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

STUDY DESIGN
This is a multi-centre, single-blind prospective, group sequential, randomised controlled trial. Randomisation will be in a 1:1 ratio and will be stratified according to whether the donor was receiving statin therapy at ICU admission.

TYPE OF PARTICIPANT TO BE STUDIED
Adult (aged 18 or above) organ donors who have been declared brain stem dead by neurological criteria, within a participating ICU.

SETTING
ICUs within Level 1 or 2 donating hospitals: defined as mean number of donors per year > 6 by NHS Blood and Transplant.

SCREENING
Adult organ donors will be identified by the Specialist Nurses in Organ Donation (SNODs). After they have been through the organ donation consent process with the donor family, they will go through the study specific consent. The SNODs will complete an eligibility checklist, which will be counter signed by the prescribing ICU doctor, if the patient is randomised to receive the intervention. No screening logs will be completed.

RANDOMISATION
Following study specific consent, participants will be randomised using an online randomisation service, called SealedEnvelope, and given a unique
Randomisation Number. The treatment allocation will also be provided.

TREATMENT
The study treatment is 80mg Simvastatin in addition to protocolised standard care. This will be compared to protocolised standard care alone. If randomised to receive the intervention, this will be prescribed by an ICU doctor and issued from hospital stock. The tablet will be crushed, mixed with 20mls sterile water (hospital stock) and administered via nasogastric tube. Nasogastric tubes are already in place for 80% of organ donors but if this is not already in place, this will be required.

FOLLOW UP
Although there will be some intervention and donor data collected by the research team onto an eCRF, most of the data from the donors, and all recipient data, is already collected as part of standard care on the UK Transplant Registry. No additional information or samples will be needed from recipients.

SAFETY REPORTING
Serious Adverse events will be reported to the REC within 15 days of the clinical team becoming aware. Due to the low risk intervention and complex patient population, serious adverse events that need reporting will be those assessed by the PI as being related to the study and unexpected. We will also record events that progress to the loss of capacity to donate as a result of study procedure.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

☑ Design of the research

- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
DESIGN
The study was presented at the NIHR BTRU Organ donation and transplantation PPI group as well as local PPIE groups and a RDS organised meeting. Two of the study co-applicants on the grant application are PPIE members and have attended management meetings.

MANAGEMENT OF RESEARCH
A dedicated PPI panel has been convened, through NHSBT's Patient and Public Advisory group, to oversee the study on an ongoing basis, provide input into donor and recipient facing materials and provide a lay perspective to the management of the trial and its dissemination. There are two lay members who will serve as independent members of the Trial Steering Committee.

DISSEMINATION
The dedicated PPI panel will be approached for their feedback and support for the dissemination of findings at the end of the study.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [x] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital

- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Patients are eligible for this trial if they meet the following inclusion criteria:
• Within a recruiting Intensive Care unit
• Patients diagnosed dead using neurological criteria
• Consent for organ donation in place, as defined by the Human Tissue Act and accompanying legislation and Codes of Practice.
• Study specific consent from donor family

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

• Aged < 18
• Planned donation after cessation of circulation (DCD)
• Known donor allergic hypersensitivity to Simvastatin

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Study Specific consent	1	no	20 minutes	Specialist Nurses in Organ Donation will consent donor families on the ICU
Randomisation	1	no	30 minutes	Specialist Nurses in Organ Donation will randomise

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).

4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Standard donor management protocol including the insertion of a nasogastric tube	1	yes	<12 hours	SNODs and ICU team
Administration of 80mg Simvastatin	1	no	20 minutes	ICU bedside nurse for the intervention arm only

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

Until organ retrieval

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Most risks associated with simvastatin are seen at multiple doses over a prolonged time, we will be giving a single dose. There is still a risk of allergic reaction to the statin, however there has only been one case of this reported in the literature. All organ donors will receive the standard donor care bundle which will include a large dose of steroids which will minimise the risk of allergic reaction.

The study intervention will be given via nasogastric tube. This will be in place for around 80% of donors but will be required if randomised to receive the intervention. There is a risk that this could be misplaced and the donor may not receive the intervention, however we ask that sites follow their local guidelines for insertion and checking the insertion of the nasogastric tube.

Specialist Nurses in Organ Donation are experts in the consent process with donor families, taking responsibility for this under the Human Tissue Act, and recently recognized as the principal clinical experts by the Organ Donation (Deemed Consent) Act 2020 Bill and associated Codes of Practice. As such they approach donor families for consent in a very careful way that minimises the distress to the donor family.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

There will be no benefit to organ donors participating in the study. People receiving an organ which has been treated with simvastatin may have better outcomes, and we hope that this will mean we are able to transplant more organs successfully.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

None. Patients are eligible if they have been confirmed dead by neurological criteria and there is consent for organ donation in place. The intervention of a single dose of simvastatin is limited to prior to organ retrieval.

A26. What are the potential risks for the researchers themselves? *(if any)*

None.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Specialist Nurses (SNs) will be having conversations with potential organ donor families. This may occur face to face in Intensive Care Units, Emergency Departments or by video/telephone if the family are unable to be present in person.
As part of delivering the standard donor care protocol, SNs will be screening potential participants for inclusion in the SIGNET trial. Donor families will be approached for consent for organ donation. If they wish to proceed with this, they will also be asked to consider their loved one participating in the SIGNET study. If the donor family agrees, consent for organ donation and the SIGNET study will be taken.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
ICU teams and SNODs will review medical records when identifying potential donors for organ donation.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

SNODs have a memorandum of understanding in place with participating hospitals and are fully trained and aware of their duty of confidentiality. ITU teams are contracted and trained and are aware of their duty of confidentiality. Both SNODs and ITU team members have professional registration which relies on maintaining confidentiality.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

(●) Yes ( ) No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

(●) Yes ( ) No

If Yes, please give details below.

Donor families are asked to consent for the use of their relatives identifiable data. This will include their donor ID which is used to link to recipient data on the UK Transplant Registry to follow up organ outcomes.

Transplant recipients (not direct participants) will not be consented as this data is already collected as part of the organ transplant process and is stored on the UK Transplant Registry. Patients on the organ transplant waiting list will be given a study letter and information sheet, explaining the study and use of their data, when joining the transplant waiting list . Patients already on the waiting list will also be contacted. This information will be

disseminated via the transplant coordinators at the transplant centres, of which many will already be participating sites, and we will also be disseminating this information centrally through the various organ specific patient associations, national advisory groups, the UK Organ Donation and Transplantation Research Network (UKODTRN) and social media/study website . The UK Transplant Registry is owned and maintained by NHSBT. Recipient identifiable personal information will only be accessed by the independent trial statistician who already has access to data on the UK Transplant Registry. They will link the recipient and donor data and remove any identifiers. NHSBT Information Governance have reviewed our Data Protection Impact Assessment (DPIA) and they are happy with the security measures in place.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The families of potential organ donors will be approached by the Specialist Nurses for Organ Donation (SNOD). The SNODs have the required skills and knowledge to best judge how and when to approach families to consider research within the complex organ donation process and make the process as gentle as possible.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Consent will be obtained from a legal representative (donor family) as the patients will be incapacitated and will not regain capacity. Specialist nurses in organ donation will obtain the consent for participation in this study. This will be recorded in a'consent for research' space within the organ donation paperwork and a study specific sticker will be added to the organ donation paperwork. This consent will also be documented electronically, within the NHSBT DonorPath system. This is an auditable system, used to document the organ donation process.

There may be some situations (for example pandemic or emergencies) whereby the family are not able to visit their relative. In these situations consent will be taken over the phone and recorded. The recording is saved and there is a section on the consent form to document that this was done over the phone. The family will be directed to the study website to see a copy of the information sheet and will also be asked if they would like a copy posted or emailed.

If you are not obtaining consent, please explain why not.

This is a donor study and, as such, the donor (participant) families will be consented but we will not seek consent from organ recipients. We will not know who the recipient will be at the time. We will however be providing a letter and information sheet to patients on the transplant waiting list to inform them of the national study and how we will use their data. We do not anticipate risk to the recipients of organs treated with simvastatin; allergy is rare and the amount of drug that would be transferred with the organ would be very small. Currently 15% of organ donors are receiving statin therapy and this is not currently a reason to decline organs. This was presented to a PPIE group and feedback was that the group felt that allowing the recipient to decline an organ from a donor taking part in the study would put recipients at a disadvantage.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

The donor family may take as long as they wish to decide if they consent for their relative to take part in the study; however consent should be provided within accepted time limits for organ donation.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (●) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Any involvement in critical care research prior to recruitment will have ended at the point of death.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

The specialist nurses in organ donation would approach the next-of-kin with NHS approved translators/ telephone translation service to ensure appropriate consent has been given. If it is felt that there is not an adequate level of understanding the patient will not be considered for the study.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

The specialist nurses in organ donation would approach the next-of-kin with NHS approved translators/ telephone translation service to ensure appropriate consent has been given. If it is felt that there is not an adequate level of understanding the patient will not be considered for the study.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

not applicable

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ( ) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ( ) The participant would continue to be included in the study.
- (●) Not applicable – informed consent will not be sought from any participants in this research.
- ( ) Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

All participants will be declared brainstem dead and will not have capacity. Donor families will consent for their relatives to take part in the study.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [ ] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [x] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [ ] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
The SIGNET study will be collecting data from organ donors and recipients.

Donor data is routinely captured by the Specialist Nurses Organ Donation (SNODs) via the DonorPath electronic Register which feeds into the UK Transplant Registry. Additional data on the intervention will be collected and entered onto the MACRO trial database. Research staff will only have access to the MACRO data entry module and will be given individual password controlled MACRO accounts with the appropriate MACRO user role as specified by their task in the study. Donor families will provide consent for the use of their relative's data.

The Recipient outcome data is routinely collected on the UK Transplant Registry. Recipients will not be consented as the intervention will be given to the donor before the recipient is known. When patients join the waiting list to receive an organ transplant, they will be given an information sheet for the trial, which will include a statement about accessing their data. Patients already on the waiting list will be given the information sheet by the transplant coordinator at routine visits or via post/email, this will also be disseminated by organ specific/local patient associations.

The Donor trial ID and the UK Transplant Registry donor ID will be stored in a restricted table on MACRO which the CTU Trial Statisticians do not have access to. This table linking the two donor IDs will be downloaded by the CTU Data Managers and stored in restricted access folders only accessible to the independent Statistician and Data Managers. The folders exist on a secure NHSBT server. Access to computer terminals is restricted to those with a secure login who are employed by NHSBT. There are no paper records.

The UKTR Donor ID will be used by an independent statistician to access and link up donor data and recipient data on the UK Transplant Registry. The independent statistician will provide the Trial Statisticians with pseudoanonymised data, and no UKTR donor or recipient IDs.

Telephone consent for organ donation and study specific consent will be taken if donor families are unable to visit. This is recorded as an audio file and stored online.

Members of NHSBT CTU and the sponsor may have access to donor medical records for monitoring purposes.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Trial specific donor and intervention data will be recorded on the source data form by the SNODs which will be entered onto a dedicated MACRO database by the research teams. The relevant UKTR donor ID will also be entered onto a separate, restricted section of the MACRO database by the research teams. The dedicated MACRO database will be hosted on NHSBT servers and managed by NHSBT CTU. Access to the database is restricted and users will be given an individual password protected log in once they have completed MACRO training. MACRO has an audit trail which maintains a list of all data changes (original data/ amended data / username / date/ time of change).

During the linkage with the UK Transplant Registry, data will be stored in restricted access folders only accessible to the independent Statisticians and Data Managers. The folders exist on a secure NHSBT server. Access to computer terminals is restricted to those with a secure login who are employed by NHSBT.

The source data form will be stored in the site file in a secure office.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Access to the UK Transplant Registry is restricted. An Independent Statistician will link the donor and recipient data and generate new, unique identifiers for each recipient. This pseudonymised data will be downloaded by the Independent Statistician and stored in restricted access folders on the NHSBT server, for the Trial Statisticans. The Trial Statisticians will access the pseudoanonymised data in these folders through SAS (a statistical analysis software) for statistical analysis.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The Specialist Nurses in Organ Donation and the research nurses will document the patients UK Transplant Registry donor ID and enter it onto a secure trial database. Consent from the donor's family will be in place.

An independent statistician will then link the donor with the recipients on the UK Transplant Registry, using this donor ID, and generate new pseudonymised recipient trial IDs. The recipient trial ID will then be used by the trial statisticians for analysis. Recipients will be informed that we will access this data; we will send out a recipient information sheet to patients joining the transplant waiting list. This data is already collected by NHSBT as part of an agreement when someone receives an organ.

Members of NHSBT CTU and the sponsor may have access to donor medical records for monitoring purposes.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Trial specific donor data and relevant UK Transplant Registry donor ID and donor trial ID will be accessed from MACRO and the UK Transplant Registry. The two Donor IDs will be stored in a restricted table on MACRO which the CTU Trial Statisticians do not have access to. This table linking the two donor IDs will be downloaded by the CTU Data Managers and stored in restricted access folders only accessible to the independent Statisticians and Data Managers.

The UKTR Donor IDs will be used by an independent statistician to access and link up donor data and recipient data on the UK Transplant Registry. The independent statistician will provide the Trial Statisticians with pseudoanonymised data, and no UKTR donor or recipient IDs.

This study data will be analysed by trial statisticians (NHSBT) using SAS (Statistical Analysis Software). No data will be shared outside of NHSBT.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
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Work Telephone	01912085851		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
To accommodate the archiving period (5 years).

A44. For how long will you store research data generated by the study?

Years: 5
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

Research data will be stored securely within NHSBT when the trial ends. Electronic data will be kept on password protected databases held on NHSBT servers, accessible only by the research team.

Participating sites will archive site files via their usual arrangements.

NHSBT has archiving arrangements in place with Iron Mountain.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The trial will be registered with the ISRCTN database

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☑ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Data will be captured using a pseudo-anonymised identifier. Any identifiable data will be destroyed after linkage and will not be made available for reporting purposes. Data used for publishing results will be grouped summary data.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
Study participants are confirmed dead and therefore are unable to be informed of the study results. We will engage with our PPI panel to identify appropriate ways to disseminate study results within organ donation and transplant communities.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
UK collaborators with extensive expertise in this area and the Sponsor during the development of the protocol.
It has also been reviewed by the NIHR HTA as part of the funding application to support the trial.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

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	Mrs	Helen	Thomas
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Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Composite of death, cardiac mechanical circulatory support or renal replacement therapy within the first 30 days post heart transplant.

A58. What are the secondary outcome measures?*(if any)*

All organs:
Secondary:
- Organ utilisation rate – the proportion of organs offered that were transplanted, for each organ separately
- 30-day, 3-month and 12-month graft survival
- 30-day, 3-month and 12-month patient survival
- Length of ITU and hospital stay

Cardiac:
Secondary:
- Proportion of recipients requiring cardiac mechanical circulatory support up to 30 days
- Proportion of recipients requiring renal replacement therapy up to 30 days
- 30-day patient survival
- 3- and 12-month number of treated rejection episodes

Kidney:
Primary:
- 12-month estimated glomerular filtration rate, calculated using the CKD-EPI equation

Secondary:
- Proportion of recipients with delayed graft function
- 3- and 12-month number of treated rejection episodes

Liver:
Primary:
- 3-month graft survival
Secondary:
- Number of days ventilated
- Proportion of recipients with individual post-operative complications – hepatic artery thrombosis, portal vein thrombosis, IVC/hepatic vein occlusion, haemorrhage requiring reoperation, biliary tract leaks, biliary tract stricture requiring intervention
- 12-month serum creatinine, bilirubin and alkaline phosphatase

Lung:
Primary:
- 3-month patient survival
Secondary:
- 12-month FEV1 (both absolute and % predicted)

Pancreas and simultaneous pancreas-kidney:
Primary:
- 3-month graft survival
Secondary:
- Proportion of recipients with initial graft function

- 3- and 12-month number of treated rejection episodes
- Causes of graft loss
- Proportion of recipients with pancreatitis up to 3 months

Pancreas islets:
Primary:
- 3-month meal tolerance test stimulated C-peptide

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 2600
Total international sample size (including UK): 2600
Total in European Economic Area:

Further details:
2600 organ donors will be randomised, we will follow up organ outcomes in all transplant recipients

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

The primary outcome is a binary composite outcome in heart transplant recipients, defined as death or the requirement for renal replacement therapy or cardiac mechanical support within the first 30 days. UK data from adult DBD heart transplants between Apr 2016 - Mar 2019 show the event rate of this composite outcome was 51.4%. This study is designed to have 90% power to detect a reduction in this composite outcome to 36.0% (a relative risk of 0.7, informed by Nykanen et al using a 5% level of significance and a two tailed test)

A group sequential design with O'Brien Fleming stopping boundaries has been used to allow for the Data Monitoring Committee to review the primary outcome for evidence of harm, benefit or futility after 238 and 356 heart transplant recipients have been followed-up for 30 days. Allowing for the interim analyses in this way, the required sample size is 474 heart transplants in total. Using data on the proportion of DBD donors which proceed to heart transplant, and a small loss to follow-up rate of 3%, we need to recruit 2600 donors in total.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Allocation will be conducted using Sealed Envelope (a centralised web-based randomisation system).

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The primary outcome in heart transplant recipients will be determined as the proportion of heart transplant recipients who had any of the following events in the first 30 days: death; need for cardiac mechanical circulatory support; or need for renal replacement therapy. The primary outcome will be analysed using a mixed logistic regression model, with adjustment for whether the donor was receiving statin therapy at ICU admission and allowing for correlation in recipient outcomes within transplant centres by including a random effect term for transplant centre. The odds ratio, confidence interval and p-value for the treatment arm term in this mixed effect model will be the primary analysis.

The three elements of the composite primary outcome will also be assessed as individual secondary outcomes. Death within 30 days will be analysed using the same methodology as for the primary outcome, while need for mechanical circulatory support and renal replacement therapy will each be analysed using a competing risks framework with death as the competing risk. Binary outcomes for the other organ groups will also use a mixed logistic regression model or competing risks framework as appropriate. Organ utilisation will be analysed for each organ separately using a logistic regression model with adjustment for use of statin therapy at ICU admission. Three- and

twelve-month patient and graft survival will be presented using Kaplan-Meier plots and analysed using Cox proportional hazards regression. Other outcomes will be presented as mean and standard deviation, or median and interquartile range as appropriate, and analysed using mixed linear regression, Poisson regression, Fine and Gray models or non-parametric methods as appropriate. All organ outcomes will be adjusted for whether the donor was receiving statin therapy at ICU admission and a random effect or frailty term for transplant centre. The kidney transplant outcome analyses will use a cross-classified model to allow for non-nested random effects for transplant centre and donor. Adjustment for other risk factors (published in NHSBT organ specific reports) will be carefully considered for highly prognostic factors for each organ separately and specified in the SAP in advance

The analysis will include a donor dataset, used to assess the proportion of each organ offered for transplantation that is donated and transplanted by trial arm. Analysis of donor outcomes will follow an intention to treat approach. There will also be an analysis dataset for each transplanted organ to compare recipient outcomes by arm. These will be modified intention to treat cohorts since outcome information will be unavailable for donors where that organ was not transplanted. Multi-organ transplants (apart from kidney and pancreas transplants) will also be excluded from the transplant outcome analyses, due to differences in outcomes. Since randomisation occurs at the time of donation, this randomised balance between arms will follow through to each of the organ transplant datasets. While the same donors may appear in more than one transplant dataset, the recipients within each organ transplant dataset will be distinct and hence there will be no adjustment for multiple testing.

Per protocol analyses will be considered secondary analysis and will only be conducted for the primary outcomes for each organ, and for the secondary outcomes of death, cardiac mechanical circulatory support and renal replacement therapy within 30 days for heart transplant recipients. For per protocol analyses, donors randomised in error and donors who do not receive the full dose of simvastatin will be excluded.

For the primary outcome, any missing data for death, cardiac mechanical circulatory support or renal replacement therapy will be imputed to have not had the event. A sensitivity analysis will be conducted with cases with missing primary outcome data excluded. Missing data for whether the donor was on statin therapy at admission to ICU and any other pre-specified risk adjustment factors will be imputed using multiple imputation with full conditional specification. Missing secondary outcome data will not be imputed.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

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	Title	Forename/Initials	Surname
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Post	Professor of Transplantation, University of Cambridge		

Qualifications	
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
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Post Qualifications	Head of Clinical trial statistics

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Title	Forename/Initials	Surname
Mrs	Hilary	Yates

Post	BTRU PPIE group
Qualifications	
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Title	Forename/Initials	Surname
Mrs	Andrea	Fallow

Post	Trustee for the Donor Family Network
Qualifications	
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Post Code	
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Mobile	
Work Email	andrea.j.fallow@gmail.com

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry

Commercial status: Non-Commercial

- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

If Other, please specify:

Contact person

Name of organisation	Newcastle Upon Tyne Hospitals NHS Foundation Trust
Given name	Rebecca
Family name	Johnson
Address	Regulatory Compliance Team, c/o Newcastle Joint Research Office, Level 1, Regent Point, Regent Farm
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Post code	NE3 3HD
Country	
Telephone	0191 282 4454
Fax	
E-mail	tnu-tr.sponsormanagement@nhs.net

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)
Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU

Contact person

Name of organisation	
Given name	
Family name	
Address	
Town/city	
Post code	
Country	
Telephone	
Fax	
E-mail	

A65. Has external funding for the research been secured?

Please tick at least one check box.

- ☑ Funding secured from one or more funders
- ☐ External funding application to one or more funders in progress
- ☐ No application for external funding will be made

What type of research project is this?

- (●) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
Address	University of Southampton, Alpha House, Enterprise Road Southampton
Post Code	SO16 7NS
Telephone	
Fax	
Mobile	
Email	netspostawardsetup@nihr.ac.uk

Funding Application Status: (●) Secured ( ) In progress

Amount: £1,333,914.72

Duration
Years: 5
Months: 9

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
Health Technocolgy Assessment

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (●) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
Ms	Rebecca	Johnson

Organisation	Newcastle Joint Research Office
Address	Regulatory Compliance Team, c/o Newcastle Joint Research Office, Level 1, Regent Point, Regent Farm Road Gosforth, Newcastle Upon Tyne
Post Code	NE3 3HD
Work Email	tnu-tr.sponsormanagement@nhs.net
Telephone	0191 282 4454
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

North East and North Cumbria

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/07/2021
Planned end date: 30/06/2026
Total duration:
Years: 4 Months: 11 Days: 30

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 80

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England 68

☑ NHS organisations in Wales	4
☑ NHS organisations in Scotland	6
☑ HSC organisations in Northern Ireland	2
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	80

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Monitoring will be undertaken but the Clinical Trials Unit, NHS Blood and Transplant.

A monitoring plan will be written and followed. Central monitoring will be undertaken by the Clinical Trials Unit which will include the monitoring of SAEs and consent. The data managers will review the eCRFs for errors and missing data. Calls will be held with site teams to ensure the team are happy with trial progress, the site file is up to date and training is up to date. Site teams will be asked to re-confirm eligibility and intervention details for a proportion of patients as part of these calls.

Data from the UK Transplant Registry will not be monitored by the trial team; the data is checked and validated upon entry as part of standard procedure.

Particular attention will be given to the ongoing training and education of local site staff in the inclusion/exclusion criteria. All designated site staff will receive dedicated training from the research team.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

A formal Data monitoring committee will be convened and will meet twice a year.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

If the safety data indicated significant harm in the treatment group, the DMC can advise on a change to study or early termination.

There will be two interim analyses for harm, benefit or futility after 238 and 356 heart transplants have been followed up for 30 days. These analyses will use O'Brien Fleming stopping boundaries to guide the DMC and are used to preserve an overall 5% significance level.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [ ] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [x] Other insurance or indemnity arrangements will apply (give details below)

Newcastle University insurance for study design

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [ ] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

◯ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◯ Yes ◉ No ◯ Not sure

B. All research other than CTIMPs

In this sub-section, an adult means a person aged 16 or over.

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

Participants in the study are organ donors who have been declared dead by brainstem testing

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

This is an organ donor study, organ donors must be declared dead for donation to proceed and therefore will not be able to consent to the study themselves. The donor family will be approached for consent for organ donation and research consent in line with the Human Tissue Act (2004). Following this, they will be approached for study specific consent for their relative's participation in the study.

B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

An ICU doctor will diagnose the donor brain stem dead according to neurological criteria.

The SNODs will have a conversation with the donor family and have training to do this.

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

○ Yes ◉ No

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◉ Yes ○ No

If Yes, please explain how the research will achieve this:

This research will further inform clinical care and management of organ donors in the future.

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

○ Yes ◉ No

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

Specialist Nurses (SNs) will be having conversations with potential organ donor families. Donor families will be approached for consent for organ donation. If they wish to proceed with this, they will also be asked to consider their loved one participating in the SIGNET study. If the donor family agrees, consent for organ donation and the SIGNET study will be taken. As part of this conversation they will be asked to consider the wishes of their relative.

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

○ Yes ◉ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.

As part of standard procedure for organ donation the donor family must provide consent for research in organ donation even if consent for organ donation is deemed. If the Specialist Nurses cannot contact a relative then the participant will not be included in the study.

Question B7-1 applies to any participants recruited in Scotland.

B7-1. What arrangements will be made to identify and seek consent from a guardian or welfare attorney or, if there is no such person, from the participant's nearest relative?

Specialist Nurses (SNs) will be having conversations with potential organ donor families. Donor families will be approached for authorisation for organ donation. If they wish to proceed with this, they will also be asked to consider their loved one participating in the SIGNET study. If the donor family agrees, authorisation for organ donation and the SIGNET study will be taken. As part of this conversation they will be asked to consider the wishes of their relative.

Please enclose a copy of the written information to be provided and the consent form to be used. The information sheet should provide information about the research similar to that which might be given to participants able to consent for themselves.

Questions B7-2 and B8-2 apply to any participants recruited in Northern Ireland.

B7-2. What arrangements will be made to consult a close relative or close friend able to advise on the inclusion of the participant and on their likely wishes?

Specialist Nurses (SNs) will be having conversations with potential organ donor families. Donor families will be approached for consent for organ donation. If they wish to proceed with this, they will also be asked to consider their loved one participating in the SIGNET study. If the donor family agrees, consent for organ donation and the SIGNET study will be taken. As part of this conversation they will be asked to consider the wishes of their relative.

B8-2. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to consult with a close relative or close friend?

○ Yes ◉ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants.

The donor family must consent to research in organ donation, including study specific consent, for the patient to be enrolled into the study. If the Specialist nurses are not able to contact a relative, the patient will not be included in the study.

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

The organ donor will only be entered into the study if the donor family has consented to their relative's participation in the study. As part of standard procedure the Specialist nurses will be contacting potential organ donor relatives and having conversations about organ donation. This may occur face to face in Intensive Care Units, Emergency Departments or by video/telephone if the family are unable to be present in person.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

The organ donor participating in the study will not be provided with any information about the study.

The Specialist Nurses will discuss the study with the donor family and go through the donor family information sheet. They will also offer to post the information sheet and inform them that they can find a copy on the study website. The family will be asked to consider their relative's wishes. This conversation will be had with the specialist nurses who are experts in consent and organ donation.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

No. Organ donors will be declared brainstem dead.

B12-1. What will be the criteria for withdrawal of participants?

Donor families have the right to withdraw their relative at any point in the study, without giving a reason, and without their relative's care or legal right's being affected.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

The Specialist nurses will discuss organ donation and the study with the donor family. If it is felt that the donor would object to organ donation or participation in the study then the donor will not be included in the study.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

If the patient has opted out of organ donation they will not be considered for organ donor and will therefore not be enrolled in the study.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Robert Parker ROBERT.PARKER@liverpoolft.nhs.uk
	Organisation name	LIVERPOOL UNIVERSITY HOSPITALS NHS FOUNDATION TRUST		
	Address	ROYAL LIVERPOOL UNIVERSITY HOSPITAL PRESCOT STREET LIVERPOOL		
	Post Code	L7 8XP		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Robert Ferguson Robert.Ferguson@YORK.NHS.UK
	Organisation name	YORK TEACHING HOSPITAL NHS FOUNDATION TRUST		
	Address	YORK HOSPITAL WIGGINTON ROAD YORK		
	Post Code	YO31 8HE		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...) Country	Ahilanadan Dushianthan Ahilanadan.Dushianthan@uhs.nhs.uk
	Organisation name	UNIVERSITY HOSPITAL SOUTHAMPTON NHS FOUNDATION TRUST		
	Address	SOUTHAMPTON GENERAL HOSPITAL		

	TREMONA ROAD
	SOUTHAMPTON
Post Code	SO16 6YD
Country	ENGLAND

IN4

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Ascanio
Middle name	
Family name	Tridente
Email	Ascanio.Tridente@sthk.nhs.uk
Qualification (MD...)	
Country	

Organisation name	ST HELENS AND KNOWSLEY TEACHING HOSPITALS NHS TRUST
Address	WHISTON HOSPITAL
	WARRINGTON ROAD
	PRESCOT
Post Code	L35 5DR
Country	ENGLAND

IN5

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Harish
Middle name	
Family name	Lad
Email	Harish.Lad@hey.nhs.uk
Qualification (MD...)	
Country	

Organisation name	HULL UNIVERSITY TEACHING HOSPITALS NHS TRUST
Address	HULL ROYAL INFIRMARY
	ANLABY ROAD
	HULL
Post Code	HU3 2JZ
Country	ENGLAND

IN6

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Dominic
Middle name	
Family name	Trainor
Email	dominic.trainor@belfasttrust.hscni.net
Qualification (MD...)	
Country	

Organisation name	Belfast Health & Social Care Trust
Address	Knockbracken Healthcare Park
	Saintfield Road

	BELFAST COUNTY ANTRIM
Post Code	BT8 8BH
Country	NORTHERN IRELAND

IN7

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	David
Middle name	
Family name	Moir
Email	david.moir3@nhs.net
Qualification (MD...)	
Country	

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL
	BECKETT STREET
	LEEDS
Post Code	LS9 7TF
Country	ENGLAND

IN8

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	Mark
Middle name	
Family name	Dunn
Email	Mark.Dunn@nhslothian.scot.nhs.uk
Qualification (MD...)	
Country	

Organisation name	NHS Lothian
Address	Waverley Gate
	2-4 Waterloo Place
	Edinburgh Scotland
Post Code	EH1 3EG
Country	SCOTLAND

IN9

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	Dan
Middle name	
Family name	Harvey
Email	Dan.Harvey@nhsbt.nhs.uk
Qualification (MD...)	
Country	

Organisation name	NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST
Address	TRUST HEADQUARTERS
	QUEENS MEDICAL CENTRE
	DERBY ROAD NOTTINGHAM
Post Code	NG7 2UH
Country	ENGLAND

IN10

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	BETSI CADWALADR UNIVERSITY LHB
Address	EXECUTIVE OFFICES, YSBYTY GWYNEDD PENRHOSGARNEDD BANGOR GWYNEDD
Post Code	LL57 2PW
Country	WALES

Forename	David
Middle name	
Family name	Southern
Email	davidsouthern@doctors.org.uk
Qualification (MD...)	
Country	

IN11

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address	FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON NEWCASTLE UPON TYNE
Post Code	NE7 7DN
Country	ENGLAND

Forename	Alan
Middle name	
Family name	Sweenie
Email	alan.sweenie@nhs.net
Qualification (MD...)	
Country	

IN12

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NORTH BRISTOL NHS TRUST
Address	SOUTHMEAD HOSPITAL SOUTHMEAD ROAD WESTBURY-ON-TRYM BRISTOL
Post Code	BS10 5NB
Country	ENGLAND

Forename	Ian
Middle name	
Family name	Thomas
Email	Ian.Thomas@nbt.nhs.uk
Qualification (MD...)	
Country	

IN15

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD
Post Code	S5 7AU
Country	ENGLAND

Forename	Jim
Middle name	
Family name	Hoyle
Email	jim.hoyle@nhs.net
Qualification (MD...)	
Country	

IN16

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	EAST LANCASHIRE HOSPITALS NHS TRUST
Address	ROYAL BLACKBURN HOSPITAL HASLINGDEN ROAD BLACKBURN
Post Code	BB2 3HH
Country	ENGLAND

Forename	Carole
Middle name	
Family name	Pilkington
Email	Carole.Pilkington@elht.nhs.uk
Qualification (MD...)	
Country	

IN17

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	LANCASHIRE TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	ROYAL PRESTON HOSPITAL SHAROE GREEN LANE FULWOOD PRESTON
Post Code	PR2 9HT
Country	ENGLAND

Forename	Catherine
Middle name	
Family name	Roberts
Email	Catherine.Roberts@lthtr.nhs.uk
Qualification (MD...)	
Country	

IN18

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	COUNTY DURHAM AND DARLINGTON NHS FOUNDATION TRUST
Address	DARLINGTON MEMORIAL HOSPITAL HOLLYHURST ROAD DARLINGTON
Post Code	DL3 6HX
Country	ENGLAND

Forename	Sheshank
Middle name	
Family name	Jajur
Email	sheshank.jajur@nhs.net
Qualification (MD...)	
Country	

IN19

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	PORTSMOUTH HOSPITALS UNIVERSITY NATIONAL HEALTH SERVICE TRUST
Address	QUEEN ALEXANDRA HOSPITAL SOUTHWICK HILL ROAD COSHAM PORTSMOUTH
Post Code	PO6 3LY
Country	ENGLAND

Forename	Richard
Middle name	
Family name	Clinton
Email	Richard.Clinton@porthosp.nhs.uk
Qualification (MD...)	
Country	

IN20

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	NORFOLK AND NORWICH UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	COLNEY LANE COLNEY NORWICH
Post Code	NR4 7UY
Country	ENGLAND

Forename	Deborah
Middle name	
Family name	Easby
Email	Deborah.easby@nnuh.nhs.uk
Qualification (MD...)	
Country	

IN21

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	WEST HERTFORDSHIRE HOSPITALS NHS TRUST
Address	TRUST OFFICES WATFORD GENERAL HOSPITAL VICARAGE ROAD WATFORD
Post Code	WD18 0HB
Country	ENGLAND

Forename	Valerie
Middle name	
Family name	Page
Email	valerie.page2@nhs.net
Qualification (MD...)	
Country	

IN22

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	BEDFORDSHIRE HOSPITALS NHS FOUNDATION TRUST
Address	LEWSEY ROAD LUTON
Post Code	LU4 0DZ
Country	ENGLAND

Forename	Stephen
Middle name	
Family name	Brosnan
Email	Stephen.Brosnan@ldh.nhs.uk
Qualification (MD...)	
Country	

IN23

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS BRISTOL AND WESTON NHS FOUNDATION TRUST
Address	TRUST HEADQUARTERS MARLBOROUGH STREET BRISTOL
Post Code	BS1 3NU
Country	ENGLAND

Forename	Fran
Middle name	
Family name	O'Higgins
Email	Fran.OHiggins@uhbw.nhs.uk
Qualification (MD...)	
Country	

IN24

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	NORTHUMBRIA HEALTHCARE NHS FOUNDATION TRUST
Address	NORTH TYNESIDE GENERAL HOSPITAL RAKE LANE NORTH SHIELDS
Post Code	NE29 8NH
Country	ENGLAND

Forename	Bryan
Middle name	
Family name	Yates
Email	Bryan.Yates@northumbria-healthcare.nhs.uk
Qualification (MD...)	
Country	

IN25

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	MEDWAY NHS FOUNDATION TRUST
Address	MEDWAY MARITIME HOSPITAL WINDMILL ROAD GILLINGHAM
Post Code	ME7 5NY
Country	ENGLAND

Forename	Paul
Middle name	
Family name	Hayden
Email	paulhayden@nhs.net
Qualification (MD...)	
Country	

IN26

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST
Address	TRUST HEADQUARTERS ACRE STREET LINDLEY HUDDERSFIELD
Post Code	HD3 3EA
Country	ENGLAND

Forename	Paul
Middle name	
Family name	Knight
Email	paul.knight@cht.nhs.uk
Qualification (MD...)	
Country	

IN27

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	LONDON NORTH WEST UNIVERSITY HEALTHCARE NHS TRUST
Address	NORTHWICK PARK HOSPITAL WATFORD ROAD HARROW
Post Code	HA1 3UJ
Country	ENGLAND

Forename	Michael
Middle name	
Family name	Dean
Email	mdean1@nhs.net
Qualification (MD...)	
Country	

IN28

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	THE WALTON CENTRE NHS FOUNDATION TRUST
Address	LOWER LANE LIVERPOOL
Post Code	L9 7LJ
Country	ENGLAND

Forename	Gerald
Middle name	
Family name	Smith
Email	Gerald.Smith@thewaltoncentre.nhs.uk
Qualification (MD...)	
Country	

IN29

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	ST GEORGE'S HOSPITAL BLACKSHAW ROAD TOOTING LONDON
Post Code	SW17 0QT
Country	ENGLAND

Forename	Argyro
Middle name	
Family name	Zoumprouli
Email	azoumprouli@nhs.net
Qualification (MD...)	
Country	

IN30

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	BOLTON NHS FOUNDATION TRUST
Address	THE ROYAL BOLTON HOSPITAL MINERVA ROAD FARNWORTH BOLTON
Post Code	BL4 0JR
Country	ENGLAND

Forename	Hannah
Middle name	
Family name	Durrant
Email	Hannah.Durrant@boltonft.nhs.uk
Qualification (MD...)	
Country	

IN31

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	ANEURIN BEVAN UNIVERSITY LHB
Address	HEADQUARTERS - ST CADOC'S HOSPITAL LODGE ROAD CAERLEON NEWPORT GWENT
Post Code	NP18 3XQ
Country	WALES

Forename	Matthew
Middle name	
Family name	Carwardine
Email	Matthew.Carwardine@wales.nhs.uk
Qualification (MD...)	
Country	

IN32

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	BLACKPOOL TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	VICTORIA HOSPITAL WHINNEY HEYS ROAD BLACKPOOL
Post Code	FY3 8NR
Country	ENGLAND

Forename	Jason
Middle name	
Family name	Cupitt
Email	dr.cupitt@nhs.net
Qualification (MD...)	
Country	

IN33

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	SOUTH TEES HOSPITALS NHS FOUNDATION TRUST
Address	JAMES COOK UNIVERSITY HOSPITAL MARTON ROAD MIDDLESBROUGH
Post Code	TS4 3BW
Country	ENGLAND

Forename	Steven
Middle name	
Family name	Williams
Email	steven.williams4@nhs.net
Qualification (MD...)	
Country	

IN34

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	FRIMLEY HEALTH NHS FOUNDATION TRUST
Address	PORTSMOUTH ROAD FRIMLEY CAMBERLEY
Post Code	GU16 7UJ
Country	ENGLAND

Forename	Elaine
Middle name	
Family name	Hipwell
Email	
Qualification (MD...)	
Country	

IN35

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	SALFORD ROYAL NHS FOUNDATION TRUST
Address	SALFORD ROYAL STOTT LANE SALFORD GREATER MANCHESTER
Post Code	M6 8HD
Country	ENGLAND

Forename	Chris
Middle name	
Family name	Booth
Email	Chris.Booth@srft.nhs.uk
Qualification (MD...)	
Country	

IN36

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST
Address	THE BAYS ST MARYS HOSPITAL SOUTH WHARF ROAD LONDON
Post Code	W2 1BL
Country	ENGLAND

Forename	Richard
Middle name	
Family name	Stumpfle
Email	richard.stumpfle@nhs.net
Qualification (MD...)	
Country	

IN37

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	CWM TAF MORGANNWG UNIVERSITY LOCAL HEALTH BOARD
Address	DEWI SANT HOSPITAL ALBERT ROAD PONTYPRIDD MID GLAMORGAN
Post Code	CF37 1LB
Country	WALES

Forename	Jayaprakash
Middle name	
Family name	Singh
Email	Jayaprakash.Singh@wales.nhs.uk
Qualification (MD...)	
Country	

IN38

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	Western Health & Social Care Trust
Address	MDEC Building Glenshane Road DERRY COUNTY LONDONDERRY
Post Code	BT47 6SB
Country	NORTHERN IRELAND

Forename	Adrian
Middle name	
Family name	Donnelly
Email	adrian.donnelly@westerntrust.hscni.net
Qualification (MD...)	
Country	

IN39

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	EAST KENT HOSPITALS UNIVERSITY NHS FOUNDATION TRUST
Address	KENT & CANTERBURY HOSPITAL ETHELBERT ROAD CANTERBURY
Post Code	CT1 3NG
Country	ENGLAND

Forename	Christine
Middle name	
Family name	Vimalanathan
Email	christine.vimalanathan1@nhs.net
Qualification (MD...)	
Country	

IN40

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	COUNTESS OF CHESTER HOSPITAL NHS FOUNDATION TRUST
Address	COUNTESS OF CHESTER HEALTH PARK LIVERPOOL ROAD CHESTER
Post Code	CH2 1UL
Country	ENGLAND

Forename	Kathryn
Middle name	
Family name	Tizard
Email	k.tizard@nhs.net
Qualification (MD...)	
Country	

IN41

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	EAST SUSSEX HEALTHCARE NHS TRUST
Address	ST ANNES HOUSE 729 THE RIDGE ST. LEONARDS-ON-SEA
Post Code	TN37 7PT
Country	ENGLAND

Forename	Sinan
Middle name	
Family name	Bahlool
Email	sinan.bahlool@nhs.net
Qualification (MD...)	
Country	

IN42

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	CARDIFF & VALE UNIVERSITY LHB
Address	WOODLAND HOUSE MAES-Y-COED ROAD CARDIFF
Post Code	CF14 4HH
Country	WALES

Forename	Matt
Middle name	
Family name	Wise
Email	mattwise@doctors.org.uk
Qualification (MD...)	
Country	

IN43

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	EAST SUFFOLK AND NORTH ESSEX NHS FOUNDATION TRUST
Address	COLCHESTER DIST GENERAL HOSPITAL TURNER ROAD COLCHESTER
Post Code	CO4 5JL
Country	ENGLAND

Forename	Kate
Middle name	
Family name	Turner
Email	kate.turner@esneft.nhs.uk
Qualification (MD...)	
Country	

IN44

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS PLYMOUTH NHS TRUST
Address	DERRIFORD HOSPITAL DERRIFORD ROAD DERRIFORD PLYMOUTH
Post Code	PL6 8DH
Country	ENGLAND

Forename	Colin
Middle name	
Family name	Bigham
Email	c.bigham@nhs.net
Qualification (MD...)	
Country	

IN45

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST
Address	WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY
Post Code	CV2 2DX
Country	ENGLAND

Forename	Robert
Middle name	
Family name	Green
Email	Robert.Green@uhcw.nhs.uk
Qualification (MD...)	
Country	

IN46

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NHS Greater Glasgow and Clyde
Address	J B Russell House Gartnavel Royal Hospital 1055 Great Western Road Glasgow Glasgow Scotland
Post Code	G12 0XH
Country	SCOTLAND

Forename	Kathryn
Middle name	
Family name	Puxty
Email	Kathryn.Puxty@ggc.scot.nhs.uk
Qualification (MD...)	
Country	

IN47

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST
Address	DENMARK HILL LONDON
Post Code	SE5 9RS
Country	ENGLAND

Forename	Shahana
Middle name	
Family name	Uddin
Email	shahanauddin@nhs .net
Qualification (MD...)	
Country	

IN48

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS DORSET NHS FOUNDATION TRUST
Address	MANAGEMENT OFFICES POOLE HOSPITAL LONGFLEET ROAD POOLE
Post Code	BH15 2JB
Country	ENGLAND

Forename	Michelle
Middle name	
Family name	Scott
Email	Michelle.Scott@uhd.nhs.uk
Qualification (MD...)	
Country	

IN49

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	MANCHESTER UNIVERSITY NHS FOUNDATION TRUST
Address	COBBETT HOUSE OXFORD ROAD MANCHESTER
Post Code	M13 9WL
Country	ENGLAND

Forename	Malachy
Middle name	
Family name	Columb
Email	malachy.columb@mft.nhs.uk
Qualification (MD...)	
Country	

IN50

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS OF NORTH MIDLANDS NHS TRUST
Address	NEWCASTLE ROAD STOKE-ON-TRENT
Post Code	ST4 6QG
Country	ENGLAND

Forename	Nageswar
Middle name	
Family name	Bandla
Email	Nageswar.Bandla@uhnm.nhs.uk
Qualification (MD...)	
Country	

IN51

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	WORCESTERSHIRE ACUTE HOSPITALS NHS TRUST
Address	WORCESTERSHIRE ROYAL HOSPITAL CHARLES HASTINGS WAY WORCESTER
Post Code	WR5 1DD
Country	ENGLAND

Forename	Steven
Middle name	
Family name	Haynes
Email	Steven.haynes@nhs.net
Qualification (MD...)	
Country	

IN52

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	THE ROYAL WOLVERHAMPTON NHS TRUST
Address	NEW CROSS HOSPITAL WOLVERHAMPTON ROAD HEATH TOWN WOLVERHAMPTON
Post Code	WV10 0QP
Country	ENGLAND

Forename	Shameer
Middle name	
Family name	Gopal
Email	shameer.gopal@nhs.net
Qualification (MD...)	
Country	

IN53

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	ROYAL UNITED HOSPITALS BATH NHS FOUNDATION TRUST
Address	COMBE PARK BATH
Post Code	BA1 3NG
Country	ENGLAND

Forename	Jerry
Middle name	
Family name	Nolan
Email	jerry.nolan@nhs.net
Qualification (MD...)	
Country	

IN54

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	GREAT WESTERN HOSPITALS NHS FOUNDATION TRUST
Address	GREAT WESTERN HOSPITAL MARLBOROUGH ROAD SWINDON
Post Code	SN3 6BB
Country	ENGLAND

Forename	Malcolm
Middle name	
Family name	Watters
Email	malcolm.watters@nhs.net
Qualification (MD...)	
Country	

IN55

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NHS Tayside
Address	Kings Croos Clepington Road Dundee Scotland
Post Code	DD3 8EA
Country	SCOTLAND

Forename	Pauline
Middle name	
Family name	Austin
Email	Pauline.Austin@nhs.scot
Qualification (MD...)	
Country	

IN56

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	ROYAL FREE LONDON NHS FOUNDATION TRUST
Address	ROYAL FREE HOSPITAL POND STREET LONDON
Post Code	NW3 2QG
Country	ENGLAND

Forename	Kulwant
Middle name	
Family name	dhadwal
Email	kulwant.dhadwal@nhs.net
Qualification (MD...)	
Country	

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor John Dark on 15/06/2021 16:46.

Job Title/Post:	Professor of Cardiothoracic Surgery
Organisation:	Newcastle University
Email:	j.h.dark@ncl.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Miss Rebecca Johnson on 15/06/2021 14:07.

Job Title/Post:	Deputy Regulatory Compliance Manager
Organisation:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Email:	rebecca.johnson4@nhs.net