The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

Statins for Improving orGaN outcomE in Transplantation

A multi-centre, single-blind prospective, group sequential, randomised controlled trial to evaluate the benefits of a single dose of Simvastatin given to potential organ donors declared dead by neurological criteria on outcomes in organ recipients

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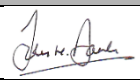
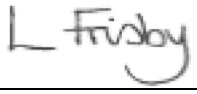
Protocol Development Group:

Name	Affiliation	Authors' Contributions
John Dark	University of Newcastle upon Tyne	*JD and DH conceived of the study. JD, DH, NS, CW, AF, JS, GM, DM, HY and Afa initiated the study design and AD, CF and AE helped with implementation. JD is the grant holder. HT provided statistical expertise in clinical trial design and will oversee the primary statistical analysis. All authors contributed to refinement of the study protocol and approved* the final version
Dan Harvey	Nottingham University Hospitals	
Claire Foley	NHSBT	
Alison Deary	NHSBT	
Helen Thomas	NHSBT	
Amy Evans	NHSBT	
Neil Sheerin	University of Newcastle upon Tyne	
Christopher Watson	University of Cambridge	
Andrew Fisher	University of Newcastle upon Tyne	

James Shaw	University of Newcastle upon Tyne	
Guy MacGowan	University of Newcastle upon Tyne	
Danny McAuley	The Queen's University of Belfast	
Hilary Yates	PPIE UK based	
Andrea Fallow	PPIE UK based	

Approved by:

Name	Role	Signature	Date
John Dark	Co-Chief Investigator		13/12/2022
Dan Harvey	Co-Chief Investigator		13/12/2022
Helen Thomas	Head of Clinical Trial Statistics		12/12/2022
Laura Frisby	Sponsor Representative		13/12/2022

SUPPORTED BY NIHR | National Institute for Health Research
UKODTRN organ donation and transplantation research network
NHS Blood and Transplant

General Information

This document was constructed using the National Health Service Blood and Transplant Clinical Trials Unit (NHSBT CTU) Protocol Template FRM4898 Version 1.0, which is based on the MRC CTU Protocol template Version 4.0 and the SPIRIT guidelines 2013.(1, 2) It describes the SIGNET trial, coordinated by the NHSBT CTU and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the Trial Manager to confirm they have the most up to date version.

Compliance

SIGNET has been confirmed as a non-CTIMP study by the MHRA and therefore it will be conducted in compliance with the approved protocol, the Declaration of Helsinki [2013] the Principles of Good Clinical Practice (GCP), the UK Data Protection Act, the National Health Service UK Policy Framework for Health and Social Care Research and any other applicable national regulations.

Sponsor

The Newcastle Upon Tyne Hospitals NHS Foundation Trust is the primary trial Sponsor and has delegated responsibility for the overall management of the SIGNET trial to the NHSBT CTU. Queries relating to the sponsorship of the trial should be addressed to the Regulatory Compliance Team, c/o Newcastle Joint Research Office, Level 1, Regent Point, Regent Farm Road, Gosforth, Newcastle Upon Tyne NE3 3HD email tnu-tr.sponsormanagement@nhs.net or via the trial team.

Funding

The SIGNET trial has been funded by an award from the NIHR via the Health Technology Assessment Programme, award ref: NIHR131124.

Authorisations and Approvals

This trial was approved by the National Institute of Health Research and is, therefore, part of the Critical Care research network portfolio.

Trial Registration

This study is registered with the ISRCTN Clinical Trials Register.

Trial Administration

Please direct all enquiries to the Trial Manager in the first instance. Clinical queries will be passed to the Chief Investigator via the Trial Manager.

CTU Details

NHSBT CTU	Administration Office:	01223 588088
NHS Blood and Transplant	Email:	SIGNET@nhsbt.nhs.uk
Long Road		
Cambridge		
CB2 0PT		

Coordinating CTU Staff Details

Trial Manager	Amy Evans	Tel:	01223 588016
		Email:	amy.evans@nhsbt.nhs.uk
Data Manager	Roshni Paul	Tel:	07440 400262
		Email:	Roshni.Paul@nhsbt.nhs.uk
Statistician	Daphne Kounali	Email:	daphne.kounali@nhsbt.nhs.uk
Clinical Operations Manager	Claire Rourke	Tel:	07385 964361
		Email:	claire.rourke2@nhsbt.nhs.uk

Chief Investigator

Professor	John Dark	Tel:	01912085851
Dept of	Translational and Clinical Research Institute	Email:	j.h.dark@ncl.ac.uk
Hospital	University of Newcastle upon Tyne		
Address Line 1			
Address Line 2			
City	Newcastle		
County, Post Code			
Country	UK		
Co-Chief Investigator			
Dr	Dan Harvey	Tel:	07815138205
	Queens Medical Centre, Nottingham University Hospitals NHS Trust,	Email:	Dan.Harvey@nhsbt.nhs.uk

	Derby Road, Nottingham NG7 2UH		

Co-Investigators

Professor Christopher Watson	Professor of Transplantation, University of Cambridge
Professor Andrew Fisher	Professor of Respiratory Transplant Medicine, University of Newcastle upon Tyne
Professor Neil Sheerin	Professor of Nephrology, University of Newcastle upon Tyne
Professor Guy MacGowan	Honorary Professor of Heart Failure, University of Newcastle upon Tyne
Professor James Shaw	Clinical Professor/Consultant, University of Newcastle upon Tyne
Professor Danny McAuley	Clinical Professor, Professor of Intensive Care, The Queen's University of Belfast
Sophie Vickery	Head of Operations, NHSBT
Helen Thomas	Head of Clinical Trial Statistics, NHSBT
Hilary Yates	PPIE
Andrea Fallow	PPIE

For full details of Trial Committees, please refer to Section 1717.3

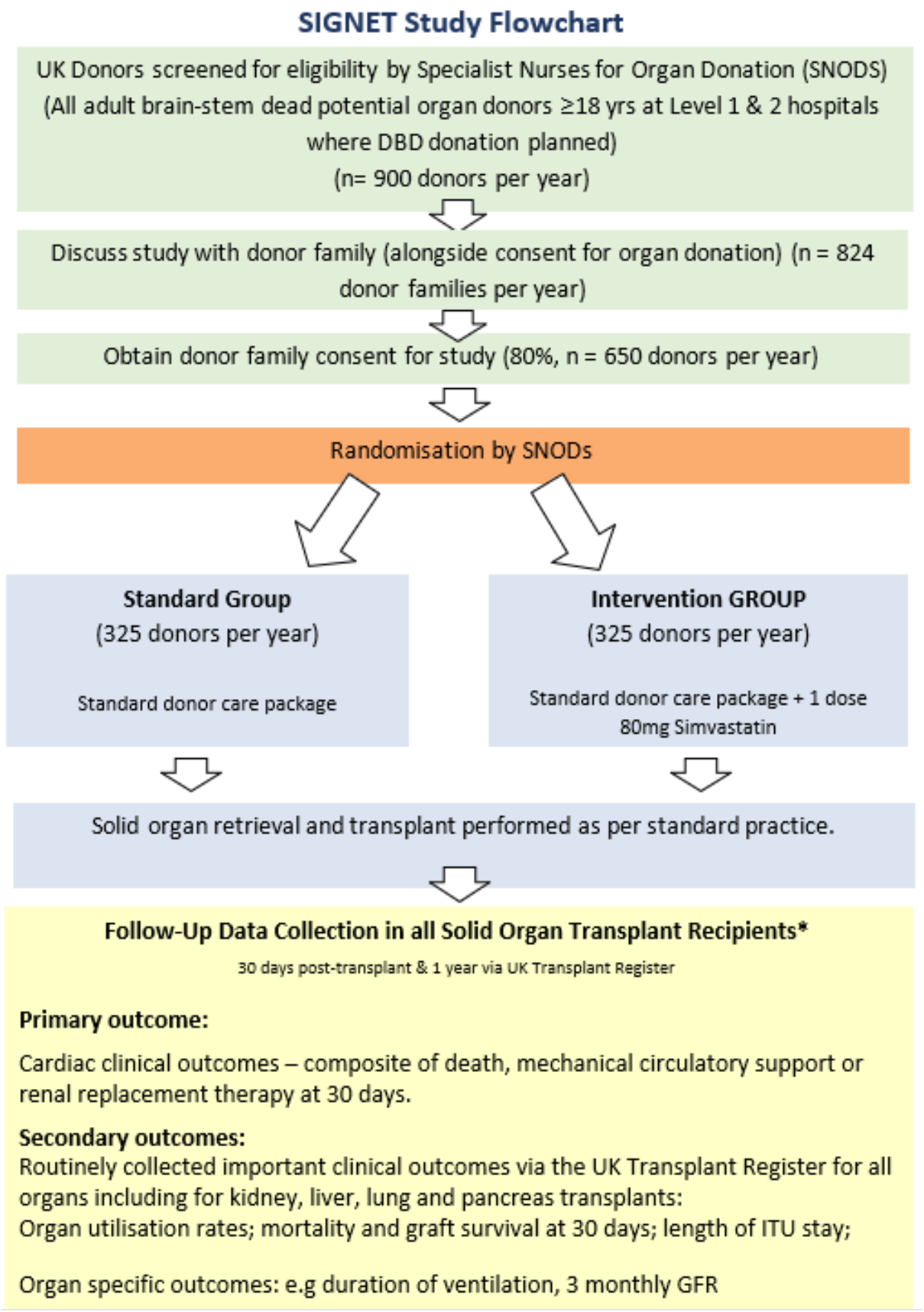
Study Synopsis

Scientific title of clinical study	Statins for improving organ outcome in transplantation A multi-centre, single blind, prospective randomised controlled trial to evaluate the benefits of a single dose of Simvastatin given to potential organ donors declared dead by neurological criteria on outcomes in organ recipients
Public title of clinical study	Statins for Improving Organ Outcome in Transplantation
Protocol Short Title/Acronym	SIGNET
Protocol Version and Date	2.0 7th December 2022
Primary Sponsor	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Funder	NIHR Health Technology Assessment Programme
Primary Clinical Trials Registry number	This study is registered with the ISRCTN Clinical Trials Register, ISRCTN11440354.
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.
Health Condition(s) or Problem(s) Studied	Inflammatory mediated organ damage in organs offered for donation from potential organ donors confirmed dead by neurological criteria.
Key inclusion and exclusion criteria	Adult patients confirmed dead using neurological criteria Consent for organ donation in place, as defined by the Human Tissue Act and accompanying legislation and Codes of Practice Within a recruiting ICU Study specific consent from donor family
Setting	ICUs within Level 1 or 2 donating hospitals: defined as mean number of donors per year > 6 by NHS Blood and Transplant. Some level 3 Trusts will be selected based on donor numbers.
Interventions to be compared	Simvastatin 80 mg administered by NG tube in addition to protocolised standard care versus protocolised standard care
Study hypothesis	Does treatment of potential organ donors with simvastatin during protocolised care after diagnosis of death using neurological criteria improve outcomes in patients undergoing transplantation? To determine if simvastatin given to the donor confers an improvement in clinical outcomes in cardiac transplant recipients To determine if simvastatin in the donor has a beneficial effect on other solid organs, particularly the liver and lung To determine if simvastatin is safe in all organ transplant recipients (cardiac, renal, lung, liver and pancreas)

Primary outcome measure(s)	Composite of death, mechanical circulatory support or renal replacement therapy within the first 30 days post heart transplant
Key Secondary outcome measures	Organ utilisation rate for all organs 30-day, 3-month and 12-month graft survival for all organs 30-day, 3-month and 12-month patient survival for all organs Length of ITU and hospital stay Other organ specific outcomes described in section 7.2
Duration of Study	Duration of recruitment: 48 months Duration of intervention (donor): Single dose Duration of follow-up for each participant (recipient): 12 Months Trial Duration: 60 months
Countries of recruitment	United Kingdom including England, Scotland, Wales and Northern Ireland
Target Sample Size	1300 donors per arm, 2600 in total.
Date of first enrolment	Anticipated July 2021
Ancillary Studies/sub-studies	Separate studies investigating the mechanistic basis of statin action in DBD donors are planned
Contact Details for Public Queries	Amy Evans SIGNET@nhsbt.nhs.uk
Contact Details for Scientific Queries	Prof John Dark john.dark@newcastle.ac.uk Dr Dan Harvey Dan.harvey@nhsbt.nhs.uk
Lay Summary of Study	We wish to investigate whether giving deceased organ donors a single dose of the drug Simvastatin, a very inexpensive and safe drug, is beneficial for transplant recipients. Background: 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. Clinical Problem: 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. Trial Design and Methods to be used We plan to enrol 650 adult brain dead donors across the UK per year in a randomised controlled trial. Half the donors will receive the drug (in addition to their standard donor care), compared to the other half of donors who will receive standard care only. The drug is given through a tube running into the stomach, already present in 80% of donors, but required to be placed in the other 20%. The drug will be given as soon as the donor family have consented to both organ donation and involvement of their loved one in research. Half of all the recipients will receive a heart from a donor given the drug. We will follow the results of transplant, focussing on the heart recipients, but for all those receiving these organs, comparing what happens in those who received the drug-treated organs, and those who did not. This is done with data already collected in the national transplant database. No extra data or blood samples will be needed from recipients.

Study Schema



Contents

Abbreviations and Glossary

AE	Adverse event
AR	Adverse reaction
BSA	Body Surface Area
CF	Consent form
CI	Chief Investigator
CLOD	Clinical Lead for Organ Donation
CLRN	Comprehensive Local Research Network
COM	Clinical Operations Manager
eCRF	Electronic Case Report Form
CTU	NHSBT Clinical Trials Unit
DBD	Donation after Brainstem Death
DCD	Donation after Circulatory Death
DCF	Data Clarification Form
DH	Department of Health
DM	Data Manager
DMC	Data Monitoring Committee
ERC	Endpoint Review Committee
GCP	Good Clinical Practice
GP	General Practitioner
HE	Health Economics
IB	Investigator's Brochure
ICU	Intensive Care Unit
ISRCTN	International standard randomised controlled trial number
IRAS	Integrated Research Application System
ITU	Intensive Therapy Unit
MHRA	Medicines and Healthcare Regulatory Authority
MRC	Medical Research Council
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
NIHR-CSP	National Institute for Health Research Coordinated System for gaining NHS Permission
NRES	National Research Ethics Service
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
RN	Research Nurse
SAE	Serious adverse event
SNOD	Specialist Nurse for Organ Donation
SOP	Standard operating procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Background

1.1 Introduction

What is the problem being addressed?

Despite a decade long increase in the number of deceased organ donors, and the likely benefits of deemed consent legislation, there is a considerable shortfall of organs available for transplantation. The total number of transplants fell in 2018-19; 400 patients died waiting and 777 were removed from the waiting list (ultimately leading to death) in that year. There was an 8% reduction in the number of heart transplants (1).
Many offered organs, 75% for the heart and lung, are turned down for transplantation because of pre-existing disease or temporary brain-stem death related dysfunction. Despite this highly selective approach, more than 30% of recipients still required short-term mechanical cardiac support, reflecting donor heart dysfunction. Almost all the early deaths, 18% mortality in the first year, are in this group (2).

Successful organ transplantation has substantial benefits for all recipients, with dramatically improved survival, improved quality of life and reduced costs. Median survival after cardiac transplantation is 12 years in the UK, with excellent quality of life (3). The health economic advantages are greatest for the kidney, with a saving of c£30k for every year free of dialysis, and an 85% 5 year graft survival (4,5). Similar benefits have been reported for cardiac and pulmonary transplantation.

Strategies to improve organ function in the donor might increase organ utilisation (number of transplants) but have potentially the greatest impact in the recipient (organ transplant function). Post-transplant organ dysfunction in the recipient, be it the need for mechanical support for the heart, prolonged ventilation for the lung or delayed graft function and need for renal dialysis in the kidney, have huge short-term morbidity, mortality and cost, and for every organ reduces long term survival (6,7). PPIE input to development of the study emphasised the value of reducing early post-transplant morbidity.

The families of organ donors tell us that improving the quality of donated organs maximises the gift of donation and is a priority for them, unsurprisingly this is also a priority for transplant recipients.

1.2 Summary of existing knowledge

The pathophysiology of brain-stem death, with a catecholamine storm followed by a massive release of pro-inflammatory cytokines, has been well described in both animal models and the human setting (8,9). The pro-inflammatory state in the donor is reflected in events in the recipient. For instance, levels of IL6 and TNFa, in both serum and in terms of RNA expression in cardiac tissue, predicted which donor hearts were too dysfunctional for acceptability for transplantation (10). Levels of the pro-inflammatory cytokine IL8 in broncho-alveolar lavage of lung donors predicted early impaired gas exchange, longer duration of ventilation and survival in recipients (11). The same linkage between markers in the donor, in this case IL6 and TNFa, and outcome after liver grafting can be demonstrated (12).

Proof of concept for simvastatin to improve donor cardiac function

Based on their studies of heart transplantation and kidney ischaemia in the rat (13,14), where there was a clear benefit to animals pre-treated with statins, a group in Helsinki performed a randomised prospective study in brain-stem dead donors of a single dose of

simvastatin 80mg via nasogastric tube early after consent for organ donation. They randomised 84 donors very likely to donate for cardiac transplantation, 42 patients received a heart from a statin treated donor (15). There was a striking reduction in early heart injury (measured by serial troponin levels), an improvement in early cardiac function (assessed by postoperative NT-proBNP), and a reduction in early rejection rates. There was no difference in early or one-year survival, however the study was not powered for clinical outcomes. The recipients had a reduced pro-inflammatory cytokine profile. In patients receiving other organs from the statin-treated donors, there was a significant reduction in Alanine Transferase (a marker of liver injury) at one week in liver recipients, and a non-significant improvement in gas exchange in the lung recipients. Importantly there were no safety concerns in any organ recipient group.

Statins are 3-hydroxy-3-methyl coenzyme A reductase inhibitors, with many pleiotropic effects which may modulate the inflammatory processes in donors after brain stem death . Elevated IL6 is associated with donor heart dysfunction in organ donors (16), and pre-admission treatment with statins reduces IL6 levels in patients with sepsis (17). Statins reduce pulmonary and systemic inflammation in acute lung injury (ALI) (18,19), a process which shares many features with lung injury and the related systemic inflammation in the brain-stem dead donor. The protective effect of statins against contrast-induced nephropathy, an analogous example of acute renal injury, has been reported (20).

1.3 Need for a trial

A randomised, controlled trial of simvastatin in addition to standard, protocolised donor management is needed to determine primarily the effect on patient centred clinical outcomes in cardiac recipients, in addition to secondary outcomes in lung, kidney, liver and pancreas recipients.

1.4 Dose selection of intervention

Simvastatin 80mg once only dose administered by naso-gastric tube as soon as possible after specific study consent. This dose has been used in multiple trials within critically ill patients with organ failure in the ICU and was used in a smaller preliminary study in Finland.

1.5 Explanation for choice of comparators

Clinical management of the potential organ donor after the diagnosis of death using neurological criteria (brain stem death) and after consent for organ donation is protocolised in the UK, and implemented by a specialist nurse for organ donation and the intensive care team. The most up to date version of the donor care protocol can be found on NHSBT's clinical website (https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/donor-optimisation/). The protocol is already strongly advised by NHSBT although clinical decision-making authority remains with the treating ICU team. SIGNET is a pragmatic study within existing practice and will not assess the compliance with this protocolised care.

Primary and secondary outcomes in the SIGNET study are within the recipient population. The study is single blinded such that knowledge of the intervention is unknown to the retrieval and transplant teams. Clinical teams in intensive care cannot influence the primary or secondary outcomes and thus a placebo is unnecessary.

1.6 Potential benefits and risks of the intervention

The rationale for the intervention benefits in the recipient population are outlined above.

Simvastatin is a widely prescribed and well tolerated medication, already prescribed in a small percentage of donors. It has been studied in similar populations of critically ill patients with no statistical difference in adverse outcomes when compared against placebo. As a single dose of Simvastatin will be given, adverse events are predicted to be negligible. Adverse events and safety reporting are considered in section 9.

No measurable drug is transferred to recipient within donated organs, the potential impact of the intervention is by alteration of inflammatory responses and subsequent organ function prior to transplant, rather than a drug effect in the recipient.

Prolonged statin therapy has been associated with elevations in liver enzymes and alterations in pancreatic function which have theoretical risks in recipients of these organs. The precursor study by Nykanen et al showed improvements in liver enzymes in recipients of statin treated donors, and no adverse effects in recipients of non-cardiac organs. These potential recipient non-cardiac effects are defined secondary outcomes within the study.

1.7 Specific objectives or hypotheses

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

To determine if simvastatin given to the donor confers an improvement in clinical outcomes in cardiac transplant recipients

To determine if simvastatin in the donor has a beneficial effect on other solid organs, particularly the liver and lung

To determine if simvastatin is safe in other organ transplant recipients (cardiac, renal, lung, liver and pancreas) as per section 7

1.8 Description of trial design

This is a multi-centre, single-blind prospective, group sequential, randomised controlled trial. Randomisation will be in a 1:1 ratio, using permuted blocks of varying, undisclosed size, and will be stratified according to whether the donor was previously receiving statin therapy at ICU admission. There will be two interim analyses for harm, benefit or futility after 238 and 356 heart transplants have been followed up for 30 days. Recipient follow-up will be conducted using routinely collected data on the UK Transplant Registry.

2. Study Setting

Adult Intensive Care Units in Level 1 and 2 donating hospitals as defined by NHS Blood and Transplant.

> Level 1 Hospitals have donation potential > 12 / year (averaged over previous 2 years)
>
> Level 2 Hospitals have donation potential > 6 and < 12 / year (averaged over previous 2 years)
>
> At SIGNET study commencement there were 80 Level 1 or 2 Trusts

Working with NHSBT operations and local research teams we intend to open SIGNET in these hospitals, which will become SIGNET study sites. Some Level 3 Trusts will be selected based on donor numbers.

3. Selection of Sites/Clinicians

In the UK, adult Intensive Care Units in Level 1 and 2, and some Level 3, donating hospitals will be included in this study.

The trial sponsor has overall responsibility for Site and Investigator selection, overseen by the Trial Management Group (TMG).

3.1 Site/Investigator Inclusion Criteria

To participate in the SIGNET trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been prepared by the SIGNET Trial Management Group (TMG) and are defined below:

Adult Intensive Care Unit > 6 donors per year (Level 1 or 2 as defined by NHSBT), some level 3 Trusts will be selected based on donor numbers.

Clinical lead for organ donation (CLOD) or other clinical lead doctor responsible for donor management at a local level

Research lead with expertise in managing interventional studies in critical care at that site

Research infrastructure with appropriate staff to coordinate interventional studies at a local level

Sites with access to Specialist Nurses for Organ Donation (SNOD) to support delivery

3.1.1 PI Qualifications and Agreements

The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up to date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, and/or the regulatory authorities.

Some hospitals will have single individuals who hold all the relevant experience and expertise, but a local research team with a Co-PI is strongly encouraged to build resilience, expertise and experience. This team would ideally include;

Consultant PI with previous suitable experience. The consultant would ideally be based in Critical Care, but this is not essential.
Nursing support with expertise and experience of research in Critical Care – e.g research nurse
Linked or embedded Specialist Nurse for Organ Donation
Associate PI – a senior trainee in critical care with an interest in organ donation and / or research.

3.2 Recruitment and Consent

This protocol should be read in conjunction with the Trial Manual adopted as study specific Standard Operating Procedure by NHSBT.

Recruitment and consent for research within the organ donation process is a specialist area of clinical practise. The Specialist Nurse for Organ Donation (SNOD) has the required skills and knowledge to best judge how and when to approach families to consider research within the complex organ donation process, and SNODs have extensive training in consent to fulfil their duties as outlined in the Human Tissue Act. Seeking research consent is a routine aspect of the organ donation consent conversation, and may be

“Generic” - consent is sought for research use of any organs, samples or tissues unable to be used for transplantation

“Specific” - consent is sought for a specific, named and explained study involving alterations to the process of organ donation for the purposes of research

The SIGNET study has been planned in partnership with NHSBT to enable recruitment to form a part of usual clinical care of donors and their families

Specialist Nurses for Organ Donation will receive specific training on the SIGNET trial protocol, consent, randomisation and delivery. This will include proportionate training in the principles of GCP.

The approach for research consent will follow consent for organ donation according to the Human Tissue Act, which may have been first person (Organ Donor Register), deemed or from family members.

SIGNET requires specific consent from donor family members regardless of the basis for organ donation consent. Specific research consent cannot be “deemed” even if this is the basis for consent for organ donation.

Some families will consent for organ donation prior to neurological testing and then request no further contact. Consent for SIGNET may be taken prior to neurological death testing if this is deemed appropriate by the consenting SNOD, but donors will not be randomised to the study until after confirmation of neurological death.

The hypothesis for the SIGNET study is a potential reduction in damage to the heart (and other organs) during the period after diagnosis of death and prior to organ retrieval. Therefore, families who give consent to take part in the study may maximise the altruistic gift via organs of more value and benefit to recipients. This positive impact on donors, families and recipients was an important reason why this study was strongly supported by patient, donor family and recipient representatives.

It is likely that the trial intervention will be more effective the earlier it is given following the diagnosis of death. Taking into account and prioritising the needs of donor families, ICU staff and the organ donation process, research teams should seek to reduce the elapsed time between: diagnosis of death / approach for organ donation consent / research consent / randomisation / study intervention as much as possible. This aligns with NHSBT operational guidance which seeks to reduce the duration of the organ donation process after diagnosis of death.

The rights of the patient *(in the case of SIGNET, patient’s Next of Kin as defined in the Human Tissue Act)* to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol at any stage, if he/she feels it is in

the best interests of the participant. The reason for doing so should be recorded. The participant will remain within the trial for the purposes of follow up and for data analysis. Similarly, the participant's Next of Kin must remain free to change their mind at any time about the protocol treatment and trial follow up without giving a reason and without prejudicing the participant's or family's further treatment.

Consent will not be sought from recipients because the organ donors will receive the intervention and we do not anticipate risk to recipients. Potential recipients on the organ transplant waiting list will be provided with a letter and information sheet informing them of the study and how their data will be used.

4. Selection of Participants

There will be no exceptions to eligibility requirements at the time of randomisation. Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

4.1 Participant 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

4.2 Participant Exclusion Criteria

Aged < 18

Planned donation after cessation of circulation (DCD)

Known donor allergic hypersensitivity to simvastatin

Prisoners will not be excluded.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver. Protocol waivers are not permitted.

4.3 Screening Procedures and Pre-randomisation Investigations

The local SNOD, RN or PI will be responsible for identifying suitable patients and inviting them to participate in the trial.

The eligibility checklist will be completed.

5. Randomisation

NHSBT have adopted the SIGNET Trial Manual as a Standardised Operating Procedure which will ensure that the study procedures are correctly followed and documented within the complex organ donation pathway.

The allocation sequence will be produced by Sealed Envelope and quality checked by the trial statistician. Randomisation will be in a 1:1 ratio, using permuted blocks of varying, undisclosed size, and will be stratified according to whether the donor was previously receiving statin therapy at ICU admission.

5.1 Allocation – concealment mechanism

Allocation will be conducted using Sealed Envelope (a centralised web-based randomisation system). The randomisation list will only be accessible to the trial statisticians and Sealed Envelope.

5.2 Allocation – implementation

Before randomisation, consent from the donor family for organ donation and the SIGNET study must be in place. Eligibility for enrolment must be assessed, with reference to inclusion and exclusion criteria. Eligible patients will be randomised to SIGNET in participating Intensive Care Units by the SNODs, using an interactive web response system, provided by Sealed Envelope. The SNODs will be given log in details and a password for the randomisation system. After confirming eligibility, the donor will be randomised to either intervention or control in a 1:1 ratio.

Once randomised the team will be provided with the allocation (Simvastatin 80mg or Standard Donor Care) and the participant's randomisation number. The participant ID (randomisation) number will be in the form of RXXXX and will be used on all subsequent study documentation.

Following randomisation, an email notification will be sent to the site research team and central research team.

If randomised to receive 80mg Simvastatin, the SNODs will ask a member of the ICU team to prescribe the intervention. The ICU nursing staff will administer the intervention.

RANDOMISATIONS

To randomise, please visit

www.sealedenvelope.com

Choose the SIGNET trial from the drop down list and log-on as instructed.

5.3 Co-enrolment Guidelines

Formal co-enrolment is not required with other concurrent studies in critical care as they will have met their primary end point (death) before recruitment into SIGNET.

The patient recruited to SIGNET cannot subsequently take part in another study, however retrieved organs may enter studies or technological service improvement projects prior to transplantation, and the recipients of organs may consent to subsequent studies. Whilst formal co-enrolment of patients is clearly not required in such circumstances, data sharing agreements between such studies will be required in order to ensure confounding is recognised, reduced or excluded. This will allow co-enrolment at an organ, but not at an individual patient, level.

Data sharing arrangements with other studies will be considered on an individual study basis and must be approved by the Trial Management Group, Co-Chief Investigators and the Sponsor.

An up to date list of studies with co-enrolment agreements with SIGNET can be found on the dedicated study website.

5.4 Blinding

The ICU and organ donation team caring for donor and family will not be blinded to the intervention. Retrieval teams, Theatre teams and Recipient Transplant teams will be blinded to the study intervention. The mechanisms for maintenance of this blinding are described in the Trial Manual.

Documentation of the organ donation process is electronic within NHSBT's DonorPath system. All approaches to donor families should be documented within this system and within the medical record using the below statements:

"SIGNET: consent RXXXX"
"SIGNET: decline"
"SIGNET: Not approached"

The allocated intervention study drug will be prescribed as per local hospital policy.

5.5 Unblinding

Unblinding is predicted to be an extremely rare event. Only circumstances where a recipient would be predicted to come to harm or treatment would be altered if the study allocation were not known should be grounds for unblinding, for example a known severe hypersensitivity to simvastatin (the risk of transfer of even trace quantities of active drug is very unlikely, and this would only be required if an organ from a donor previously treated with a statin would also have been declined).

5.5.1 Emergency unblinding

A request to reveal the donor intervention allocation can be made by a potential recipient's treating consultant (surgical or medical) by direct communication with the central study team in the first instance, or direct with the donor site Principal Investigator. The central clinical team can access the treatment allocation from the randomisation software. If either are

unavailable a direct request to reveal the treatment allocation by donor clinical team (SNOD and ICU team) will be made. The donor clinical team are unblinded and can disclose treatment allocation, which will be recorded in the study specific database. Only the recipient treating consultant will be informed of the treatment allocation, who will then determine if this impacts on the decision of transplant. Transplanting teams accepting organs from the same donor, or subsequent teams considering the same organ, will not be informed unless they have also requested unblinding using the same process. The treatment allocation will remain blinded within the DonorPath documentation. The trial statistician will have access to the unblinded randomisation list to produce unblinded lists for the DMC.

6. Treatment of Donors

Introduction

This trial will have a single intervention arm and a control arm. These are described in the sections below. SIGNET has been assessed by the MHRA and is not classified as a Clinical Trial of an Investigational Medicinal Product. For the purposes of this study, it is expected that ward stock of simvastatin 80mg tablets will be used for the administration of the intervention. This will not require any study specific labelling. Storage of simvastatin is expected to be in line with normal clinical practice and therefore temperature monitoring records will not be collected. Usual standard practices for documenting administration of medications will be utilised at investigating sites, no formal trial specific accountability will be expected to be completed.

6.1.1 Intervention to be studied

Single dose simvastatin 80mg via Nasogastric tube, enteral administration.

6.1.2 Comparator or placebo

Standard donor management according to NHSBT protocolised care.

6.1.3 Preparation of Study Drug

80mg Simvastatin tablet crushed well and mixed with 20mls sterile water from hospital stock supply

6.1.4 Blinding of Study Drug

No blinding of study drug

6.1.5 Administration of Study Drug

Via nasogastric tube. An NG tube is part of the current NHSBT Donor Care Bundle which represents standard therapy in the SIGNET study.

The intervention should be given as soon as possible following the diagnosis of death, in line with other priorities.

6.1.6 Study Withdrawal

In consenting to the trial, donor families are consenting to the trial treatment (donor), trial follow up and data collection. However, a participant may stop treatment early (potentially prior to single allocated intervention being given) for any of the following reasons:

Any change in the participant's condition that justifies the discontinuation of treatment in the opinion of the treating clinician
Withdrawal of consent - either research consent or consent for organ donation
Organ donation process is halted for any other reason

Donors and recipients should remain in the study for the purpose of follow up and data analysis, unless patients or families withdraw their consent from all stages of the study, in which case, they should be withdrawn. Data collected until the time of withdrawal will be retained and included in the analysis.

Patients who discontinue treatment allocation early will not be replaced.

6.2 Adherence to intervention

Local study teams will ensure that interventions are given according to randomised allocation unless withdrawn for the reasons above.

Care of the potential donor should follow the standard NHSBT protocol (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/3654/dbd_care_bundle.pdf) and study teams should ensure that treatment adheres to this as closely as possible.

6.3 Medications not permitted

No change to other treatments

7. Study Outcomes

7.1 Primary Outcome Measure(s)

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

A robust and clinically meaningful composite primary end point has been chosen, encapsulating all early adverse outcomes post-heart transplant, namely death, mechanical cardiac support and renal replacement therapy. Mechanical support is required to support life if there is significant cardiac injury. It has a very significant effect on one-year mortality (21), so is effectively a surrogate for early death. The need for renal support is linked to less severe early cardiac injury and resulting systemic hypo-perfusion. It again is linked to both one year and much later mortality (22)

7.2 Secondary Organ Specific Outcome Measures

Secondary - All Organs

- 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, with the exception of kidney recipients as this data is not collected on the UK Transplant Registry
- **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 (need for dialysis in first 7 days)
    - 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

8. Assessments and Follow-up

8.1 Trial Assessment Schedule

Donor:

Timepoint*	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
Eligibility Screen	X					
Informed Consent	X					
Randomisation/Allocation		X				
INTERVENTIONS						
Simvastatin 80mg in addition to standard donor management protocol		X				
Standard donor management protocol only		X				
ASSESSMENTS						
Donor Demographics	X					
Donor Medical History	X					
Intervention Data		X	X			
Organ Utilisation			X			

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 –3 months following transplant

$T_4$12 months following transplant

Recipient:

Timepoint*	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
All patients on organ waiting list given recipient information	X					
INTERVENTIONS						
Organ transplant		X				
ASSESSMENTS						
Recipient Clinical Outcome				X	X	X

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 – 3 months following transplant

T_4 - 12 months following transplant

8.2 Procedures for Assessing Efficacy

Outcomes in organ recipients from randomised donors will be collected through routinely collected data submitted to the UK Transplant Registry. All UK organ recipients' clinical outcome data are submitted even if patients transition between transplant centres. The registry is held by NHSBT and outcomes are pseudonymised for analysis. Linkage of donor treatment allocation and recipient outcome for analysis purposes will be outlined in the statistical analysis plan.

8.3 Procedures for Assessing Safety

Safety in the organ donor is described using serious adverse events procedures as described in section 9 below.

Safety in the recipient will be assessed via routine data collected on the UK Transplant Registry. Early complications and 30-day graft and patient survival rates are the key safety outcomes of interest.

Patients who discontinue treatment allocation early will not be replaced.

8.4 Patient transfers

The national nature of the UK Transplant Registry ensures that individual organ outcome will continue to be included for statistical analysis even if they move between transplant centres.

8.5 Loss to Follow-Up

Recipient outcome is tracked via the UK Transplant Registry, and any loss to the registry will also be a loss to follow up for the SIGNET study. There are no additional measures to collect recipient data.

8.6 Trial Closure

The trial will end 15 months after the final donor has been recruited. This will allow for the 12 month follow up data to be collected for all recipients. Once the trial is closed, participating centres will be contacted to ensure that all documentation is filed and ready for archive.

9. Safety Reporting

All eligible patients will be potential organ donors who have been diagnosed dead by neurological criteria. As such any events that are unexpected and deemed related to the research procedures, from the point of randomisation to organ retrieval, will be reported to the REC.

SAEs in recipients will not be reported.

9.1 Definition of Serious Adverse Events Related to Donors

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 diagnosed dead by neurological criteria

This study will be looking at Serious Adverse Events (SAEs) that are **related to the study** (i.e they resulted from application of any of the research procedures) and **unexpected** (i.e not listed in the protocol as an expected occurrence). This would also include an adverse event which progresses to the point of loss of capacity to donate as a result of the study procedures.

9.2 Anticipated Serious adverse events in donors excluded from recording and expedited reporting

Any anticipated serious adverse events will not need recording or reporting in this trial.

Patients diagnosed dead using neurological criteria have well recognised multi system sequalae, and usually require significant invasive organ support. As such development and progression of organ failures and associated complications may occur as a result of the underlying pathophysiology, and are not reportable as serious adverse events within the study. The following is a list of commonly encountered events in the context of brain stem death, but is not exhaustive and the judgement of clinical teams is required:
Cardiovascular instability, including tachyarrythmia, bradycardia, hypotension, hypertension, cardiac failure.
Respiratory failure including hypoxia, hypercapnia, pulmonary oedema.
Renal failure including central or renal diabetes insipidus
Metabolic / hormonal disturbance including diabetes insipidus, hypo or hyperglycaemia requiring intervention.
Hepatic impairment including transaminitis or biliary stasis

9.3 Serious adverse events in donors which require recording but not expedited reporting

The single serious adverse event that requires recording (but not expedited reporting) is an adverse event which progresses to the point of loss of capacity to donate **as a result of the study procedures**, in the opinion of the site study team.

9.4 Reporting procedures for serious adverse events in Donors

A serious adverse event (SAE) occurring to a participant should be reported to the REC where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).
SAEs must be reported on the SAE Reporting Form (on the eCRF). Each report added to the eCRF will be automatically notified to NHSBT CTU. If the eCRF is unavailable for any reason, a paper version of the form should be emailed to serious_adverse_events@nhsbt.nhs.uk. NHSBT CTU will perform an initial check of the report, request any additional information if required. Additional and further requested information (follow-up or corrections to the original case) should also be added to eCRF. NHSBT CTU will ensure that all SAEs are reported to the Sponsor as required.

9.5 Recipients

SIGNET is a donor study. Statin medication is hypothesised to effect inflammatory response in the donor, and not in the recipient. Specifically, the quantity of active free drug transferred by organ donation from donor to recipient will be negligible. A precursor study in Finland was unable to detect simvastatin in recipient organs (*personal communication with lead author*). Statin therapy is a recommended post-transplant therapy in cardiac recipients in general, and currently recipients with known statin sensitivity are transplanted organs from donors who may have been previously treated with statin medication as a matter of routine. This information is unknown to transplant recipient and not requested by transplanting clinical team. Approximately 15% of current organ donors have been treated with statin therapy. As such, there is no requirement for ongoing safety reporting in the recipient of statin treated donors in the SIGNET study. All impacts in the recipient are mediated via the impact on organ function, rather than as a direct drug effect, and as such are captured within the study outcomes (primary and secondary) for all transplanted organs. Organ outcomes will be assessed in the analysis.

9.6 CTU Responsibilities

NHSBT CTU is delegated by the trial sponsor to report any SAEs considered related and unexpected to the research ethics committee (REC) should any occur. NHSBT CTU will inform all investigators concerned or relevant information about SAEs that could adversely affect the safety of subjects.
SAEs and safety issues must be reported to the Research Ethics Committee as soon as possible but not later than 15 calendar days after NHSBT CTU has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.
NHSBT CTU is also delegated by the trial sponsors to prepare any annual safety reports to the REC.

10. Quality Assurance and Control

10.1 Risk Assessment

A Risk assessment has been conducted which acknowledges the potential risks to the trial. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place, as agreed with the Sponsor, to ensure the trial is performed and data generated and recorded in accordance with the principles of GCP.

10.2 Central Monitoring at CTU

The CTU data managers will review all data received for errors and missing data points. UK Transplant Registry (UKTR) data is checked by OTDT Information Services using validation rules at time of data entry, and missing forms are queried.

10.3 On-Site Monitoring

The frequency, type and intensity for routine monitoring and the requirements for “for cause” monitoring will be detailed in a separate monitoring plan as agreed with the Sponsor.

10.3.1 Direct access to patient records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required.

10.3.2 Confidentiality

The data will be handled in accordance with the principles of the UK Data Protection Act.

10.4 Auditing

In addition to potential GCP inspections or audits by the local R&D department, the Sponsor / NHSBT CTU reserves the right to conduct site audits, either as part of its ongoing audit programme, or in response to adverse observations during monitoring visits.

10.5 UK Transplant Registry

Recipient outcomes will be followed up using data on the UK Transplant Registry, which is owned and housed by NHSBT. Data on the UK Transplant Registry is checked and validated upon entry as part of standard procedure and will not be monitored by the study team.

11. Statistical Considerations

11.1 Method of Generating Allocation Sequence

The randomisation list will be produced by Sealed Envelope and quality checked by the trial statistician. Randomisation will be in a 1:1 ratio, using permuted blocks of varying, undisclosed size, and will be stratified according to whether the donor was previously receiving statin therapy at ICU admission. Randomisation will not be stratified by transplanting centre (unknown at the time) or donation hospital (standard donor management applies at all hospitals and there is no evidence that donor hospital influences transplantation rates or recipient outcomes).

11.2 Sample size

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.

11.3 Interim Monitoring and Analyses

An interim pilot phase will be completed after a full 12 months of recruitment. The stop-go criteria for expanding to compete the full trial is detailed below. Performance in the green category will lead directly to trial continuation. Any items in the amber category will lead to targeted interventions and sharing of best practice among sites to improve performance. Performance in the red category for any item will lead directly to Trial management committee discussions with the TSC and the HTA for consideration of trial progression from the pilot phase.

- Open sites. Target all Level 1 & 2 sites (80 Trusts at current definitions). Green=100%, Amber>60%, Red<60%.
- Donor recruitment against target (80% of eligible donors -, target of 500 donors), Green >100%, Amber>60%, Red<60%.
- We will track all organ transplants from randomised donors and measure trial performance against number of heart transplants to achieve the required power over trial duration (target of 90 heart transplants). Green >100% to time and target, Amber >70% time and target, Red<70% time and target.
- Adherence to intervention – donors being given or not given a statin as randomised. Green>100%, Amber>75%, Red<75%.

There will be two interim analyses for harm, benefit or futility after 238 and 356 heart transplants have been followed up for 30 days. O'Brien Fleming stopping boundaries will be used at these interim analyses to guide the DMC and preserve an overall 5% significance level. By default, the overall event rate and the event rate by arm will only be

shared with the DMC, who will make recommendations to the TSC accordingly. The TSC will make the final decision regarding terminating the trial and, if considering early termination, may request access to the interim analysis data to inform this decision; blinded data would preferentially be shared. The DMC will regularly review outcome and safety data across all organs, including at these interim analyses.

We will use the following success criteria/milestones:
Milestone 1: Regulatory approvals
Milestone 2. First patient (donor) first visit (FPFV)
Milestone 3: Completion of feasibility study: "green light to full trial"
Milestone 4: Completion of recruitment
Milestone 5: Final report available
Good adherence (>75%) in the intervention arm
High rates of data completeness of follow-up

11.4 Analysis Plan (Brief)

The analyses will be described in detail in a full Statistical Analysis Plan (SAP). This section summarises the main issues.

Baseline characteristics of the donor and organ transplant cohorts will be presented by trial arm, along with CONSORT diagrams to show the flow of donors and recipients through the study. All analyses will be two-sided and the significance level will be 5%. 95% confidence intervals will be presented for all estimates of treatment effect.

11.4.1 Analysis of primary and secondary outcomes

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 organs will also use a mixed logistic regression model or competing risks framework as appropriate. Organ utilisation for each organ will be analysed using a multivariate 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.

11.4.2 Other Analyses

A further analysis will be conducted to assess the effect of time from fixed and dilated pupils in the donor to statin administration on outcome. The time will be dichotomised at the median value and the odds ratio and 95% confidence interval for the primary outcome in heart transplant recipients will be presented for each of these groups relative to the control arm. It is hypothesised that outcomes will be better for those with shorter times to statin administration. Analysis Population and Missing Data

11.4.3 Analysis Population and Missing Data

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) and re-transplants will be excluded from the main transplant outcome analyses, due to differences in outcomes, but will be reported separately. Non-eligibility for NHS treatment patients (NHS Group 2) and overseas transplants (including Dublin) are also excluded from main analysis, as they may receive different standards of care and follow-up data completeness is poor.

Paediatric transplants from adult donors will be included in main analysis, along with urgent and super-urgent transplants. These groups could be explored further as a secondary analysis.

Different types of partial or double/single transplants are included in main analysis and analysed together, except for heterotopic and auxiliary liver transplants which are excluded. Pancreas alone transplants will be analysed with SPK transplants but may be explored further as a secondary analysis if there is sufficient data. Only first routine islet transplants will be included in the analyses. Exclusions regarding islet transplants are for either a) a second or subsequent routine islet graft after the patient's previous graft has failed or b) a patient with a functioning graft but listed for a priority graft longer than 12 months and changed to a routine status for the offering scheme.

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 analyses 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 the registry data completeness is 98%, and any missing data for death, cardiac mechanical circulatory support or renal replacement therapy will be queried. If it remains unavailable a complete case analysis will be conducted. For the primary

outcome variables, the amount and patterns of missingness will be explored to identify drivers of missingness along with clinical considerations to inform sensitivity analyses to be undertaken when significant amount of missingness (>5%) are present. Multiple imputation models with full conditional specification will be used to address missingness in predictors. Multiple imputation for missing outcomes will be considered when good predictors for the outcomes exist and are observed, the assumption of missingness completely at random cannot be justified and the proportion of missing outcomes is not small. Best and worse case scenarios for missing outcomes will also be considered and consist of replacing all missing outcome events as non-events and events, respectively. Complete case analyses will be conducted with cases with missing primary outcome data excluded, when the assumption of missingness completely at random can be justified. Missing secondary outcome data will not be imputed.

12. Data Management

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1 Source Data

Source documents are where data are first recorded, and from which eCRF data are obtained.

The below table details the source for data:

Data	**Source**
Randomisation number and site code	SealedEnvelope
Site and name of specialist nurse completing form	Source Data Form
Date of organ retreival and ODT number	DonorPath
Eligibility Checklist	DonorPath
Consent/Authorisation	DonorPath
Randomisation	SealedEnvelope with the exception of whether the donor was receiving statin therapy on ICU admission for which the source will be the patient medical notes.
Intervention	Patient medical notes
Withdrawal of Consent	DonorPath
End of Study	DonorPath with the exception of any SAE data which will come from the paient medical notes.
Unblinding	Source data form

Where this has not been documented in the patient medical notes or on DonorPath, the source data form will be considered source. This will be retained in the investigator site file.

The recipient data from the UKTR is also considered source data for the purposes of this study.

12.2 Data Collection

Please refer to the study manual for further guidance on data collection. The Principal Investigator has overall responsibility for data collection at Sites.

Data will be collected onto paper source data forms by the Specialist Nurses and this will then be entered onto the study eCRF (MACRO database) by the local research teams.

Participants will be identified by a trial specific number. The participant's donor ID will be collected in a restricted part of MACRO and will be used for linkage with other donor data and with the transplant recipients, by an independent statistician.

The source data form and eCRF will collect the following data:

Consent/Authorisation: date and methods of consent/authorisation for organ donation and study specific consent, use of study specific sticker, person taking consent

Eligibility checklist

Randomisation: Date and time of randomisation, randomisation number, allocation, statin therapy on ICU admission

Intervention: reconfirmation of eligibility, name of person re-confirming eligibility, date and time of prescription, prescriber, date and time of administration, reasons for intervention not being administered

End of study: organ donation proceeding, reason organ donation did not proceed and SAEs

Withdrawal: date of withdrawal, reason for withdrawal, continued data collection

Unblinding: date of request, requestor team, reason for request, allocation reveal

12.3 MACRO Compliance

The SIGNET study database will utilise Ennov's MACRO software which is FDA 21 CFR part 11 and ICH-GCP compliant. The MACRO database is specifically designed to collect and store clinical trial data and provides the tools to review data and raise queries to site staff in order to ensure data collection is as accurate as possible before data extract.

13. Ancillary Studies

13.1 Mechanistic investigations of SIGNET participants via Quality in Organ Donation Biobank

The families of organ donors are routinely approached to consider recruitment into the QUOD biobank study which is open nationally in level 1 hospitals, with significant overlap with planned SIGNET study trial sites.

The QUOD study is covered by separate funding, protocol, recruitment and consent procedures, which can be found at https://quod.org.uk/.

The QUOD study includes collection of blood, urine and tissue samples at 4 time points throughout the DBD organ donation pathway.

Consent for QUOD and SIGNET are entirely independent, donor families may consent for either or both.

Separate studies investigating the mechanistic basis of statin action in DBD donors are planned. These will be regulated by application to access the QUOD national biobank via the existing process.

In order to identify SIGNET participants and an appropriately matched control group, a co-enrolment agreement with QUOD will be agreed to allow data sharing

14. Ethical and Regulatory Issues

14.1 Compliance

This trial complies with the Declaration of Helsinki [2013]

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) UK Policy Framework for Health and Social Care Research

14.1.1 Site Compliance

The site will comply with the above regulations and guidelines. A site agreement will be in place, setting out respective roles and responsibilities.

Protocol deviations and non-compliances should be documented on a file note and reported to SIGNET@nhsbt.nhs.uk. A risks and issues log will be maintained by NHSBT CTU and will be reviewed by the TMG on a monthly basis.

14.1.2 Serious Breaches

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial”.

In the event that a serious breach is suspected NHSBT CTU must be contacted as soon as possible. Serious breaches will be reported to the REC as required, within 7 days.

Serious breaches/incidents will be investigated by NHSBT CTU in accordance with the quality management system, supported by Quality Assurance specialist and may include root cause analysis and corrective action/preventative action plans where required.

14.1.3 Data Collection and retention

Source data forms, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 5 years after the end of the trial or as required by any subsequent clinical trial regulations. During this period, all data should be accessible to the competent authorities and the Sponsor with suitable notice.

14.1.4 Access to Data

Custody of the final data set will reside with the Chief Investigator and NHSBT CTU (for audit purposes). Access to the final data set for additional analyses will be permitted under the agreement of the Trial Steering Committee, according to the publication policy in section 16.

15. Ethical Conduct of the Study

15.1.1 Ethical Considerations

Before initiation of the trial at each clinical site, the protocol, all informed consent forms and any information to be provided to the prospective participant's family and any potential organ

recipients will be submitted to a Research Ethics Committee for ethical approval. Any subsequent amendments will be submitted to, and approved by, the same Research Ethics Committee.

15.2 Confidentiality

Individual participants will not be identified in the resulting publications and presentations from the trial. This trial will comply with the UK Data Protection Act (2018) and the General Data Protection Regulation.

15.3 Other approvals

The study will be subject to HRA approval and local Trust capacity and capability assessments. Copies of approvals will be maintained by NHSBT CTU.

16. Indemnity

The NHS indemnity scheme applies to this trial when it is being conducted in the UK. Section 4 of the non-commercial clinical trial agreement 2008 describes the indemnity arrangements as follows:

As both sponsor and site are NHS bodies, i.e NHS bodies/NHS Foundation Trusts in England, Wales or Northern Ireland and are indemnified by the same Indemnity Scheme (being one of the NHS Litigation Authority clinical negligence or the Welsh Risk Pool or the Clinical Negligence Fund in Northern Ireland) and the Party incurring any loss can recover such loss under one of the Indemnity Schemes, then such Party shall rely on the cover provided by the Indemnity Scheme and not seek to recover the Loss from the other Party (ies). Where the other Party (ies) caused or contributed to the Loss, it undertakes to notify the relevant Indemnity Scheme(s) to take this into account in determining the future levies of all Parties in respect of the indemnity schemes.
If:
The Parties are members of the same Indemnity Scheme in England, Wales or Northern Ireland and the Party incurring the Loss is not indemnified for that Loss by its Indemnity Schemes; or
All Parties are NHS bodies in Scotland; or
The Parties are NHS bodies/Foundation Trusts established in different jurisdictions within the United Kingdom;

Then the Parties shall apportion such Loss between themselves according to their respective responsibility for such Loss. Should the Parties be unable to agree the apportionment the matter shall be resolved in accordance with clause 16.5.
If one or more Parties are NHS Foundation Trusts and the Party incurring the Loss is not responsible for all or part of the Loss and is not indemnified in respect of the Loss by one of the Indemnity Schemes then the Party incurring the Loss shall be entitled to recover the Loss from the other Party (ies) pursuant to the provisions of this Agreement.

17. Finance

17.1 Funding

Funding arrangements will be provided in the Trust agreement with the Sponsor.

The SIGNET trial is funded by the NIHR Health Technology Assessment Programme, award ref: NIHR131124.

17.2 Declaration of interests

None of the individuals named in this protocol have any competing interests to declare. The NHSBT CTU requires serving members of all Oversight Committees to sign a declaration of interests form on appointment and declare any competing interests which may develop during the conduct of the trial to be declared at the start of every meeting.

17.3 Oversight and Trial Committees

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

17.4 Trial Management group (TMG)

A Trial Management Group (TMG) comprising the Chief Investigators, other lead investigators, a Sponsor representative and members of the CTU. The TMG will be responsible for the day to day running and management of the trial. It will meet at least four times a year, more often during set up and close down phases of the trial.

17.5 Trial Steering Committee

The Trial Steering Committee (TSC) has membership from the TMG and independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its' independent chair. The ultimate decision on continuation of the trial lies with the TSC.

17.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) with independent members will be convened specifically for the SIGNET study. This group will review unblinded data and provide advice to the Chair of the TSC and can recommend premature closure of the trial.

17.7 Patient and Public Involvement

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

17.8 Role of Study Sponsor

Newcastle Upon Tyne Hospitals NHS Foundation Trust as Sponsor for the SIGNET trial is responsible for the initiation and management of the study, whereby activities are delegated to NHSBT CTU as appropriate.

17.9 Role of Study Funder(s)

NIHR Health Technology Assessment board will receive detailed progress reports as required throughout the trial, but have no role

18. Publication

18.1 Dissemination

The final study data set will be analysed and results published as soon as possible following completion of study follow-up, final data checks and database lock. Individual clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications. Study findings will be presented to academic and non-academic groups. The PPI group will play an important part in disseminating the study findings into the public domain. Dissemination to non-academic audiences including service users, commissioners, clinicians and service providers will be facilitated through the use of existing networks e.g. email lists, social media. All research teams and PPI members involved in the study will be invited to a close out meeting to discuss the findings of the study. Open access, peer reviewed academic outputs and research reports together with associated summaries and key findings will be produced for funders, policy makers and NHS audiences and held on the study website. Any publications arising from this study will adhere to the NIHR funding and support outputs guidance.

18.2 Authorship

Authorship for any publications arising from this study will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship http://www.icmje.org/ethical_1author.html

18.3 Approvals

Study results will be embargoed and not disseminated until authorised by the CI and TSC. Final manuscripts and presentations will be approved by the CI and TSC prior to publication. Similarly, any subsequent sub-study analysis will require authorisation by the CI and TSC prior to publication. Sub-study manuscripts must not be published prior to the publication of the main study.

18.4 Identification

A trial identifier will be included on all presentations and publications.

18.5 Acknowledgements

For the main report of this study submitted for publication, together with associated methodology and health economic papers or posters/presentations, we will use the International Committee of Medical Journal Editors definitions of Authorship and Contributorship http://www.icmje.org/ethical_1author.html). The members of the TSC and DMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication and the support of the NHSBT Clinical Trials Unit, and Sponsor and Funder acknowledged in all publications/presentations.

19. Protocol Amendments

Revision History:

Version	Author	Date	Reason for revision
2.0	Trial Management Group	22/11/2022	Clarification of consent procedures, inclusion of level 3 Trusts, change in prescribers, administrative changes, clarification in analysis population and clarification of source data

20. References

1. Organ Donation and Transplantation Activity Report 2018-19. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16537/organdonation-and-transplantation-activity-report-2018-2019.pdf. Accessed 20/11/2019

2. Singh SAS, Banner NR, Rushton S et al ISHLT Primary Graft Dysfunction Incidence, Risk Factors, and Outcome: A UK National Study Transplantation 2019; 103 (2), 336- 343

3. ODT Annual Report, Cardiothoracic Activity, https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16416/section-7-cardiothoracic-activity.pdf Accessed 20/11/19

4. Economic Costs and Benefits of Transplantation. European Commission 2013. https://ec.europa.eu/health//sites/health/files/blood_tissues_organs/docs/ev_2013 1007_co03_en.pdf Accessed 20/11/2019

5. https://www.england.nhs.uk/wp-content/uploads/2014/04/a07-renal-transpl-ad0414.pdf Accessed on 20/11/19

6. Fisher, AJ, Wardle J, Dark JH, Corris PA. Non-immune acute graft injury after lung transplantation and the risk of subsequent bronchiolitis obliterans syndrome J Heart-Lung Tx 2002; 21:1206-1212

7. Pareja E, Cortes M, David Hervas D et al A Score Model for the Continuous Grading of Early Allograft Dysfunction Severity. Liver Transplantation 2015; 21:38–46

8. Avlonitis VS, Fisher AJ, Kirby JA, Dark JH. Pulmonary Transplantation: the Role of Brain Death in donor lung injury. Transplantation 2011; 75:1928-33

9. Watts RP, Thom, O and Fraser JF. Inflammatory Signalling Associated with Brain Dead Organ Donation: From Brain Injury to Brain Stem Death and Posttransplant Ischaemia Reperfusion Injury. Journal of transplantation, 2013, doi.org/10.1155/2013/521369

10. Birks EJ, Burton PBJ, Owen V et al. Elevated Tumor Necrosis Factor-a and Interleukin6 in Myocardium and Serum of Malfunctioning Donor Hearts. Circulation. 2000;102[suppl III]:III-352-III-358

11. Fisher AJ, Donnelly SC, Hirani N, Haslett C, Strieter RM, Dark JH, Corris PA Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation Am J Respir Crit Care Med 2001;163:259-265

12. Murugan R, Venkataraman R, Wahed AS et al Increased plasma Interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. Critical Care Medicine 2008;36:1810-16

13. Tuuminen R, Nyka¨nen AI, Saharinen P et al Donor Simvastatin Treatment Prevent Ischemia-Reperfusion and Acute Kidney Injury by Preserving Microvascular Barrier Function Am J Transplant 2013; 13: 2019–2034

14. Tuuminen, R. Syrjala, S. Krebs, R. Combined donor simvastatin and methylprednisolone treatment prevents ischemia-reperfusion injury in rat cardiac allografts through vasculoprotection and immunomodulation. Transplantation 95:1084-91

15. Nykänen, AI, Holmström EJ, Tuuminen R et al, Donor Simvastatin Treatment in Heart Transplantation: A Randomized and Blinded Clinical Trial. Circulation. 2019;140:627–640.

16. Avlonitis VS, Fisher AJ, Kirby JA, Dark JH. Pulmonary Transplantation: the Role of Brain Death in donor lung injury. Transplantation 2011; 75:1928-33

17. Kruger P, Bailey M, Bellomo R et al, A Multicenter Randomized Trial of Atorvastatin Therapy in Intensive Care Patients with Severe Sepsis. Am J Respir Crit Care Med, 2013; 187: 743-750

18. Shyamsundar M, McKeown STW, O'Kane CM, Craig TR, Brown V, Thickett DR, Matthay MA, Taggart CC, Backman JT, Elborn JS, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. Am J Respir Crit Care Med 2009; 179:1107–1114

19. Craig T, Duffy M, Shyamsundar M, O'Kane C, Elborn J, McAuley D. Simvastatin reduces inflammation and improves clinical outcomes in ALI: results of the HARP study. Thorax 2009;64:A2–A4

20. Prophylactic atorvastatin prior to intra-arterial administration of iodinated contrast media for prevention of contrast-induced acute kidney injury: A meta-analysis of randomized trial data .Sun YY, Liu LY, Sun T, Wu MY, Ma FZ. Clin Nephrol. 2019 Sep;92(3):123-130.
21 Singh S Banner N, Rushton S et al Primary Graft Dysfunction Incidence, Risk Factors, and Outcome: A UK National Study Transplantation 2019;103: 336–343
22 Wang L, Wang T, Rushton SN, Parry G, Dark JH, Sheerin N
The Impact of Severe Acute Kidney Injury Requiring Renal Replacement Therapy on Survival and Renal Function of Heart Transplant Recipients – A UK Cohort Study
Transplant International 2020; 33:1573-76