FULL/LONG TITLE OF THE TRIAL

Feasibility study for Randomised Controlled Trial of Custodiol-HTK vs St Thomas' solution for cardioplegia and cold static Storage of UK donation after brainstem death hearts in cardiac transplantation.

ACRONYM

F-CUSToS

RESEARCH REFERENCE NUMBERS

IRAS Number:	1007011
ISRCTN Number / Clinical trials.gov Number:	44268
SPONSORS Number:	P03062
FUNDERS Number:	TRP22-100010

PROTOCOL VERSION NUMBER AND DATE

Version 2.0, 30 January 2025

SPONSOR

Royal Papworth Hospital NHS Foundation Trust

SIGNATURE PAGE

The undersigned confirm that the following Protocol has been agreed upon and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved Protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this Protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date: ...../...../.....

.....

Name: (please print):

.....

Statistician:

Signature:

.....

Name: (please print):

.....

Position:

.....

KEY TRIAL CONTACTS

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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
BiVAD	Biventricular Assist device
CA	Competent Authority
CI	Chief Investigator
CPOi	Cardiac Power Output Index
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DBD	Donation after Brainstem Death
DCD	Donation after Circulatory Death
DSMC	Data Safety and Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
ECMO	Extra-Corporeal Membrane Oxygenation
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HRUK	Heart Research UK
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LVAD	Left Ventricular Assist Device
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHSBT	NHS Blood and Transplant
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NORS	National Organ Retrieval Service
PGD	Primary Graft Dysfunction
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Participant Information Sheet
PP	Potential Participant
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RPH	Royal Papworth Hospital NHS Foundation Trust
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCfCI	Sterile Concentrate for Cardioplegia Infusion
SDV	Source Data Verification
SNOD	Specialist Nurse in Organ Donation
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VTE	Venous Thromboembolism
WHO	World Health Organisation

iii. TRIAL SUMMARY

Trial Title	Feasibility study for Randomised Controlled Trial of Custodiol-HTK vs St Thomas' solution for cardioplegia and cold static Storage of UK donation after brainstem death hearts in cardiac transplantation.	
Internal ref. no. (or short title)	F-CUSToS	
Clinical Phase	Stage IV	
Trial Design	Single-blind, multi-centre, national, randomised feasibility study.	
Trial Participants	All adult patients undergoing heart transplantation in the UK from a DBD donor.	
Planned Sample Size	50 patients	
Treatment duration	N/A	
Follow up duration	30 days post-transplant implantation	
Planned Trial Period	12 months	
	Objectives	Outcome Measures
Primary	To assess the feasibility of conducting a randomised controlled efficacy trial comparing Custodiol-HTK and St Thomas' solution for donor cardiac allograft preservation.	Proportion of eligible donor cardiac allografts that are randomised and receive the correct intervention.
Secondary	To assess clinical outcomes and novel parameters that predict clinically important outcomes.	- Key outcome data completeness - Primary Graft Dysfunction rate within 24 hours of transplant implantation. - Cardiac Power Output Index at admission to ICU and 6 hours post-operation. - Echocardiographic parameters from trans-oesophageal echo immediately after transplant implantation, including: Left Ventricular ejection fraction, left ventricular maximal posterior wall thickness, maximal septal wall thickness, left ventricular function, right ventricular function and the presence/absence of regional wall motion abnormalities - 30-day mortality. - 6-month survival.

		- Development of post-operative complications within 30-days of surgery, including: Dysrhythmias, Myocardial Infarction, Stroke, Acute Graft rejection, Renal Replacement Therapy, Infection (from any source), Venous thromboembolism, 30-day re-admission, Hyponatraemia (serum sodium <125mEq/L). - Median length of initial ICU stay - Median length of initial in-hospital stay.
Investigational Medicinal Product(s)	Custodiol-HTK Solution; St Thomas's solution (Sterile Cardioplegia concentrate)	
Formulation, Dose, Route of Administration	i. Custodiol-HTK: at least 3.5L of cold Custodiol-HTK will be perfused into the aortic root, over at least 10 minutes. The bag will be hung at least 60cm above the level of the heart. The heart will then be stored in 2L of cold Custodiol-HTK (2°C – 8°C). ii. St Thomas' solution: Sterile Concentrate for Cardioplegia Infusion (SCfCI) will be diluted by adding 20ml of SCfCI to 1 litre of Ringers solution. The volume of reconstituted SCfCI perfused into the aortic root will depend on donor weight: 1. Donor weight 30-70 Kg: administer 1 litre of reconstituted SCfCI solution 2. Donor weight >70 Kg: administer 1.5 L of reconstituted SCfCI solution At the request of the recipient transplant surgeon, it is permissible to change the above doses dependent on logistics and/or donor physiology. The bag will be hung at least 60cm above the level of the heart and the heart will be stored in 2L of cold saline (2°C – 8°C).	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Heart Research UK	£199,294.37 for consumables. Travel expenses for attendance at meetings when required (up to £1000)
Pharmapal/Dr. Franz Köhler Chemie GMBH	Custodiol-HTK Solution provided free of charge for the duration of the study
NHS Blood and Transplant	St Thomas' solution provided as part of the National Organ Retrieval Service Protocol

v. ROLE OF TRIAL SPONSOR AND FUNDER

Royal Papworth Hospital NHS Foundation Trust undertakes to adhere to all expectations of a Sponsor as set out by the Health Research Authority Research Governance Framework 2015 and adhere to the Medicines for Human Use (Clinical Trial Regulations) 2004 Act and all applicable amendments. This includes set-up, management, financing, risk assessment, monitoring, audit, statistical oversight, analysis and dissemination of results.

Heart Research UK undertakes to provide funding through reimbursement quarterly to Royal Papworth Hospital NHS Foundation Trust, up to the sum of £199,294.37, over a period of 18 months from the commencement date of the trial.

Heart Research UK has also conducted an independent peer review of the trial by three independent reviewers.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The Data Safety and Monitoring Committee (DSMC) will contain an independent chair and an independent statistician and will provide additional independent oversight and assurance of monitoring and safety aspects of the trial. The DSMC will make recommendations to the Trial Steering Committee (TSC) on the management of the trial.

The TSC will be chaired by an independent person and contain at least one layperson. They will meet on a biannual basis and send reports to the sponsor regarding the progress of the trial and adverse events or safety concerns. The TSC will receive recommendations made by the DSMC on the management of the trial and report to the trial management group.

The Trial Management Group will consist of (as a minimum) Dr Luke Williams, Mr Marius Berman, Professor Gavin Pettigrew, a designated Clinical Project Manager from Royal Papworth Hospital, and a designated statistician from Royal Papworth Hospital. The TMG will meet on a monthly basis to discuss all aspects of the trial, with a particular focus on recruitment and any adverse events or reactions.

vii. Protocol contributors

Mr Marius Berman, Consultant Cardiac and Transplant Surgeon and National Organ Retrieval Service Lead, Royal Papworth Hospital and NHSBT

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Mr Ron Flewett, Patient and Public Involvement Group, Royal Papworth Hospital

viii. KEY WORDS: Cardiac transplant, Perfusion, Myocardial preservation, Cardioplegia, Primary graft dysfunction

ix. TRIAL FLOW CHART

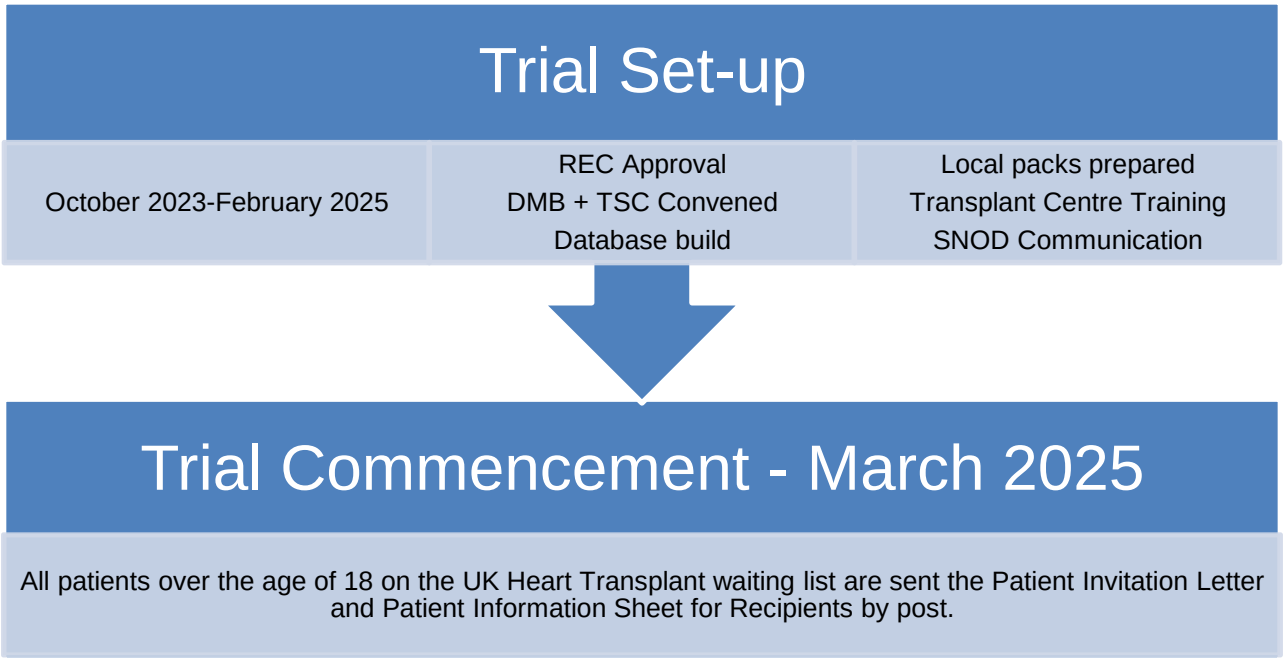


Figure 1: Trial Set-up Flow Diagram

Figure 2: Informed Consent Process Flow Diagram

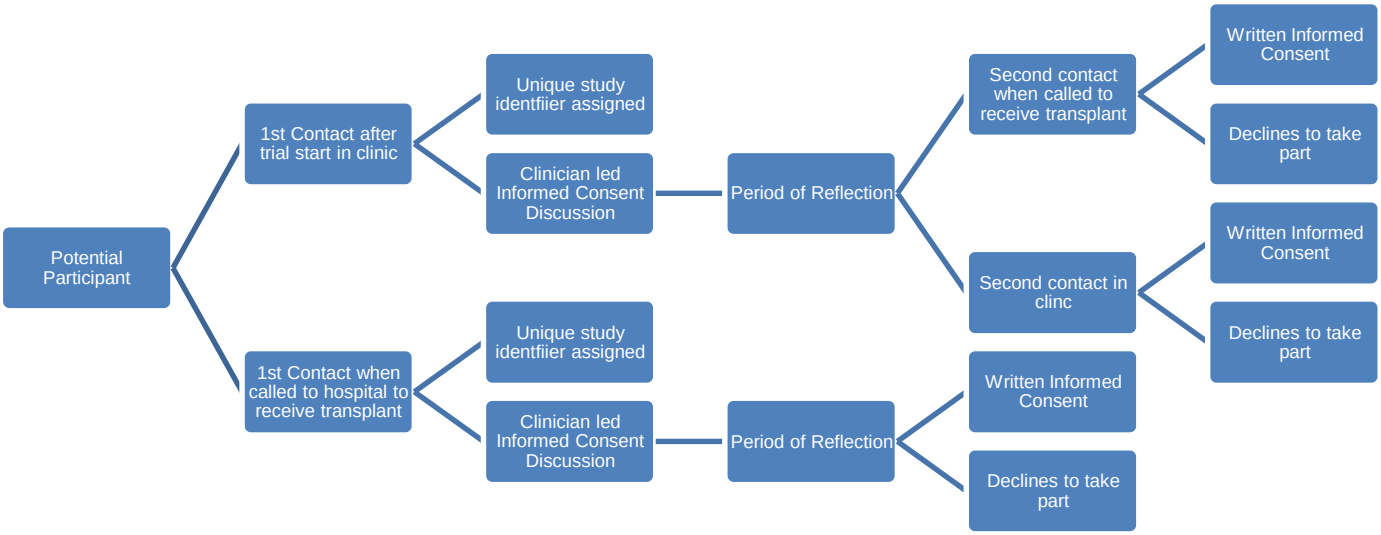
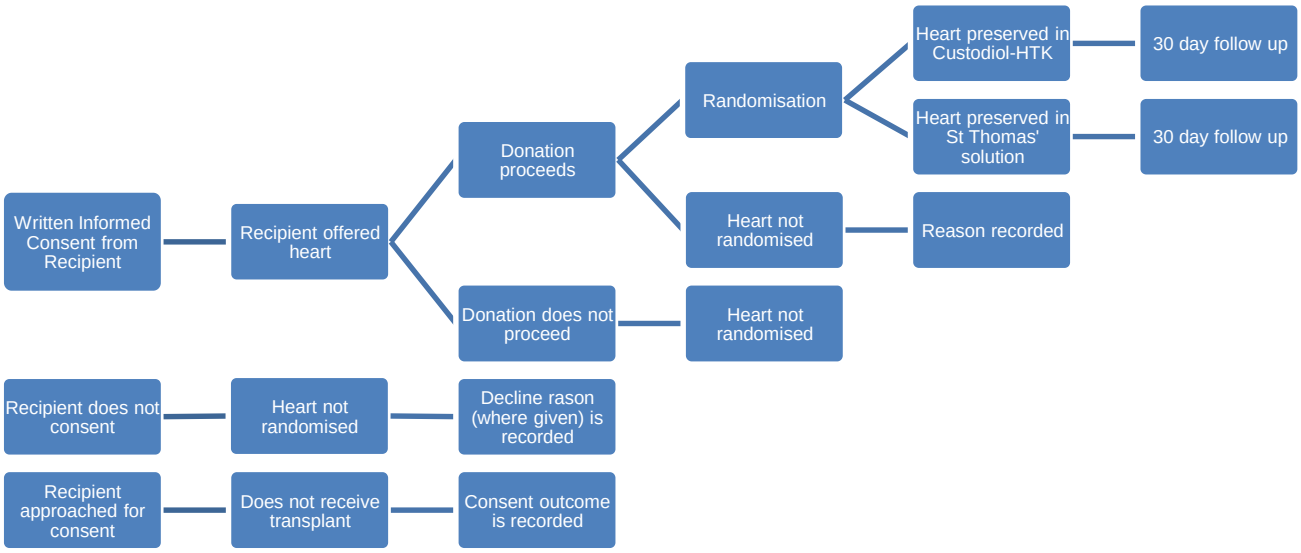


Figure 3: Potential Participant Flow Diagram



1 BACKGROUND

Primary graft dysfunction (PGD) is the leading cause of early mortality after cardiac transplantation, occurring in approximately one-third of cases, with a mortality rate of around 20%(1). PGD was defined, in an ISHLT consensus statement in 2014, as graft failure occurring in the first 24 hours after transplant, not as a result of a discernible cause(2). As a result of this definition, the causes of PGD are complex and difficult to investigate. Lund et al.(3) highlighted the importance of cold ischaemic time as a predictor of mortality, with increasing cold ischaemic time leading to increased short- and long-term mortality. Outcomes significantly deteriorate with a cold ischaemic time greater than 6 hours(4). The principal issues affecting the cold ischaemic heart are the loss of Adenosine Triphosphate (ATP), cellular swelling, extra-cellular oedema, cellular acidosis, calcium overload, endothelial injury and the build-up of oxygen free radicals, which contribute to mitochondrial damage(5). In turn, the release of these toxic metabolites on reperfusion of the heart can cause further injury, termed reperfusion injury. It is the purpose of the cardioplegia/myocardial preservative solution to mitigate these effects and the consensus statement of 2014 specifically highlights “better preservation”, including “different additives in solutions”, as a prevention strategy for PGD(2).

There are several solutions available and approved for use as myocardial preservatives in cardiac transplantation around the world. In the UK only two solutions are in current use: Sterile Concentrate for Cardioplegia Infusion (Martindale Pharmaceuticals), commonly referred to as St Thomas’ Solution, and sometimes marketed as Plegisol; and Custodiol-HTK solution (Dr Franz Köhler Chemie GMBH), sometimes referred to as Bretschneider solution. Currently, St Thomas’ solution is used in around 90% of UK heart transplants, primarily because of familiarity and cost, having been developed in the UK and being slightly cheaper than Custodiol-HTK.

St Thomas’ solution arrests the heart through its high potassium concentration and the addition of procaine but contains no additives to mitigate the effects of anaerobic metabolism during cold ischaemia(6). Custodiol-HTK contains histidine as a buffer to combat cellular acidosis, mannitol to reduce cellular oedema and α-ketoglutarate and tryptophan to act as free radical scavengers. During routine cardiac surgery, St Thomas’ solution must be administered every 20 minutes to maintain cardiac arrest, whilst the cardioplegic effects of Custodiol-HTK have been shown to last for more than 2 hours without reperfusion(7). The national median ischaemic time for Donation after Brainstem Death (DBD) cardiac transplantation is approximately 3 hours – this includes the time from delivery of the myocardial preservative solution to reperfusion of the heart within the recipient(8). During this time no reperfusion of preservative solution can be performed. We, therefore, hypothesise that the use of Custodiol-HTK as cardioplegia and preservative solution for donor hearts will improve outcomes in cardiac transplantation, by providing enhanced cellular protection during cold static storage.

A large retrospective analysis of the American United Network for Organ Sharing (UNOS) database showed that solutions designated by the research team as “cardioplegia solutions”, which included St Thomas’ and similar solutions, lead to significantly worse outcomes than Custodiol-HTK in heart transplantation(9). Several small animal studies have also suggested improved cardiac preservation with Custodiol-HTK over St Thomas’ solution(6, 10-12). A systematic review and meta-analysis of Custodiol-HTK as a cardioplegia solution in cardiac surgery contained a qualitative review of the only 6 human studies investigating Custodiol-HTK in heart transplantation: three case series, two cohort studies and one randomised controlled trial with 48 patients that was insufficiently powered to detect a difference between three solutions (Custodiol-HTK, UW and Celsior)(13). Unfortunately, this merely highlighted the paucity of evidence comparing myocardial preservative solutions in transplantation, with the authors concluding: “The pre-clinical data is sufficient to encourage large-scale, quality randomised trials to answer the compelling question of which preservation solution provides optimal protection for the cardiac allograft.”

2 AIMS

Custodiol-HTK and St Thomas' solution have never been directly compared in a randomised controlled trial of human cardiac transplantation. The overall aim of this research project is to investigate the two solutions currently in use in the UK, by performing a high-quality, multi-centre, randomised controlled trial comparing St Thomas' solution with Custodiol-HTK for myocardial preservation during cold static storage of cardiac allografts from DBD donors. The solutions will be compared in the post-marketing authority state, delivered in the form and administration route for which they are approved. The primary outcome of interest is PGD, as this is a significant clinical challenge in cardiac transplantation and its incidence is highly likely to be affected by the quality of myocardial preservation during cold static storage, as highlighted by the ISHLT 2014 consensus statement(2). PGD not only results in higher earlier mortality and morbidity but also has significant cost implications for the healthcare provider. For example, patients with PGD have a median length of ICU stay of 14 days, compared to 5 days without PGD(14). Furthermore, patients without PGD have significantly lower use of mechanical circulatory support (MCS), as well as significantly lower use of renal replacement therapy, need for a return to theatre and inotrope use(14). Just one extra night in ICU is thought to cost around £1,600(15), whilst one day of extra-corporeal membrane oxygenation (the main type of MCS used in this setting) costs approximately £6,000-£12,000(16), without factoring in increased staffing and other resource costs. Therefore, if our trial shows a reduction in PGD with one solution, this could have significant cost implications for the NHS.

Despite the potential cost savings and healthcare outcome benefits of any reduction in PGD, detecting a clinically meaningful difference between the two solutions will require a large sample size. Informing this sample size calculation is complex, because of the lack of high-quality data comparing the two solutions. A power calculation for a superiority trial based on the development of primary graft dysfunction as the primary outcome showed that a sample size of 400 patients would allow detection of a 14% absolute risk reduction in PGD between the two solutions of interest (from 36% to 22%) corresponding to an odds ratio of 0.5 (or 17 cases of PGD prevented per year) with a probability (power) of 0.85 with a type I error of 0.05 when considering a two-sided test of difference in proportions. As approximately 120 adult DBD heart transplants are performed in the UK each year, we estimate that the larger trial will take 5 years to complete (i.e., 80 x 5 = 400).

Therefore, we intend to perform a feasibility study to see if we can recruit sufficient patients within a reasonable timeframe, in order to justify undertaking such a large national clinical trial.

The research project has been discussed at a focus group with the Royal Papworth Hospital patient representatives Dr Marijecke Veltman-Grisenthwaite and Mr Ron Flewett. They felt this to be a very worthwhile study and that the primary outcome is likely to be achievable. The study Protocol was modified based on their feedback.

2.1 Assessment and management of risk

This trial is categorised as Type A (No higher than the risk of standard medical care).

Both St Thomas' solution and Custodiol-HTK hold MHRA approval for use as cardioplegia and preservative solutions during cardiac transplantation in the UK. Both have excellent safety profiles and are routinely used, although St Thomas' solution is used most frequently as it forms part of the UK National Organ Retrieval Service (NORS) Protocol for cardiac allograft retrieval. Therefore, there is

not thought to be any additional risk, beyond the risks associated with undergoing a cardiac transplant, to participants as a result of taking part in this study.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To assess the feasibility of conducting a national, single-blind, randomised controlled efficacy trial comparing the effect of using Custodiol-HTK or St Thomas' solution as cardioplegia and preservative solution during cardiac transplantation of UK DBD donor hearts on the rate of PGD.

Hypothesis:
It is feasible to conduct the above trial in the UK within 5 years.

3.2 Secondary objectives

Secondary Objective 1:
To compare the effect of Custodiol-HTK solution and St Thomas' solution on the outcomes of cardiac transplantation from donation after brainstem death (DBD) donors.

Hypothesis 1:
There will be a difference between the two solutions in terms of primary graft dysfunction and 30-day mortality.

Secondary Objective 2:
To investigate the effects of Custodiol-HTK solution on the transplanted heart in terms of haemodynamic performance.

Hypothesis 2:
There will be a difference between the two preservation methods in terms of haemodynamic performance, specifically cardiac power output index in the first 6 hours after transplant.

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint

The proportion of eligible donor cardiac allografts that are randomised and receive the correct intervention. This is a composite outcome. For the purposes of this study, eligible cardiac allografts are defined as hearts from adult (age>18 at time of donation) DBD donors, where an offer has been made to an adult (age>18 at time of transplant procedure) recipient at a UK transplant centre and the donor cardiac allograft is retrieved from the donor and implanted into the recipient. The composite outcome, therefore, is defined by the product of the following proportions:

i. The proportion of eligible donor cardiac allografts where the recipient has consented to take part in this study.
ii. The proportion of (i.) where randomisation occurs according to the Protocol.
iii. The proportion of (ii.) where the heart is preserved in the allocated preservative solution.

We feel this composite outcome provides the best estimate of the feasibility of the larger trial. A proportion that falls within or above the upper limit of the 95% Jeffreys credible interval defined assuming that a probability of 2/3 of meeting the primary target and a sample size of 50 will be considered a success, as it would indicate the potential to recruit approximately 80 hearts per year, a yearly number corresponding to a probability of 0.85 (power) of detecting the primary effect in the 5-

year main study. A proportion that falls below the 95% credible interval of two-thirds of eligible donor cardiac allografts but above one-third would be considered potentially successful, with the option to continue to perform the randomised controlled efficacy trial, providing appropriate changes can be made to address any concerns.

3.3.2 Secondary endpoints

i. The proportion of eligible recipients who consent to take part in the study.
ii. The proportion of eligible donor cardiac allografts where randomisation occurs according to the Protocol.
iii. The proportion of eligible donor cardiac allografts where the heart is preserved in the correct randomly allocated solution.
iv. Key outcome completeness
v. The development of Primary Graft Dysfunction, according to the 2014 ISHLT Consensus Definition(2), within 24 hours of transplant implantation.
vi. Echocardiographic parameters from trans-oesophageal echo immediately after transplant implantation, including:
    a. Left Ventricular ejection fraction
    b. Left ventricular maximal posterior wall thickness
    c. Maximal septal wall thickness
    d. Left ventricular function
    e. Right ventricular function
    f. The presence/absence of regional wall motion abnormalities
vii. 30-day all-cause mortality.
viii. 6-month survival rates, determined at the end of the study.
ix. Development of the following post-operative complications will be recorded:
    a. Dysrhythmias (defined by the clinical team) within 30-days of transplant implantation
    b. Myocardial Infarction (defined according to ESC definitions of myocardial infarction post cardiac surgery) within 30-days of transplant implantation
    c. Stroke (defined by radiological evidence of ischaemia/haemorrhage and clinical symptoms of stroke) within 30-days of transplant implantation
    d. Transplant rejection (defined by the clinical team and confirmed on histopathology of biopsy material or post-mortem) within 30-days of transplant implantation
    e. The need for post-operative renal replacement therapy within 30-days of transplant implantation
    f. Infection (from any source requiring antibiotic therapy) within 30-days of transplant implantation
    g. Venous thromboembolism (defined by radiological evidence and need for treatment) within 30-days of transplant implantation
    h. Re-admission to any UK hospital within 30 days of transplant implantation
    i. Hyponatraemia within 24 hours of transplant implantation (Na<125mEq/L on any serum laboratory-analysed sample, not blood gas analysis)
x. Median length of initial ICU stay in hours
xi. Median length of initial hospital stay in days

3.3.3 Exploratory endpoints

Cardiac Power Output Index (CPOi) at admission to ICU post-transplant implantation and at 6h post-operation will be recorded. The difference between CPOi within individuals at admission to ICU and 6h post-operation will be calculated. Cardiac Power Output is defined as the hydraulic energy created by the ventricles per unit time. It is the product of Cardiac Output (CO), measured by Swan Ganz, and the Mean Arterial Pressure (MAP), taking into account the filling state of the individual and indexed to body size. It has been validated as a measure of pump failure in patients with cardiogenic shock. Primary graft dysfunction is effectively the failure of the cardiac allograft to generate sufficient cardiac output and therefore it has been hypothesised that low cardiac power output after transplantation will correspond to the development of PGD and the requirement for mechanical circulatory support. CPOi on admission to ICU has been shown to be correlated with donor to recipient heart mass ratio and inversely correlated to cardiopulmonary bypass time. Previous work from Birmingham has determined a rule-in, rule-out algorithm for cardiac power index as a predictor of severe PGD and early mortality.

3.3.4 Table of endpoints/outcomes

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective: To assess the feasibility of conducting the CUSToS study.	The proportion of eligible donor cardiac allografts that are randomised and that receive the correct intervention.	At the end of recruitment.
Secondary Objectives: To compare the effect of Custodiol-HTK solution and St Thomas' solution on the outcomes of cardiac transplantation from donation after brainstem death (DBD) donors.	i. The proportion of eligible recipients who consent to take part in the study. ii. The proportion of eligible donor cardiac allografts where randomisation occurs according to the Protocol. iii. The proportion of eligible donor cardiac allografts where the heart is preserved in the correct randomly allocated solution. iv. Key outcome completeness v. The development of PGD, measured at 24-hours post-transplant vi. Left Ventricular ejection fraction, left ventricular maximal posterior wall thickness, maximal	i.-iv., vii.-viii., x.-xi. At the end of recruitment v.-vi. 24-hours post-transplant ix. 30-days post-transplant

	septal wall thickness, left ventricular function, right ventricular function and the presence/absence of regional wall motion abnormalities measured on trans-oesophageal echo immediately after transplant implantation vii. 30-day all-cause mortality viii. 6-month survival ix. Development of post-operative complications within 30 days of transplant x. Median length of initial ICU stay in hours xi. Median Length of initial hospital stay in days	
Exploratory Objectives: To assess CPOi as an outcome measure for predicting PGD	Cardiac Power Output Index, absolute differences between the groups (PGD/No PGD and Custodiol-HTK/St Thomas') and change over time within and between groups	At admission to ICU and 6 hours post admission to ICU

4 TRIAL DESIGN

This is a feasibility study of a single-blind, national, multi-centre, randomised controlled trial. The purpose of the trial is to assess the methodology and feasibility of conducting an appropriately powered efficacy randomised controlled trial comparing Custodiol-HTK with St Thomas' solution for donor cardiac allograft preservation during cardiac transplantation. The design, therefore, replicates a larger efficacy randomised controlled trial, differing only in its primary outcome, as described above.

The trial will be conducted at all six UK adult cardiothoracic transplant centres. Donor hearts included in the study will be randomly allocated on a 1:1 basis to receive either Custodiol-HTK or St Thomas' solution as cardioplegia and preservative solution during the organ retrieval process. Participants (recipients of donor cardiac allografts that have received one of the above treatments as part of the random allocation process) will be blinded to their treatment allocation. It is not possible to blind the healthcare staff involved in the transplant process as the solutions have different volumes and methods of administration and are different colours. Healthcare staff who look after the recipient but were not directly involved in the transplant retrieval or implant procedures should not be informed of the treatment allocation.

5 TRIAL SETTING

The trial will be conducted at all six UK adult cardiothoracic transplant centres. These are Birmingham Queen Elizabeth Hospital, Glasgow Golden Jubilee Hospital, Manchester Wythenshawe Hospital, Harefield Hospital, Newcastle Freeman Hospital and Royal Papworth Hospital. A list of the cardiothoracic transplant units in the UK can be found at https://www.odt.nhs.uk/transplantation/cardiothoracic/cardiothoracic-transplant-units/.

London Great Ormond Street Hospital is a UK cardiothoracic transplant centre but is not participating in the study because only paediatric transplants are performed there.

All potential recipient participant recruitment and follow-up will be conducted in the UK transplant centre where they are listed to undergo their cardiac transplant.

Donor recruitment will also take place in any UK hospital that has a specialist nurse in organ donation and offers an adult cardiac allograft to the NORS.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

i. Recipient population: All adult patients who are on the NHSBT waiting list for a cardiac transplant in the UK.
ii. Donor Population: Any adult cardiac allograft donated to a UK recipient will be considered eligible.
iii. Age:
   (i) Recipient population: The recipient must be aged 18 or over. Recipients who turn 18 on or after the day that they receive a cardiac transplant in the UK will be eligible for inclusion provided there is sufficient time for the informed consent process to take place after midnight on the day of their 18th birthday.
   (ii) Donor population: Any donor aged 18 or over on the day of their donation will be eligible.
iv. Urgency Status: All categories of listing including urgent and super-urgent will be eligible.
v. Pathology: All pathologies leading to the requirement for a heart transplant will be eligible.
vi. Multiple transplants: Second, third or subsequent heart transplants within the same individual will be eligible provided this subsequent transplant does not occur in an emergency setting during the same hospital admission as the index heart transplant. The index transplant would remain eligible for inclusion in the trial in this case.
vii. Multiple studies: Patients who are simultaneously enrolled in other trials will be considered eligible to take part in this study, providing the trial Protocol does not interfere with the treatment Protocols laid out in this document.

6.2 Exclusion criteria

i. Age: Recipients under the age of 18 at the time of transplantation. Donors under the age of 18 at the time of transplantation.
ii. Emergency re-transplant patients, where the re-transplant occurs within the same admission as the index transplant.
iii. Patients who receive hearts procured from donation after circulatory death (DCD) donors. These patients are excluded from the study because the process of organ retrieval from DCD is very different, involving ex-situ perfusion of the beating heart with oxygenated blood, rather than maintenance of the heart in the cold arrested state with a preservative solution. The system for doing this ex-situ perfusion is called the organ care system (OCS). Currently, approximately 10% of UK heart transplants are performed using a DCD heart.
iv. Patients who receive hearts from DBD donors procured using the organ care system device or thoracic-abdominal normothermic regional perfusion (NRP). This rarely occurs. Please note hearts procured alongside ongoing abdominal normothermic regional perfusion (which does not interfere with or alter the process for heart procurement in any way) will be eligible.
v. Patients receiving a heart-lung block, multi-visceral transplant or other multi-organ transplant.
vi. Donor cardiac allografts which have been offered to a UK recipient but are subsequently turned down after assessment by the NORS team.
vii. Donor cardiac allografts where the donor family or representative have not consented for the organ to participate in research.

viii. Donor's or recipients with a known allergy or hypersensitivity to the active ingredients or excipients of either of the IMPs. These include:

(i) Procaine (St Thomas' solution)
(ii) Disodium Edetate (St Thomas' solution)
(iii) Sodium Hydroxide (St Thomas' solution)
(iv) Potassium chloride (Both)
(v) Magnesium chloride hexahydrate (Both)
(vi) Sodium chloride (Custodiol-HTK)
(vii) Calcium Chloride dihydrate (Custodiol-HTK)
(viii) Histidine (Custodiol-HTK)
(ix) Histidine hydrochloride monohydrate (Custodiol-HTK)
(x) Tryptophan (Custodiol-HTK)
(xi) Mannitol (Custodiol-HTK)
(xii) α-Ketoglutarate (Custodiol-HTK)
(xiii) Potassium hydroxide (Custodiol-HTK)

6.3 Diversity and Inclusion Statement

The research team is committed to ensuring equal opportunity to participate in research. No potential participant will be denied the opportunity to participate in this study as a result of their gender, race, disability, religion or sexual orientation.

7 TRIAL PROCEDURES

See appendix 2 for a schedule of trial procedures.

7.1 Recruitment

Eligible potential transplant recipient participants will be identified by their status on a UK heart transplant waiting list. Eligible potential donor participants will be identified at the time of the offer of a donor cardiac allograft to the UK NORS. Anonymised information on potential transplant recipient participants who decline to take part, or are not randomised, will be recorded in accordance with the primary objective of this feasibility study. In accordance with the requirements for CONSORT reporting this anonymised data will include:

i. age,
ii. sex,
iii. ethnicity,
iv. the reason for declining to take part (where given),
v. the reason not randomised.

7.1.1 Participant identification

Eligible potential transplant recipient participants will be identified by the PIs in each centre from their centre's heart transplant waiting list. All eligible patients will then be sent a letter by their transplant centre advertising the study and containing the participant information sheet. Access to personally identifiable information will be performed by the PI or delegated individual in each centre, who is a member of the transplant care team. The letters will be addressed and sent by the PI or delegated individual(s). This process will not be contracted to a third-party mailing service.

Eligible potential donor cardiac allografts will be identified by the transplant coordinator or designated person in the recipient centre at the time of the offer of a donor cardiac allograft to the UK NORS.

The eligibility of potential transplant recipient participants will be confirmed by the designated person taking informed consent in their UK cardiothoracic transplant centre, at the time when the informed consent discussion takes place.

The eligibility of potential donor cardiac allografts will be confirmed by a member of the retrieving UK NORS team.

7.1.2 Screening

Eligibility screening will require the potential transplant recipient participant's transplant clinician to review their medical notes and ensure that they meet the eligibility requirement prior to commencing the informed consent discussion. There will be no extra investigations, procedures or questionnaires required to confirm eligibility. The process and outcome of eligibility screening should be recorded in the screening and eligibility log.
Potential transplant recipient participants may become ineligible or eligible during the study, as their status on the Heart Transplant waiting list is subject to change, depending on their clinical circumstances. Final confirmation of eligibility and informed consent will occur just prior to their receipt of a transplant.

7.1.3 Payment

No payments will be made to potential participants, confirmed participants, organ donors or their families for their involvement in this study. It is not anticipated that participants or donors will incur any extra costs as a result of taking part in this study.

7.2 Consent

7.2.1 Potential Transplant Recipient Participants

For potential transplant recipient participants, the informed consent process will take place over a period leading up to their receipt of a cardiac transplant in the UK. See the Informed Consent Process Flow Diagram (Figure 2, p. 13) for an overview.

The process will begin with the receipt of an invitation letter and participant information sheet in the post. The letters will be sent by the direct care teams in each centre. PIs or delegated individuals who are members of the transplant care team in each of the individual centres will access the names and addresses (personal identifiable information) of all patients on the waiting list for a heart transplant at their institution for this purpose.

The next step in the process will take place during the next in-hospital contact between the potential recipient participant and their transplant team. This is most likely to be their next follow-up appointment in clinic at their transplant centre but may occasionally be when they are called to the hospital to receive their transplant or have an inpatient admission at their transplant centre for another reason. The preferred option is for this contact to take place in the clinic.

The Chief Investigator (CI) delegates the responsibility to take informed consent to the Principal Investigator (PI) in each centre. The PI in each centre may delegate responsibility to take informed consent to clinicians or specialist nurses in each transplant centre, once they have received training during their location centre induction, provided evidence of GCP training and signed the Delegation and Training Logs in their local centre.

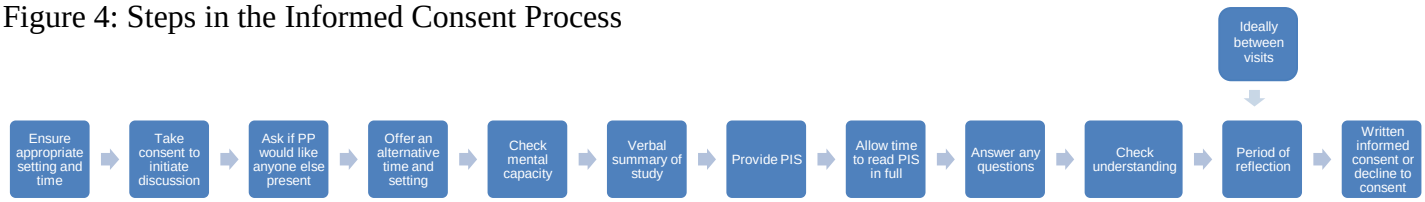
The approach to participate in an informed consent discussion should be made at an appropriate time and in an appropriate setting, as decided by the person taking consent. The informed consent discussion should start by taking consent to participate in the discussion about the study. Implied consent through the continuation of the discussion will be acceptable for this. The potential participant should be offered the opportunity to have other individuals present for support if they wish. The potential participant should also be offered the opportunity to take part in the discussion at an alternative time or in an alternative setting that is more convenient to them. The potential participant should be provided with the participant information sheet, given a verbal summary by the person taking consent and then afforded time to read the participant information sheet in full. The person taking consent should answer any questions that the potential participant or their family or other representatives (where present) have. The potential participant should then be offered a period of reflection prior to taking written evidence of informed consent. Ideally, this should not take place until the next in-hospital contact, to allow the potential participant to reflect at home and discuss participation with their family. The next in-hospital contact may be their next clinic appointment, an in-patient admission or when they are called to the hospital to receive their transplant. Where requested by the potential participant, written evidence of informed consent may be taken in the same in-hospital episode as the first approach, after a period of reflection. Where the potential participant declines to consent, this should be recorded, and no further approaches should be made unless expressly requested by the potential participant. The person approaching potential

participants for an informed consent discussion must always check their local centre pack to ensure that the patient has not been approached before and declined to consent. Any potential participant who declines to consent should be informed that they do not need to give a reason for declining. Where a reason is given, this should be recorded.

Where the approach is made when the potential participant is called to receive their transplant, the member of the direct care team who will be taking consent will ensure the approach is made at an appropriate time, in an appropriate setting and that adequate time is left for the potential participant to read the participant information sheet, reflect and ask questions before taking written evidence of informed consent. Where the approach is made during hospital admission for another reason, the approach should not be made until the potential participant is sufficiently recovered to take a full and active part in the informed consent discussion. This will be judged by the potential participant's direct care team. The potential participant should be offered the opportunity to decline to take part in the discussion at that time and be offered an alternative time.

All potential participants, regardless of when they provided written evidence of informed consent, must have their ongoing consent confirmed just before their receipt of a transplant. Verbal confirmation of consent, documented on the consent form, by an appropriate person listed in the Delegation Log, is acceptable for this purpose.

Figure 4: Steps in the Informed Consent Process



7.2.2 Potential Donor Participants:

Potential donor participants' families are approached by the specialist nurse in organ donation (SNOD) to take part in an informed consent discussion regarding organ donation. There will be no changes to this process as a result of this study. This discussion includes a question on whether the donor family consent for the organs to participate in research. In order for a donor heart to be eligible to be included in this study the donor family must have given consent for the organs to participate in research. This consent will be checked at randomisation against the eligibility criteria.

During the development of this Protocol, the consent process has been extensively discussed within NHS Blood and Transplant's Research and Quality Assurance teams, who are responsible for maintaining regulatory compliance and act as advocates for our donors and their families. This concluded that specific donor consent for participation in this study is not required. The primary reason for this is that perfusion fluid is not discussed with a donor family and organ perfusion with any licensed product is an integral part of consent for organ donation.

Other reasons include:

i. Donor families often feel burdened by the amount of information provided as part of the organ donation consent process. Asking for specific consent is not only unnecessary but may also be detrimental to donor families at a time of grief.

ii. The intervention being applied by random allocation in this study will not have an effect on the donor, who is deceased, but may have an effect on the recipient, who therefore must provide informed consent.

iii. No relevant material is being removed as part of the study and therefore consent is not required under the Human Tissue Act (2004).

iv. No additional data is being collected on the donor. Any donor-related data required by the study will be routinely collected by NHSBT and supplied to the research team in a secure and anonymised form.

7.2.3 Translation:

Where English is not the participant's first language, or if a verbal translation is requested, this will be via a hospital interpreter, where available. When a hospital interpreter is not available in person, hospital-provided telephone translation services are acceptable. Written material will be translated on request to the trial manager, who will contract an NHS-approved translation service for this purpose. As all centres are in England or Scotland, written material will not routinely be provided in Welsh, but can be requested in Welsh by any potential participant, whereupon the trial manager will arrange translation by an NHS-approved translation service, as above.

7.2.4 Participant Withdrawal:

Recipient participants are free to withdraw at any time on request to the CI or their local PI. Where given, a reason for withdrawal from the study will be recorded. Discontinuation of the trial treatment or withdrawal of consent by the recipient for any reason should be communicated to the Sponsor as soon as possible by email.

Where transplant recipient participants withdraw consent prior to organ retrieval, the donor heart will not be randomised and no additional data, beyond the minimum dataset of age, sex, ethnicity, approach to consent and outcome of consent discussion, will be collected on the recipient. Data on donors whose corresponding recipient withdraws consent, or did not provide consent, will not be requested from NHSBT. Where transplant recipient participants withdraw consent after organ retrieval, data collected up to that point will be included in the data reported for the trial. No outcome data will be collected from that recipient but data from the NHSBT Transplant registry may still be accessed unless the withdrawing participant expressly denies this. They should be offered the opportunity to deny this consent, and the outcome should be recorded on the withdrawal of consent form. Furthermore, data on the donor of a participant who withdraws consent after organ retrieval may be requested from NHSBT.

Please note, for the definition of withdrawal of consent before and after organ donation/retrieval, the point of organ donation/retrieval will be considered the point at which the WHO pre-operative briefing commences in the operating theatre. This time point has been chosen because the entire surgical retrieval team must know whether there will be a randomisation process during the retrieval operation and prepare accordingly. It would not be safe to change the plan after this time. Where consent is withdrawn prior to this point, the retrieval will still proceed but no trial treatment will be applied, and the heart will be preserved in whichever solution the surgeon prefers; this would normally be STH in accordance with current NORS Protocols.

7.3 The randomisation scheme

Randomisation of hearts will occur after consent of the recipient has been secured and after the heart has been deemed acceptable by the medical team. Permuted blocks will be used to randomise each heart to one of the two treatments while ensuring a 1:1 overall allocation ratio. The randomisation will be performed using the secure online platform SealedEnvelope (Sealed Envelope Ltd. 2022. Simple randomisation service. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/ [Accessed 25 May 2023]). Once consent to participate in the study has been confirmed on the part of the recipient and the suitability of the heart for transplant has been confirmed, the PI, or delegated individual at the transplant recipient centre, will access SealedEnvelope, via a secure and traceable login and generate a random allocation, which will be sent via email to the randomiser and the trial manager. Please note that the randomisation procedure should not be conducted until the intention to proceed with cardiac donation to the named recipient has been confirmed. This should be after the retrieval operation has begun and the retrieval team have assessed the heart in situ and confirmed its suitability for transplant. It is routine for the recipient transplant coordinator to be contacted via telephone during the retrieval operation once suitability to transplant has been confirmed and therefore the randomisation should occur at this stage. This will not delay the retrieval operation. The retrieval team must include the instructions for delivery of both solutions at the WHO pre-operative briefing. It will be the randomiser's responsibility to inform the NORS team of the outcome of the randomisation in a timely manner, via telephone.

Each NORS team will maintain both treatments, and the equipment required to use either treatment, at all times and take both treatments with them to the retrieval centre. Once they have been informed of the treatment allocation, they will prepare and administer the treatment in accordance with the methods set out in this Protocol. Refer to the trial's 'Registration and Randomisation Guidelines for Sites' for more information.

7.4 Blinding

The trial is single (participant) blind. Care providers involved in the transplant process cannot be blinded due to the different administration regimes for each treatment. Anyone who is not directly involved in the organ retrieval or transplant operations should not be informed of or seek to discover the treatment allocation. It will be the responsibility of the local PI in each centre to minimise the number of individuals who are aware of the treatment allocation.

Ideally, the outcome assessor who inputs clinical outcome data to the database should be blind to the treatment allocation. However, this is unlikely to be practically possible, due to the limited number of people involved in the transplant process. In order to assess the feasibility of keeping outcome assessors blind, each time an outcome assessor inputs data to the database they will be asked to record whether it would have been possible for them to remain blinded (i.e., did they already know the treatment allocation through previous involvement in the transplant). It is the responsibility of the local PI to ensure that appropriate individual(s) are in place to record clinical outcome data.

Local induction packs and training will stress the importance of the treatment allocation remaining unknown to anyone outside of the teams directly involved in performing the organ retrieval and transplant implantation procedures. However, it will be necessary to record the preservative solution and its method and volume of administration on the operation note. The CI acknowledges that any healthcare individual with access to the patient's operation notes and medical records may have access to this. However, doing so in order to discover the treatment allocation, except under the circumstances outlined below in Emergency Unblinding, would be in breach of the General Data Protection Regulation (GDPR) and the UK Data Protection Act (2018).

Access to medical records is monitored within all NHS organisations and should be reviewed by the PI where there is any concern of inappropriate access to identify the treatment allocation.

Donor family and transplant recipients should not be informed of their treatment allocation, except under the circumstances outlined below for Emergency Unblinding.

7.5 Emergency Unblinding

The Trial Manager will maintain an anonymised list of treatment allocations via SealedEnvelope.

The primary reason for emergency unblinding will be to allow an investigator/treating clinician rapid access to the treatment allocation, should it be required to treat the patient appropriately. As this trial is not fully blinded many of the investigators/treating clinicians may already be aware of the treatment allocation. However, emergency unblinding will be permitted in the following circumstances:

i. In the event that a clinician, who was not directly involved in the organ retrieval or transplant implantation procedures (and therefore does not already know the treatment allocation), caring for the participant feels that they need to know the treatment allocation to treat the transplant recipient in an emergency.

ii. In the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR), where unblinding is required for reporting to the MHRA.

Emergency unblinding can be achieved in the following ways:

i. Contact the PI who can assess the request and choose to reveal the treatment allocation where they feel it is clinically indicated;

ii. Contact the Trial Manager who can access the list of treatment allocations and provide emergency unblinding;

iii. Contact any member of the transplant team who was involved in the transplant procedure to reveal the treatment allocation, providing they inform the PI ex post facto;

iv. Access the operative records themselves, provided they inform the PI ex post facto.

The PI must record the reasons for any unblinding and communicate these to the CI, as well as recording them in the site file and the medical notes. Any emergency unblinding will also be documented at the end of the trial in any final trial report.

The CI must notify the Sponsor in writing as soon as possible following unblinding detailing the necessity of the code break. The CI/PI will also notify the relevant authorities. The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DSMC Charter. This is the responsibility of the CI.

7.6 Baseline Data

7.6.1 Donor Baseline Data

Donor baseline data will be obtained from the NHSBT Transplant registry. The recipient identifier will be used to match to the donor identity in the Transplant registry. Collaboration with NHSBT in order to access this data via the transplant registry reduces the workload on the research and clinical teams and prevents unnecessary duplication of data collection.

i. The following baseline data will be collected for all eligible donors:
i. ABO blood group
ii. Height
iii. Weight
iv. BMI
v. Pathology leading to brainstem death
vi. History of Hypertension
vii. History of Pulmonary disease
viii. History of cardiac disease
ix. History of liver disease
x. History of Diabetes mellitus
xi. Insulin use
xii. Renal function (serum creatinine)
xiii. Liver function (serum bilirubin)
xiv. History of infection during admission
xv. Malignancy
xvi. Left Ventricular Ejection Fraction
xvii. Ischaemic time
xviii. Current or past smoker
xix. History of Drug abuse
xx. Inotrope score

7.6.2 Recipient Baseline Data

Recipient Baseline Data will be obtained from the NHSBT Transplant Registry. The NHS number and NHSBT OTDT Recipient number of all participants will be recorded in the CRF. This will be stored in a password-protected site file.

The following baseline data will be recorded for all eligible participants:

i. age,
ii. sex,
iii. ethnicity.

The following additional baseline data will be recorded for eligible participants who are approached but do not consent to take part in the study:

i. the reason for declining to take part (where given).

The following additional baseline data will be collected for all eligible recipients who consent and receive a transplant:

i. ABO blood group
ii. Height
iii. Weight
iv. BMI
v. Pathology leading to need for transplant
vi. 1st, 2nd, 3rd or more heart transplant
vii. History of Hypertension
viii. History of Diabetes mellitus
ix. Renal function (eGFR and serum creatinine)
x. Liver function (bilirubin)
xi. Left Ventricular Ejection Fraction prior to transplant
xii. Current smoker (>5 a day within last 6 months)
xiii. Use of inotropes at time of transplant
xiv. Mechanical Circulatory Support immediately prior to transplant
xv. Previous cardiac surgery
xvi. Pre-operative mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output.

7.7 Trial assessments

Assessment of eligibility: Upon trial commencement, the PI at each centre will access the heart transplant waiting list at their centre. Each potential participant will be assessed for eligibility according to the inclusion/exclusion criteria laid out in section 6 of this Protocol. All eligible potential participants will be assigned a unique study identifier and sent an invitation letter. Every interaction should be recorded in the medical notes as per local Trust policies and all trial paperwork should be filed in the Individual Site File (ISF).

When a new patient is added to the centre's heart transplant waiting list the PI of the listing centre should be informed and assess eligibility to participate in the study. If the patient is eligible to participate, they should be assigned a unique study identifier and sent an invitation letter.

Informed consent discussion: Whenever an eligible potential participant has an in-person interaction with their transplant team at their transplant centre, they should be considered for an informed consent discussion. It will be the responsibility of the PI to instigate a system for determining when in-person interactions happen with potential participants. At each in-person interaction, the potential participant should be screened by checking the site file to determine at what stage of the informed consent process they are at. This must include an assessment of whether they have previously declined to consent, in which case they should not be approached again.

Recipient baseline data: The minimum baseline dataset of age, sex and ethnicity should be recorded for all potential transplant recipient participants within two weeks of study initiation. Once an in-person approach to take part in an informed consent discussion has taken place this should be recorded the medical notes. Once the informed consent discussion has taken place the outcome should also be recorded. Possible outcomes include declining to take part, requesting further time to make a decision or consenting to take part. Where the potential participant declines to take part, they should not be approached again, unless they specifically request to take part in another informed consent discussion. Once written evidence of informed consent is obtained from a potential transplant recipient participant,

the individual(s) designated by the PI should input this information into the database. This should be done within 48 hours of written evidence of informed consent being filed in the site file. When a potential participant is called to hospital to receive their transplant, their ongoing consent to take part in the study must be confirmed by a designated individual in that centre. Where consent is withdrawn at this stage this should be recorded by completing the withdrawal of consent form.

Donor baseline data: The donor baseline data outlined in section 7.6.1 will be accessed from the NHSBT transplant registry. This is to avoid duplication of data collection.

Randomisation: The randomisation procedure is outlined in section 7.3 of this Protocol. The outcome of randomisation should be recorded in the CRF, by the delegated individual(s) at the recipient centre.

Organ donation: The organ donation procedure will be carried out in accordance with the UK NORS Protocol. The only change to this Protocol will be the trial treatment, as outlined in section 8 of this Protocol. The outcome of organ donation and the treatment applied should be recorded in the CRF, by the delegated individual(s) at the recipient centre.

Transplant procedure: The transplant implantation procedure will proceed according to the method chosen by the implanting surgeon. There will be no adjustments necessary as a result of taking part in this trial. Operative data will be obtained from the NHSBT Transplant registry and will not need to be recorded in the CRF.

Initial outcome data collection: The delegated individual(s) in the recipient centre should input the CPOi, echocardiogram and PGD data to the database no later than 72 hours after the transplant procedure. This should be conducted in accordance with the blinding instructions laid out in section 7.4 of this Protocol.

CPOi is a calculated variable and will be obtained by uploading the following variables to the database:

i. Cardiac Output (L/min) measured by Swan-Ganz, using the thermodilution method and taking the average of three measurements, performed as soon as possible, and not later than 1 hour, after admission to ICU.
ii. Cardiac Output (L/min) measured by Swan-Ganz, using the thermodilution method and taking the average of three measurements, performed 6 hours +/- 2 hours after admission to ICU
iii. Body surface area calculated using the DuBois and DuBois formula: Body Surface Area= 0.007184 x (Height(m)^$^{0.725}$) x (Weight(kg)^$^{0.425}$).
iv. Mean Arterial Pressure (mmHg) on invasive intra-arterial blood-pressure monitoring at the time of Swan-Ganz measurements.
v. Central Venous Pressure (mmHg) on invasive central venous pressure monitoring at the time of Swan-Ganz measurements.

As this is an exploratory outcome measure, with the intent to assess its utility based on real-world data, this will be assessed based on the above data being recorded on the intensive care electronic health record system. The measurements will be taken and recorded by the healthcare professional(s) looking after the participant. Where the outcome assessor transferring this data from the healthcare record to the trial database cannot find a measurement within the stipulated timeframe, this will be treated as missing data.

PGD will be determined based on the ISHLT consensus statement 2014 (2) and graded accordingly. PGD is defined as occurring within 24 hours, therefore all measurements included below must be taken within the first 24 hours after admission to ICU post-transplant procedure. Its definition requires the following variables to be recorded on the database:

i. Ejection fraction on echocardiogram; where multiple measurements are taken the lowest estimate of ejection fraction recorded will be inputted to the database.
ii. Haemodynamic variables taken at the time of a Swan Ganz measurement*:
    (i) Central Venous Pressure (mmHg)
    (ii) Pulmonary capillary wedge pressure (mmHg)
    (iii) Cardiac Output (L/min)
    (iv) Cardiac Index (L/min/m2)
    (v) Mean Arterial Pressure (mmHg)
    (vi) Transpulmonary gradient (mmHg)
    (vii) Pulmonary artery systolic pressure (mmHg)
iii. Vasoactive Inotrope Score (VIS), where VIS = dopamine [μg kg^{-1} min^{-1}] + dobutamine [μg $kg^{-1}min^{-1}$] + 100×adrenaline [μg kg^{-1} min^{-1}] + 50×levosimendan [μg kg^{-1} min^{-1}] + 10×milrinone [μg kg^{-1} min^{-1}] + 10 000×vasopressin [units kg^{-1} min^{-1}] + 100×noradrenaline dose [μg kg^{-1} min^{-1}].
iv. Presence/absence of an intra-aortic balloon pump (IABP).
v. Presence/absence of mechanical circulatory support (ECMO/LVAD/RVAD/BiVAD).

*Where multiple Swan Ganz measurements are taken within the first 24 hours after transplant, the set of variables taken at the same time as the highest inotrope score should be uploaded to the CRF. Where there are multiple Swan Ganz measurements with the same inotrope score the set of variables with the lowest cardiac output should be uploaded to the CRF.

The following echocardiographic parameters from trans-oesophageal echo immediately after transplant implantation will be recorded in the initial outcome data collection CRF:

i. Left Ventricular ejection fraction (% estimated by Simpson's biplane method)
ii. Left ventricular maximal posterior wall thickness (in mm)
iii. Maximal septal wall thickness (in mm)
iv. Left ventricular function (good, moderate, poor or very poor)
v. Right ventricular function (good, moderate, poor or very poor)
vi. The presence/absence of any regional wall motion abnormalities as determined by the TOE operator

30-day outcome data collection: The delegated individual(s) in the recipient centre should upload the 30-day mortality, postoperative complication, length of initial ICU stay, and length of initial hospital stay data, on the 31st day after the transplant procedure. This should be conducted in accordance with the blinding instructions laid out in section 7.4 of this Protocol. The variables will be entered into the CRF as follows:

i. 30-day mortality: alive/dead
ii. Post-operative complications:
    (i) Dysrhythmias (any within 30 days):
        1. Atrial fibrillation yes/no
        2. Ventricular tachycardia yes/no
        3. Ventricular fibrillation yes/no
        4. Other rhythm abnormality yes/no (specify)
    (ii) Myocardial Infarction within 30 days (defined according to ESC definitions of myocardial infarction post-cardiac surgery): yes/no

(iii) Stroke within 30 days (defined by radiological evidence of ischaemia/haemorrhage and clinical symptoms of stroke): yes/no
(iv) Transplant rejection within 30 days (defined by the clinical team and confirmed on histopathology of biopsy material or post-mortem): yes/no
(v) Infection within 30 days (from any source requiring antibiotic therapy): yes/no (specify suspected source)
(vi) Venous thromboembolism within 30 days (defined by radiological evidence and need for treatment): yes/no (specify PE/DVT)
(vii) 30-day re-admission to any UK hospital: yes/no
(viii) Hyponatraemia within 24 hours of transplant (Na<125mEq/L on serum sample, not blood gas analysis): yes/no
(ix) Need for renal replacement therapy (continuous veno-venous haemofiltration or dialysis): yes/no

iii. Length of initial† ICU stay in hours
iv. Length of initial† in-hospital stay in days with admission to ICU taken as the first day and the day of discharge home as the final day, counting inclusive of both.

†Initial refers to the first stay only. For example, if a patient is discharged from ICU after 24 hours but re-admitted after 48 hours, the outcome assessor would only record 24 hours as the length of initial ICU stay. Similarly, where a patient is discharged from hospital after 5 days, this would be recorded as 5 days, even if they are subsequently re-admitted and have a longer overall length of stay.

7.8 Long-term follow-up assessments

Trial closure data collection: After the 31st day after the final recruited participant has undergone their transplant the trial manager will telephone each of the PI to confirm the survival status of each recruited patient and, where a patient has died, the time to death will be measured from the date of their transplant and will be reported for all deaths due to all causes. The cause of death is to be recorded in all instances. The trial manager will also confirm with each PI the total length of in-hospital stay of any patient whose initial ICU or in-hospital stay was longer than 30 days. This should be completed within 4 weeks of the Trial Closure date.

There will be no additional long-term follow-up assessments related to participation in this trial. Long-term follow-up post-transplant is routine and life-long but will not be altered in any way as a result of participation in this trial.

7.9 Qualitative assessments

As this is a feasibility trial, our primary outcome will be determined by numeric proportions and supplemented by qualitative assessments as follows:

Recipient decline to consent: Where an eligible recipient declines to consent to participate, the delegated individual(s) taking informed consent should document the reason for decline to consent, where provided (free text). The potential participant must be informed that they do not need to provide a reason.

Randomisation failure: Where an eligible recipient has provided consent to participate in this study and receives an eligible transplant that has not been randomised, the reason for failure to randomise should be recorded by the delegated individual(s) in the recipient centre.

Treatment allocation failure: Where an eligible recipient has provided consent to participate in this study and receives an eligible transplant that has been randomised but the incorrect treatment has been applied, the reason for the application of the incorrect treatment should be recorded by the delegated individual(s) in the recipient centre.

Blinding: Delegated individual(s) who record data in the CRFs will be asked whether they could have been blinded to the treatment allocation. Data from these questions will be assessed to determine the feasibility of blinding outcome assessors in the larger trial.

7.10 Withdrawal criteria

Responsible clinician withdrawal: The clinician responsible for a patient may withdraw the patient from the trial at any time for appropriate medical reasons. As the treatment provided as part of this trial is a one-off dose provided before the transplant is conducted, there is unlikely to be any event in which this is the case. Should a clinician responsible wish to withdraw their patient from the trial for appropriate medical reasons they should inform their local PI, documenting their reasons in the medical notes and complete the withdrawal CRF, indicating whether it is a complete or partial withdrawal.

MHRA status: Should either treatment be subject to a change in MHRA regulatory status during the recruitment period the trial will be halted. The change in regulatory status will be discussed with the sponsor and DMC. The trial will only be re-commenced upon agreement of the sponsor, DSMC and MHRA. All participants who had received the treatment prior to the halting of the trial would continue to receive normal post-transplant care and would not be withdrawn from the study.

DSMC concern: Where the DSMC has concerns about one of the treatments, the trial will be halted. A concern would be raised with a primary graft dysfunction rate >50% (based on the current UK estimated PGD rate of 36%) or a 30-day survival rate <88.8% (based on the 95% confidence interval for the median 30-day survival rate after cardiac transplant in the UK currently – NHSBT figures 2020-2021).

As this trial is concerned with the feasibility of recruiting and maintaining participants within the Protocol, any withdrawal from the trial should result in the local PI and CI being informed and the reason for withdrawal should be fully documented in the medical notes.

Where a post-transplant participant is withdrawn within the recruitment period, this participant will not be replaced and, for the purposes of the primary outcome, would be considered as having had a successful primary outcome where the criteria for this had been met.

Early cessation would be considered if there was a 30% absolute risk reduction in primary graft dysfunction in one treatment arm, as this is the point at which there would be sufficient power to confidently confirm that one arm reduced primary graft dysfunction with a 5% significance level at 80% power. Early cessation will also be considered where the DSMC has concerns that one treatment leads to a significant increase in SARs and/or SAEs.

7.11 End of trial

The trial will end 31 days after the last recruited recipient participant receives their transplant. Day 1 will be considered the day that the participant is admitted to ICU following their transplant implantation procedure, with 31 days counted inclusively and the trial ending at 23:59 on the 31st day.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

8.1.1 Custodiol-HTK Solution for Cardioplegia Infusion

Custodiol-HTK Solution for Cardioplegia Infusion, also known as Custodiol-HTK and Bretschneider HTK solution is a medicinal solution indicated for Cardioplegia in cardiac surgery operations, protection of organs during operations in a bloodless field (heart, kidney, liver) and preservation of organ transplants (heart, kidney, liver, pancreas).

8.1.2 Sterile Concentrate for Cardioplegia Infusion

Sterile Concentrate for cardioplegia infusion, also known as St Thomas' Solution, is indicated for cardioplegia during cardiac surgery and is used for organ preservation during cardiac transplantation.

8.2 Regulatory status of the drug

8.2.1 Custodiol-HTK Solution for Cardioplegia Infusion

Custodiol-HTK is manufactured and licensed by Dr Franz Köhler Chemie GMBH. Marketing authorisation number: PL 41891/0001

8.2.2 Sterile Concentrate for Cardioplegia Infusion

Macarthy's Laboratories Ltd, trading as Martindale Pharmaceuticals, holds marketing authority for use in the UK. Marketing authorisation number: PL 01883/0012

8.3 Product Characteristics

The simplified IMP dossier will contain the Summary of Medicinal Product Characteristics for Sterile Concentrate for Cardioplegia Infusion and Custodiol-HTK. In the unlikely event that one of these is updated during the trial recruitment period, it will be the responsibility of the CI to circulate updated versions to the PIs in each centre. It would then be the responsibility of each PI to ensure all site files contain only the updated versions.

8.4 Drug storage and supply

All pharmacy aspects of the trial at the participating sites are the responsibility of the PI who will delegate this responsibility to the local pharmacist, or other appropriately qualified personnel. The delegation of duties must be recorded on the Delegation log. The PI or delegated individual must ensure that the IMP are stored in accordance with local practice, applicable regulatory and trial-specific requirements. Refer to the Pharmacy manual for more information.

The site Pharmacy must maintain accountability records as per their site operating procedures for all the IMPs which may include receipt, returned medication, and destruction of returned/unused IMP. The site staff responsible for the storage conditions, temperature excursions, use and transport of the IMP must also maintain accountability logs. Copies of completed IMP accountability logs must be submitted for all trial recipients upon request from the Sponsor for monitoring purposes.

Following the termination of the trial and at the request of the Sponsor, all unused IMPs will be accounted for and destroyed locally at trial sites in accordance with local practice. See the latest version of the Pharmacy manual for details. No IMP is to be returned to either supplier or Sponsor.

8.4.1 Custodiol-HTK Solution for Cardioplegia Infusion

Custodiol-HTK will be provided free of charge by the supplier (Pharmapal Ltd.). Each centre will receive a shipment at the beginning of the study, which should be sufficient for the duration of the study. In the event that a centre requires additional Custodiol-HTK, the PI in that centre will inform the supplier, who will arrange for additional Custodiol-HTK to be delivered.

Custodiol-HTK must be stored in a refrigerator at 2^{o}C – 8^{o}C and protected from light exposure. Custodiol-HTK must be stored in an insulated cool box with ice during transport to the organ retrieval site. It has a shelf life of one year. Once opened it must be used or discarded.

8.4.2 Sterile Concentrate for Cardioplegia Infusion

St Thomas' Solution will be procured by the local pharmacy at each site at market price, as would occur normally for a cardiac transplant to occur in the UK. Each site routinely maintains an adequate supply of St Thomas' solution to ensure that cardiac organ retrieval can occur.

St Thomas' solution should be stored below 25^{o}C and protected from light exposure. It has a shelf life of three years. Once opened it must be used or discarded.

8.5 Preparation and labelling of Investigational Medicinal Product

8.5.1 Custodiol-HTK Solution for Cardioplegia Infusion

Custodiol-HTK comes in a ready-to-use form and will be prepared and labelled in accordance with its current marketing authorisation, with no changes as a result of this trial.

8.5.2 Sterile Concentrate for Cardioplegia Infusion

The contents of one (20 ml) ampoule of St Thomas' solution must be diluted with 1 litre of Compound Sodium Chloride Injection BPC, immediately before use. The product will be labelled in accordance with its current marketing authorisation, with no changes as a result of this trial.

8.6 Dosage schedules

Organ retrieval proceeds according to a nationally standardised Protocol, as set by the National Organ Retrieval Service. The only change to this Protocol will be the following:

8.6.1 Custodiol-HTK Solution for Cardioplegia Infusion

Following cross-clamping of the ascending aorta, at least 3.5L of cold Custodiol-HTK will be perfused into the aortic root, over at least 10 minutes.

Perfusion technique:
After clamping the aorta and simultaneous "venting" of the left ventricle, the solution will be administered antegrade. Cardioplegic perfusion can be performed by either a roller pump with constant volume or by gravity (after cardiac arrest, the solution bag must be kept at 60 cm water column above the level of the heart, which is equivalent to a perfusion pressure of 40-50mm Hg).

Storage of donor heart for transport:

1. Inner bag: 2L of cold Custodiol-HTK (2°C – 4°C)
2. 2nd bag: 2L of cold saline (2°C – 4°C)
3. Outer bag: 2L of cold saline (2°C – 4°C)

This is a minor alteration to the method of administration laid out in the SmPC. The alteration has been discussed with and approved by the makers of Custodiol-HTK Solution and is based on a proven and successful Protocol for use in cardiac transplantation. It has also been discussed with and agreed upon by all the PIs.

8.6.2 Sterile Concentrate for Cardioplegia Infusion

Sterile Concentrate for Cardioplegia Infusion (SCfCI) will be diluted by adding 20ml of SCfCI to 1 litre of Ringers solution.

Following cross-clamping of the ascending aorta, the correct volume of reconstituted SCfCI will be perfused into the aortic root according to the donor weight as outlined below:

3. Donor weight 30-70 Kg: administer 1 litre of reconstituted SCfCI solution
4. Donor weight >70 Kg: administer 1.5 L of reconstituted SCfCI solution
5. At the request of the recipient transplant surgeon, it is permissible to change the above doses dependent on logistics and/or donor physiology.

Delivery pressure: 60-90 mmHg

Storage of donor heart for transport:

4. Inner bag: 2L of cold saline (2°C – 4°C)
5. 2nd bag: 2L of cold saline (2°C – 4°C)
6. Outer bag: 2L of cold saline (2°C – 4°C)

This method of administration is in accordance with the NORS Protocol. The SmPC for Sterile Concentrate for Cardioplegia Infusion does not state doses, delivery pressure or temperature for administration in cardiac transplantation.

8.7 Dosage modifications

Repeat doses may be given of either drug according to surgeon and perfusionist preference in the event that electromechanical cardiac arrest is not achieved or sustained with the initial dose.

8.8 Transport of treatments to retrieval site

Each NORS team will be required to transport both solutions with them to the donor site.

The NORS team should carry at least 6L of Custodiol-HTK to the donor hospital. This should be stored in a cool box with ice and protected from light exposure. Custodiol-HTK will be provided in the form of 2L bags.

The NORS team should carry at least five 20 ml ampoules of Sterile Concentrate for Cardioplegia Infusion and 5L of Compound Sodium Chloride Injection BPC. This can be stored at room temperature and should be protected from light exposure.

8.9 Heart for Valves/Research

In the unlikely event that a heart randomised to receive Custodiol-HTK is deemed not transplantable after delivery of Custodiol-HTK, this heart may be offered on to another recipient via the ODT Hub. Any accepting team would need to be informed that the heart was preserved in Custodiol-HTK and factor this into their decision-making. If the heart is not accepted after offering on, the heart may not be used for valves. Hearts for valves, according to current NHSBT protocols, must be preserved with St Thomas' solution. Where the heart is not suitable to be used for valves, it may be offered to other research projects, providing they are informed that the heart is preserved in Custodiol-HTK.

8.10 Known drug reactions and interaction with other therapies

There are no known drug reactions or interactions with other therapies for either IMP.

8.11 Concomitant medication

Any concomitant medication will be decided by the physicians caring for the transplant recipient and organ donor. No modifications to these should be made as a result of participation in this trial.

8.12 Trial restrictions

There are no trial restrictions. The aim is to exactly replicate the real-world scenario in cardiac transplantation, only altering the myocardial preservative solution.

8.13 Assessment of compliance with treatment

Compliance will be assessed by each PI and the Sponsor. Each randomised case will be reviewed for compliance with the randomisation procedure, treatment allocation and treatment dosage, in accordance with the primary outcome of the trial.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.
Detailed guidance can be found here:
http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

Refer to the SAE Guidelines for Sites for more information.

9.2 Operational definitions for (S)AEs

The operational definition for SAEs will be any adverse event (as defined above in 9.1) that occurs from the time of perfusion of the treatment into the aortic root until 24 hours post-transplant (the longest timeframe which can reasonably be attributed to have any relationship to the treatment, as the treatment is entirely washed out on reperfusion of the heart) and is not included in the below list of expected possible complications from undergoing cardiac transplantation:

i. Primary Graft Dysfunction
ii. The use of mechanical circulatory support, including intra-aortic balloon pump
iii. The need for renal replacement therapy
iv. The use of vasoactive inotrope medication
v. The ongoing need for prolonged invasive mechanical ventilation
vi. Infection requiring antibiotic treatment
vii. Return to theatre for bleeding, instigation or removal of mechanical circulatory support, chest opening or chest closure
viii. The need for blood or blood product transfusion
ix. The need for temporary or permanent cardiac pacing
x. Stroke
xi. Myocardial Infarction
xii. Acute or Hyperacute Allograft Rejection
xiii. Venous Thromboembolism
xiv. Aortic dissection
xv. The use of immunosuppression including pulsed steroids and biologic agents
xvi. The need for re-transplant
xvii. The need for further invasive procedures such as coronary angiography, plastic surgery, interventional radiology, vascular surgery, abdominal surgery or placement of intra-thoracic or intra-abdominal drains

9.3 Recording and reporting of SAEs, SARs AND SUSARs

All SAEs/SARs/SUSARs occurring from the time of perfusion of the treatment into the aortic root until 24 hours post-transplant must be recorded on the electronic AE Form **within 24 hours** of the research staff becoming aware of the event. NB 24 hours post has been chosen because all the IMP is washed out on reperfusion of the heart and cannot reasonably be expected to still be present or have any direct effect beyond 24 hours. “Post-transplant” will be defined as the time the recipient leaves the operating theatre after they receive their transplant or death where this

occurs during the transplant implantation. Death during the implantation would be considered a SAE and should be recorded as such, with the PI review of expectedness in relation to the IMP.

For each SAE/SAR/SUSAR the following information will be collected:

i. full details in medical terms and case description
ii. event duration (start and end dates, if applicable)
iii. action taken
iv. outcome
v. seriousness criteria
vi. causality (i.e., relatedness to trial drug / investigation), in the opinion of the investigator
vii. whether the event would be considered anticipated.

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

For any other complication, not listed above in section 9.2, occurring within 24 hours of the transplant implantation the information listed above must be collected. However, it will then be the responsibility of the PI to determine whether or not this is likely to be related to the IMP-treatment. If it is deemed likely to be related it will be termed an AR. The PI will also have responsibility for determining the level of seriousness, according to definitions outlined in section 9.1. If an AE/AR is assigned by the PI or delegate (or following central review) as serious it will be termed and SAE/SAR. As there is no reference safety information for either treatment in the trial, all SARs will automatically be treated as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales.

9.4 Responsibilities

All recording and reporting will be completed in accordance with the Sponsor's standard operating procedures.

Principal Investigator (PI):
PIs will additionally have responsibility for checking for AEs and ARs when participants attend for treatment / follow-up and using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and Protocol as detailed in the Trial Monitoring Plan.

5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial Protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial DSMC and / or TSC according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for and notifying PIs of updates to the Reference Safety Information for the trial at least annually.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):
In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DSMC regarding safety issues.

Data Safety and Monitoring Committee (DSMC):
In accordance with the Trial Terms of Reference for the DSMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

All deaths will be immediately reported to the Sponsor. The Sponsor, in combination with the PI will undertake an investigation and make a judgment on the relatedness of the death to the IMP. Where the IMP is felt to have probably contributed to or caused the death this will be termed a SUSAR and the Sponsor will inform the MHRA, the REC and Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales.

9.6 Pregnancy reporting

All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. Pregnancy is not considered an AE regardless of the outcome of the pregnancy, as lack of pregnancy must be confirmed prior to the transplant procedure occurring and any subsequent pregnancy cannot be considered to have been affected by the trial treatment as the treatment will no longer been in the participant's body. Therefore, there will be no additional follow-up of any pregnant participant, or any child born to a pregnant trial participant, or to the partner of a male trial participant.

9.7 Overdose

The trial treatments cannot be overdosed. However, the delegated individuals should provide the volumes of treatment administered in accordance with the trial Protocol.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.
Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

9.9 The type and duration of the follow-up of participants after adverse reactions

Any SAE or SAR that occurs within 24 hours of the transplant procedure will be recorded, as outlined above. Where this is thought to be due to the trial treatment, the participant will be looked after by their transplant team. The PI or delegated individual will follow-up the participant on discharge from ICU and on discharge from hospital, with an in-person discussion of the SAE/SAR. Their further clinical follow-up will be determined by their transplant team.

9.10 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), where relevant the Research Ethics Committee and the sponsor.
The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

This is a feasibility study, so formal sample size calculation is not required. However, 50 hearts will give a 95% confidence interval of 53%-79% assuming a primary outcome rate of 66%.

10.2 Planned recruitment rate

A proportion of two-thirds for the primary outcome will be considered successful, as it would correspond to a yearly average of approximatively 80 patients being recruited in the main study, assuming a yearly number of available hearts of 120 (corresponding to the yearly observed number of adult DBD heart transplants in the UK during the last two years).

A power calculation for a superiority trial based on the development of primary graft dysfunction as the primary outcome showed that a sample size of 400 patients would allow detection of a 14% absolute risk reduction in PGD between the two solutions of interest (from 36% to 22%) corresponding to an odds ratio of 0.5 (or 17 cases of PGD prevented per year) with a probability (power) of 0.85 with a type I error of 0.05 when considering a two-sided test of difference in proportions. As approximately 120 adult DBD heart transplants are performed in the UK each year, we estimate that the larger trial will take 5 years to complete (i.e., 80 x 5 = 400).

For this feasibility trial to meet its recruitment target, we anticipate a recruitment rate of 80 patients per year, over a period of 6-12 months. 1 patient per site per month would result in a 9-month recruitment period.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

The following baseline data will be collected for all eligible donors:

i. Consent to participate in research, a categorical variable with categories yes/no, reported as proportions
ii. age, a continuous variable which will be reported as mean age at time of donation
iii. sex, a categorical variable, which will be reported as proportions of male, female or other
iv. ethnicity, a categorical variable, which will be reported as proportions of each category, with the categories being:
    a) Asian or Asian British
        - Indian
        - Pakistani
        - Bangladeshi
        - Chinese
        - Any other Asian background
    b) Black, Black British, Caribbean or African
        - Caribbean
        - African
        - Any other Black, Black British, or Caribbean background
    c) Mixed or multiple ethnic groups
        - White and Black Caribbean
        - White and Black African
        - White and Asian

- Any other Mixed or multiple ethnic background

d) White
   - English, Welsh, Scottish, Northern Irish or British
   - Irish
   - Gypsy or Irish Traveller
   - Roma
   - Any other White background

e) Other ethnic group
   - Arab
   - Any other ethnic group

The following baseline data will be recorded for eligible donors whose family consent but who are not randomised:

i. the reason not randomised. This will take the form of free-text qualitative data, which will be analysed and grouped into categories for reporting by the trial steering committee.

The following baseline data will be collected for all other eligible donors:

i. ABO blood group, a categorical variable with groups A, B, AB and O, reported as proportions
ii. Height, a continuous variable, measured in cm and reported as means
iii. Weight, a continuous variable, measured in kg and reported as means
iv. BMI (kg/m^2), a continuous, calculated variable determined as weight in kg divided by height in metres, squared and reported as means
v. Pathology leading to brainstem death, a categorical variable with groups anoxia, stroke, trauma, malignancy and other and reported as proportions
vi. History of Hypertension, a categorical variable with categories yes/no, reported as proportions
vii. History of Pulmonary disease, a categorical variable with categories yes/no, reported as proportions
viii. History of Cardiac disease, a categorical variable with categories yes/no, reported as proportions
ix. History of Liver disease, a categorical variable with categories yes/no, reported as proportions
x. History Diabetes mellitus, a categorical variable with categories yes/no, reported as proportions
xi. Insulin use, a categorical variable with categories yes/no, reported as proportions
xii. Renal function (serum creatinine), a continuous variable with serum creatinine at time of donation in milligrams per decilitre (mg/dL) reported as mean
xiii. Liver function (bilirubin), a continuous variable measured on serum sample at the time of donation in milligrams per decilitre (mg/dL) and reported as mean
xiv. History of Infection from any source during admission, treated with antibiotics, a categorical variable with categories yes/no, reported as proportions
xv. History of Malignancy, a categorical variable with categories yes/no, reported as proportions
xvi. Left Ventricular Ejection Fraction, a continuous variable measured on the echocardiogram closest to the time of donation and given as a percentage, reported as means
xvii. Ischaemic time, a continuous variable measured in minutes, reported as medians
xviii. Current or past smoker, a categorical variable with categories yes/no, reported as proportions
xix. History of Drug abuse, a categorical variable with categories yes/no, reported as proportions

xx. Vasoactive Inotrope score (VIS), a continuous variable calculated as VIS = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + adrenaline (×100) + noradrenaline (×100), with each drug dosed in µg/kg/min. using the maximum dosing rates of vasoactive and inotropic medications (µg kg^{-1} min^{-1} or IU $kg^{-1}min^{-1}$) in the 24 h prior to organ donation, reported as medians

The following baseline data will be collected for all eligible recipients:

i. Approach to consent, a categorical variable with categories yes/no, reported a proportions
ii. age, a continuous variable, which will be reported as mean age at time of donation
iii. sex, a categorical variable, which will be reported as proportions of male, female or other
iv. ethnicity, a categorical variable, which will be reported as proportions of each category, with the categories being:
    a) Asian or Asian British
        - Indian
        - Pakistani
        - Bangladeshi
        - Chinese
        - Any other Asian background
    b) Black, Black British, Caribbean or African
        - Caribbean
        - African
        - Any other Black, Black British, or Caribbean background
    c) Mixed or multiple ethnic groups
        - White and Black Caribbean
        - White and Black African
        - White and Asian
        - Any other Mixed or multiple ethnic background
    d) White
        - English, Welsh, Scottish, Northern Irish or British
        - Irish
        - Gypsy or Irish Traveller
        - Roma
        - Any other White background
    e) Other ethnic group
        - Arab
        - Any other ethnic group

The following baseline data will be recorded for eligible recipients who are approached but do not consent:

i. the reason for declining to take part (where given). This will take the form of free-text qualitative data, which will be analysed and grouped into categories for reporting by the trial steering committee.

The following baseline data will be collected for all eligible recipients who consent and receive a transplant:

i. ABO blood group, a categorical variable with groups A, B, AB and O, reported as proportions.
ii. Height, a continuous variable, measured in cm and reported as means.
iii. Weight, a continuous variable, measured in kg and reported as means.

iv. BMI (kg/m^2), a continuous, calculated variable determined as weight in kg divided by height in metres, squared and reported as means.
v. Pathology leading to need for transplant, a categorical variable with groups dilated cardiomyopathy, ischaemic cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, valvular heart disease and other, reported as proportions.
vi. Transplant number, an ordinal variable with values, 1, 2, 3 or more, reported as proportions.
vii. History of Hypertension, a categorical variable with categories yes/no, reported as proportions.
viii. History of Diabetes mellitus, a categorical variable with categories yes/no, reported as proportions.
ix. Renal function (eGFR and serum creatinine), continuous variables with serum creatinine at time of donation in milligrams per decilitre (mg/dL) and eGFR calculated using the Cockroft-Gault equation, reported as means.
x. Liver function (bilirubin), a continuous variable measured on serum sample at the time of donation in milligrams per decilitre (mg/dL) and reported as means.
xi. Infection from any source, treated with antibiotics, a categorical variable with categories yes/no, reported as proportions.
xii. Left Ventricular Ejection Fraction, a continuous variable measured on the echocardiogram closest to the time of but prior to the transplant and given as a percentage, reported as means.
xiii. Smoking, a categorical variable with categories current, previous and never, reported as proportions.
xiv. Drug abuse, a categorical variable with categories current, previous and never, reported as proportions.
xv. Vasoactive Inotrope score (VIS), a continuous variable calculated as VIS = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + adrenaline (×100) + noradrenaline (×100), with each drug dosed in µg/kg/min. using the maximum dosing rates of vasoactive and inotropic medications (µg kg^{-1} min^{-1} or IU kg^{-1}min^{-1}) in the 24 h prior to the transplant implantation, reported as medians.
xvi. Mechanical Circulatory Support, a categorical variable with categories None, VA-ECMO, VV-ECMO, IABP, LVAD, RVAD, BiVAD, TAH, Impella and Other, determined by their use at the time of transplant (prior to implantation) and reported as proportions.
xvii. Previous cardiac surgery, a categorical variable with categories yes/no, reported as proportions.
xviii. Pre-operative mean pulmonary artery pressure (mmHg), pulmonary capillary wedge pressure (mmHg), cardiac output (L/min) and cardiac index (L/min/m2), continuous variables taken from the right heart catheter prior to transplant implantation, reported as medians.

A consort flow diagram will be produced and appended to this Protocol. This will evaluate all eligible transplant procedures as part of the primary outcome of this feasibility study, but will also record all patients approached to consent, some of whom may not be included in the primary outcome, for example recipients who have been approached to consent prior to their transplant but do not receive a transplant within the study period.

10.3.2 Primary outcome analysis

The primary outcome will be presented as a proportion with a 95% Jeffreys credible interval with equal-tail probabilities.

10.3.3 Secondary outcome analysis

Credible intervals for proportions:

(Such as "the proportion of eligible recipients who consent to take part in the study)

95% Jeffreys credible interval with equal-tail probabilities will be defined for the proportions of interest.

Tests of differences in proportions:

(Such as the difference in PGD rates between the two solutions of interest)

Difference between two proportions defined on independent samples will be assessed by means of exact fisher or score tests. 95% CI for the difference in proportions will be defined by inverting the score test. Logistic regressions may be considered to control for selected confounders. Penalised likelihood will be used in case of perfect separation of the binary outcome by a set of predictor levels.

Tests of independence between pairs of categorical variables:

(Such as the association between grade 3 PGD and treatment)

The independence of rows and columns of contingency table with fixed marginals will be assessed by means of Fisher's exact tests. Ordinal regressions may be considered to control for selected confounders. Partial proportional odds models will be considered if the proportional odd assumption is violated.

Test of equality of two independent means for continuous outcomes:

(Such as the equality of means of some echocardiographic parameter per treatment group)

Welch t-tests will be used to compare the means of two independent samples for continuous outcomes. Transformations (like log, box-cox) will be used in case of strong deviations to normality of the residuals within each group. Wilcoxon rank sum tests may be used as sensitivity analyses or when the comparison of medians (instead of means) is preferred. Linear regressions may be considered to control for selected confounders. Generalized Additive Models for Location, Scale and Shape models will be preferred in case of the presence of heteroscedasticity.

Test of equality of two independent means for bounded outcomes like proportions:

(Such as the association between left ventricular ejection fraction and treatment)

Welch t-tests will be used to compare the means of two independent samples for bounded outcomes like proportion. Transformations (like log, box-cox) will be used in case of strong deviations to normality of the residuals within each group. Wilcoxon rank sum tests may be used as sensitivity analyses. Beta regressions may be considered to control for selected confounders.

Analysis of survival outcomes:

(Such as the comparison of 30-day all-cause mortality by treatment group)

Survival rates through time of different groups will be compared by means of Kaplan-Meier plots and log rank tests will be used to compare the survival distributions per group. Cox regressions may be considered to control for selected confounders. The proportional hazard assumption will be assessed by means of Schoenfeld residual analysis.

10.4 Subgroup analyses

No subgroup analyses will be performed.

10.5 Adjusted analysis

As outlined above, risk adjustment for baseline value of CPOi (at admission to ICU) will be used in the linear regression for difference in CPOi between admission to ICU and 6 hours post-transplant. All linear and logistic regression models will be adjusted for confounders of interest and presented alongside single comparison tests, such as Fisher's exact test without adjustment.

10.6 Interim analysis and criteria for the premature termination of the trial

Interim analysis will not routinely be performed. If interim analysis is requested by the Data Safety and Monitoring Committee then this will be performed by the DSMC's independent statistician.

10.7 Participant population

The primary outcome will be analysed on an intention to treat basis. Secondary outcomes will be analysed "as randomised".

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

Any missing or spurious data identified at the time of CRF submission will result in a telephone call to the centre's PI to identify if the data can be completed. If not, missing data will be assumed to be missing at random for the purposes of secondary analyses and therefore not imputed. Robust estimators will be used if, after checks, notable outliers are remaining.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

All data will be collected on Case Report Forms (CRFs) at the individual sites. These will be considered the source data and must be stored securely at the site, before being transported securely to the Sponsor on completion of the trial for archiving. Data from the CRFs will be uploaded to a centralised secure electronic database, managed by the sponsor. This data will be pseudonymised by unique study identifier.

Data entered on the CRFs must be:

i. Accurate
ii. Legible
iii. Contemporaneous
iv. Original
v. Attributable
vi. Complete
vii. Consistent
viii. Enduring
ix. Available when needed.

Each site must keep records of all participating patients (with sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

11.2 Access to Data

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

11.3 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. The Sponsor will be responsible for archiving all trial documents. The site(s) will be responsible for ensuring safe transport of all documents to the Sponsor for archiving. All documents will be archived in accordance with Royal Papworth Hospital SOP for a minimum of 15 years. Destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and CI based on the trial risk assessment.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial Protocol, informed consent forms, participant information sheets and invitation letter. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All correspondence with the REC will be retained in the Trial Master File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

This Protocol will be peer reviewed by two independent consultant transplant surgeons.

13.3 Public and Patient Involvement

The Royal Papworth Hospital Patient and Public Involvement Group has reviewed the research proposal, participant information sheet and informed consent document for this trial, with substantial amendments made in response to their comments.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and a favourable REC opinion is obtained. The Protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

13.5 Protocol compliance

Prospective, planned deviations or waivers to the Protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Accidental Protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the Protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. It will be the responsibility of the CI and Sponsor to identify and address any frequently recurring Protocol deviations.

13.6 Notification of Serious Breaches to GCP and/or the Protocol

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

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

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

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

13.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All data uploaded to the central electronic database should be pseudonymised by unique study identifier. CRFs must be stored securely in the site file. Informed consent forms must also be stored securely in the site file. Each site must maintain a secure list of Unique Study Identifiers with linkages to NHS numbers on an NHS encrypted computer, in a password-protected file, accessible only by the PI. This allows linkage of data to hospital records where necessary. Access to this must be provided by the PI where it is required by the Sponsor or DSMC. Any electronic transfer of data must not include identifiable personal information and must therefore only be identifiable by unique study identifier and must be transferred using secure encrypted media. All data will be kept for 15 years after the study end. The data custodian will be the CI.

13.8 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management

At the time of writing, none of the individuals involved in the design or conduct of this design has any financial interest in any of the companies that manufacture or market either of the two treatment solutions. The marketer of Custodiol-HTK (Pharmapal UK) has offered to provide the Custodiol-HTK required for the trial free of charge. Sterile Cardioplegia Concentrate for Cardioplegia Infusion will be procured in the normal way, with cost negotiated by individual Trusts. Further individuals may become involved in the trial conduct at a later date. Where this is the case, they must provide any conflicts of interest, and these will be recorded.

13.9 Indemnity

Indemnity arrangements will be provided by the Sponsor. Individuals involved in the conduct of the trial will be employed by NHS organisations and covered by the NHS Indemnity Scheme.

13.10 Amendments

The Sponsor may make a non-substantial amendment at any time during a trial. These will then be communicated to all participating sites and a one-week period provided for education prior to implementing the non-substantial amendments. If the Sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the Sponsor will submit a valid notice of the amendment to the licencing authority (MHRA) for consideration. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor will submit a valid notice of the amendment to the REC for consideration. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

Amendments will also be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

All amendments will be tracked through version numbering on all documents, with a complete history of each version, including tracked changes, maintained by the Sponsor.

13.11 Post trial care

There will be no additional follow-up for participants involved in this trial. All participants will be offered the opportunity to contact the CI for further information on the trial conduct or outcomes.

13.12 Access to the final trial dataset

Only the trial steering group will have access to the full dataset. Site investigators will be allowed access to the full dataset, where a formal request describing their plans is approved by the steering group.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The Sponsor owns the data arising from the trial. On completion of the trial, the data will be analysed and tabulated, and a Final Trial Report prepared. The Final Trial Report will be accessible on application to the Sponsor. Only the Steering Group will have permission to publish the results arising from the trial and will be required to do so within 1 year of completion of the trial. No funding body or contributing organisation will have access to the dataset or rights to review the trial results prior to their publication in a peer-reviewed journal. Results of the trial will be published, along with a lay summary, on the Royal Papworth Hospital Clinical Trials Unit website (https://royalpapworth.nhs.uk/research-and-development/papworth-trials-unit-collaboration/research-projects). The trial Protocol will be made publicly available via the University of Cambridge data repository. The full trial report, anonymised participant level dataset, and statistical code for generating the results will not be made publicly available, but applications to review these will be considered by the Sponsor and released where reasonable applications are made by appropriate individuals or organisations.

14.2 Authorship eligibility guidelines and any intended use of professional writers

All PIs, the CI, the trial manager and statisticians will be acknowledged with authorship of any publications in peer-reviewed journals. The CI will be the last author on all publications. The trial manager will be first author on all publications. The contribution of NHSBT in supporting this work and providing the registry data will be acknowledged in all presentations and publications related to the study. The funding provided by Heart Research UK in supporting this study will also be acknowledged in all presentations and publications relating to the study.

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16. APPENDICES

16.1 Appendix 1 - Risk

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification:

The IMPs being used in this trial both have post-regulatory status and are indicated for use in cardiac transplantation, as cardioplegia and myocardial preservative solutions. They will be delivered in accordance with their marketing authorisation and no other changes will be made to the transplant process. Therefore, there is no additional risk compared to standard medical practice.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Cardiac Transplant	Cardiovascular System	Routine post-transplant monitoring	Daily	
Myocardial Preservative Solution	No Additional risk	Routine post-transplant monitoring	Daily	

Outline any other processes that have been put in place to mitigate risks to participant safety

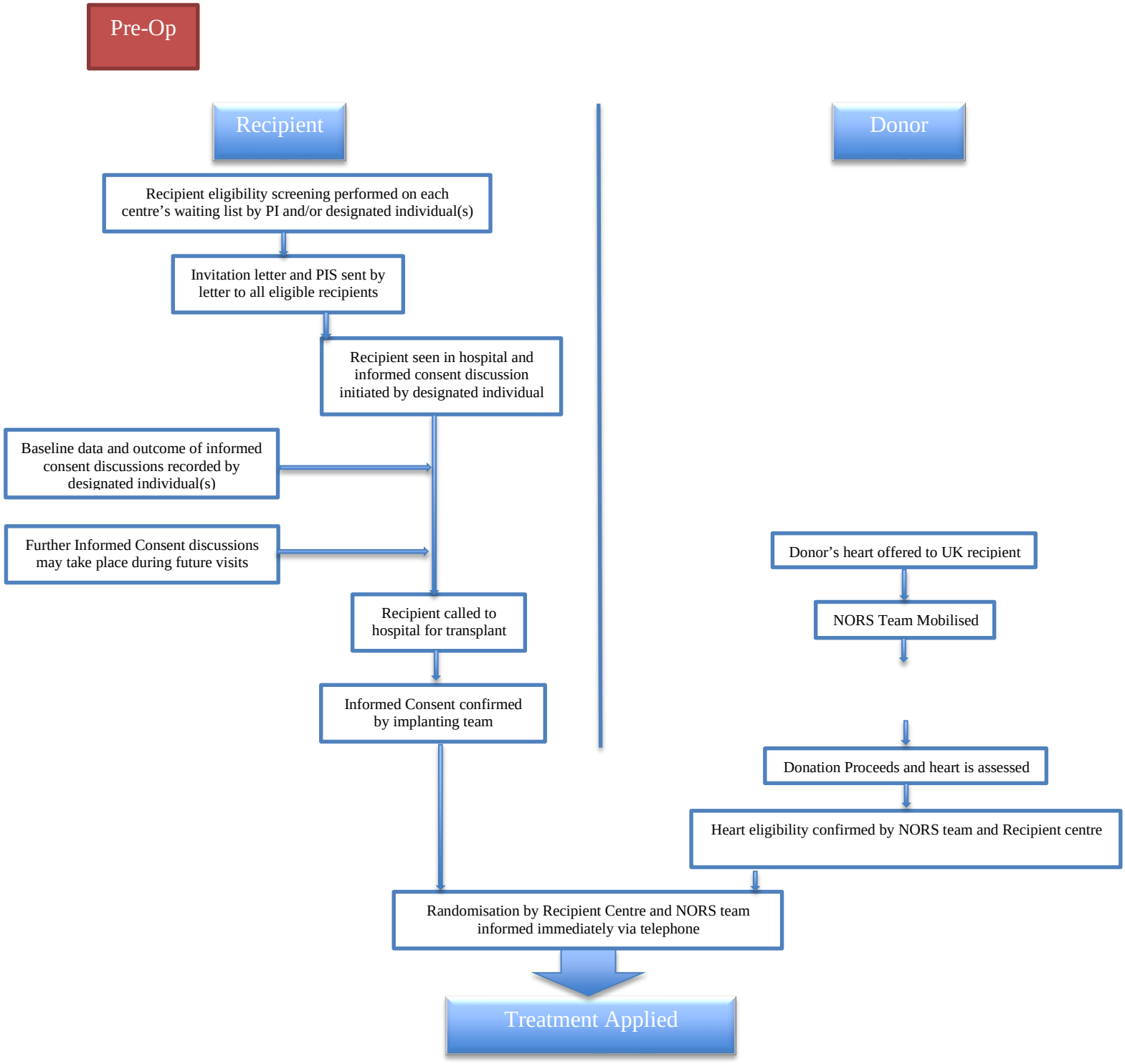
A Data Safety and Monitoring Committee will be convened to mitigate risks to participant safety.

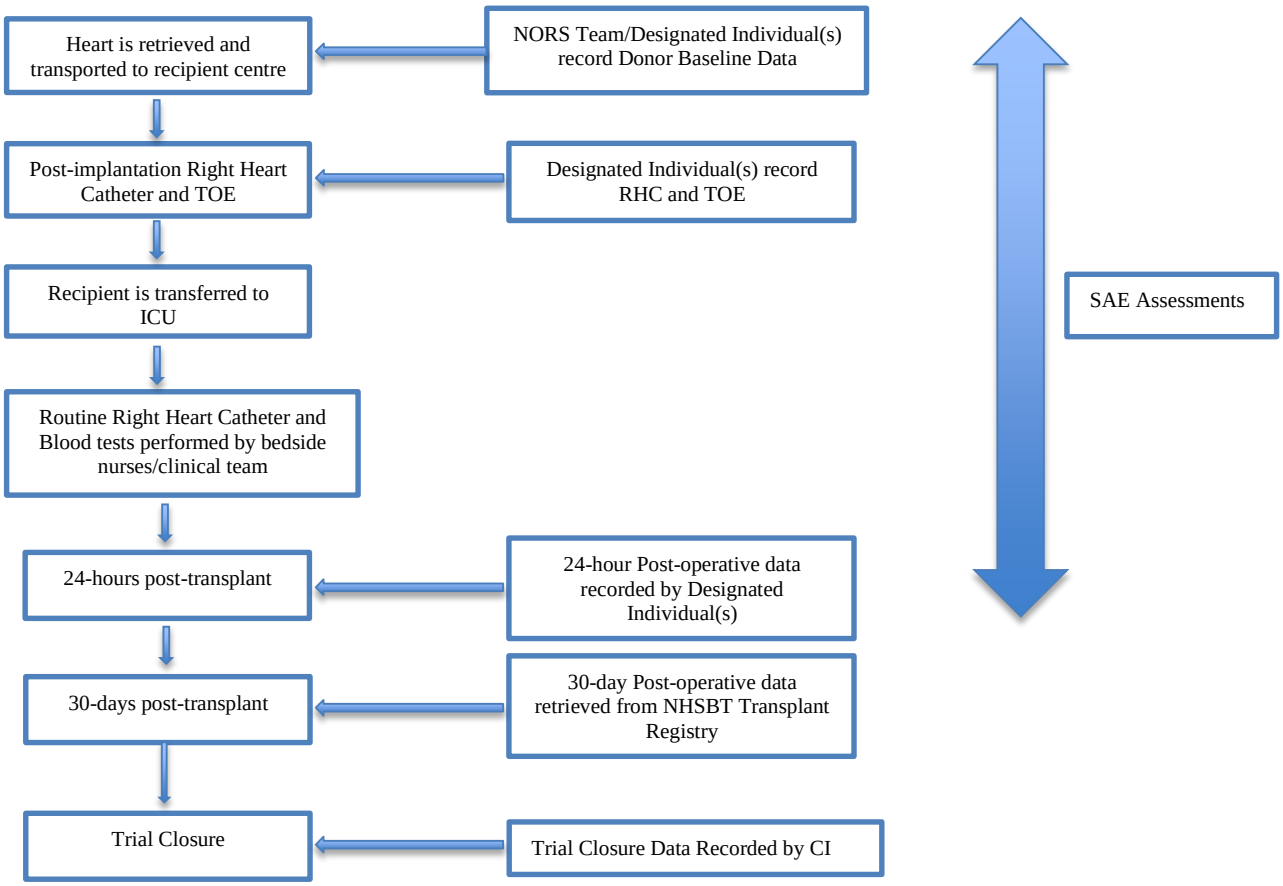
Outline any processes (e.g., IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.

16.2 Appendix 2 – Schedule of Procedures

Procedures			**Visits**					
	Recipient Screening	**Donor Screening**	**Recipient Pre-Op Clinic**	**Recipient Pre-Op**	**Donation**	**Implantation**	**24-hour follow-up**	**30-day Follow Up**
Eligibility Screening	x	x						
PIS sent by letter	x							
Provide information on the purpose of the trial			x					
Informed consent discussion			X					
Informed consent confirmation				x				
Demographics			x		x			
Baseline Data			x		X (donor)			
Randomisation					x			
Treatment					x			
Intra-op TOE						x		
Post-op Right Heart Catheter							x	
Post-op Blood tests (U&E)							x	
30-day follow-up data								x
Adverse event assessments						x ⟷	x ⟷	x
Physician's Withdrawal Checklist						x ⟷	x ⟷	x

16.3 Appendix 3 - Trial Flow Chart of Visits and Key Procedures




Heart is retrieved and transported to recipient centre
NORS Team/Designated Individual(s) record Donor Baseline Data
Post-implantation Right Heart Catheter and TOE
Designated Individual(s) record RHC and TOE
Recipient is transferred to ICU
Routine Right Heart Catheter and Blood tests performed by bedside nurses/clinical team
24-hours post-transplant
24-hour Post-operative data recorded by Designated Individual(s)
30-days post-transplant
30-day Post-operative data retrieved from NHSBT Transplant Registry
Trial Closure
Trial Closure Data Recorded by CI
SAE Assessments