

# A feasibility study for a randomised controlled trial of two different preservative fluids for heart transplantation.

<b>Submission date</b> 12/09/2023	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 27/11/2023	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 19/12/2024	<b>Condition category</b> Surgery	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Donor hearts are injected with a preservative fluid to protect them during transport to the transplant recipient. Currently, there are two different fluids used for this purpose in the UK, St Thomas' solution and Custodiol-HTK. St Thomas' is the standard fluid used in most UK transplants. Some animal studies and data from previous transplants have suggested that Custodiol-HTK may preserve the heart better. However, it is not known if this is true, because no one has ever tested this in a controlled way in humans. This study aims to conduct a randomised controlled trial (RCT) - the gold standard in research - to compare the two fluids. To test whether there is truly a difference, data from around 450 patients will need to be collected. This will take a long time. Therefore, this study will first test if enough patients will consent to take part in the study to make it realistically possible. This is called a feasibility study.

### Who can participate?

Adult patients scheduled to be heart transplant recipients aged over 18 years old

### What does the study involve?

All UK heart transplant recipients will be asked whether they wish to be involved in the trial. If they do, they will be randomly allocated with hearts that have received either Custodiol-HTK or St Thomas' solution before they are transplanted. This will be done for 50 hearts, which should take less than 1 year. The primary aim of the project is to see if more than two-thirds of eligible heart transplant recipients consent to take part and go on to receive a heart that has been correctly randomised.

### What are the possible benefits and risks of participating?

Conducting this feasibility study will hopefully prove that it is possible to conduct the RCT. By conducting the RCT the question: "Which preservative fluid should we use in heart transplantation?" can be answered, and, if one is shown to be better, change practice in the UK, saving the lives of transplant recipients.

Both of the preservative solutions involved in this trial have been extensively used and researched in the field of cardiac surgery. They have both also been used in cardiac transplantation around the world for nearly 50 years and have shown to have excellent safety profiles. They both hold MHRA approval for the specific use of myocardial preservative solutions in cardiac transplantation. Although St Thomas' solution is the most used in the UK, as it forms part of the UK standard cardiac retrieval protocol, surgeons can currently choose to use Custodiol-HTK according to their preference. Transplant recipients would not normally be informed which solution has been used. As a result, there is not thought to be any additional risk to participants as a result of taking part in this trial, beyond the risks that they are informed of when consenting to receive a cardiac transplant. The outcomes of recipients will be monitored to assess if there is a difference between the two solutions, as outlined in the secondary aims of this feasibility study.

Where is the study run from?  
Royal Papworth Hospital (UK)

When is the study starting and how long is it expected to run for?  
September 2023 to March 2026

Who is funding the study?  
Heart Research UK (UK)

Who is the main contact?  
randdenquires@nhs.net

## Contact information

**Type(s)**  
Scientific

**Contact name**  
Dr Group inbox account

**Contact details**  
Royal Papworth Hospital  
Cambridge Biomedical Campus  
Cambridge  
United Kingdom  
CB2 0AY  
+44 (0)1223 638000  
papworth.fcustos@nhs.net

**Type(s)**  
Principal Investigator

**Contact name**  
Dr Marius Berman

**ORCID ID**  
<http://orcid.org/0000-0002-9144-5376>

**Contact details**

Royal Papworth Hospital  
Cambridge Biomedical Campus  
Cambridge  
United Kingdom  
CB2 0AY  
+44 (0)1223 638000  
marius.berman@nhs.net

**Type(s)**

Scientific

**Contact name**

Dr Luke Williams

**ORCID ID**

<http://orcid.org/0000-0002-2744-6446>

**Contact details**

F-CUSToS Trial Manager  
Royal Papworth Hospital  
Cambridge Biomedical Campus  
Cambridge  
United Kingdom  
CB2 0AY  
+44 (0)1223 638289  
luke.williams5@nhs.net

**Additional identifiers****EudraCT/CTIS number**

Nil known

**IRAS number**

1007011

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

P03062, IRAS 1007011, CPMS 56717

**Study information****Scientific Title**

Feasibility study for randomised controlled trial of Custodiol-HTK vs St Thomas' solution for cardioplegia and cold static storage of UK donor hearts in cardiac transplantation (F-CUSToS)

**Acronym**

F-CUSToS

## **Study objectives**

The study team aim to conduct a randomised controlled trial (RCT) - the gold standard in research - to compare two fluids used to preserve donor hearts during heart transplantation. We want to see if one of the fluids can reduce the rate of primary graft dysfunction, which is when the heart fails immediately after being transplanted. Data from approximately 450 patients will be required to test whether there is truly a difference. This will be difficult and take a long time. Therefore, this study will first test if enough patients are willing to take part in the study to make it realistically possible. This is called a feasibility study. This intends to assess what proportion of eligible patients consent to take part and, for those that do, what proportion are enrolled properly in the study and receive the correctly allocated treatment. This will help the team to decide whether the RCT is feasible to conduct in the future.

The secondary objectives of this trial are to assess the overall methodology of the study to see if it can or should be improved for the RCT and to assess whether any difference between the two fluids is seen, even with the small number of patients (50) that will be included in the feasibility study. All aspects of the trial conduct will be assessed and data will be collected on clinical outcomes after transplant, such as the development of primary graft dysfunction (heart failure in the first 24 hours), death within 30 days and post-operative complications.

## **Ethics approval required**

Ethics approval required

## **Ethics approval(s)**

Approved 23/11/2023, South Cambridge REC (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8084, (0)207 104 8194; cambridgesouth.rec@hra.nhs.uk), ref: 23/EE/0224

## **Study design**

Randomized controlled single-blind study

## **Primary study design**

Interventional

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Hospital

## **Study type(s)**

Efficacy

## **Participant information sheet**

See study outputs table

## **Health condition(s) or problem(s) studied**

Organ preservation during cardiac transplantation

## **Interventions**

Donor cardiac organ retrieval will proceed according to the nationally standardised protocol, as set by the National Organ Retrieval Service (NORS). The only change to the protocol will be the randomisation, using SealedEnvelope, to receive either Custodial-HTK or St. Thomas' solution. Donor hearts included in the study will be randomly allocated on a 1:1 basis to receive either Custodial-HTK or St Thomas' solution as cardioplegia and preservative solution during the organ retrieval process.

For the Custodial-HTK (treatment) arm:

Following cross-clamping of the ascending aorta, at least 3.5L of cold Custodial-HTK will be perfused into the aortic root, over at least 10 minutes at a perfusion pressure of 40-50mm Hg. The heart will then be stored in 2L of cold Custodial-HTK solution for transport.

For the St Thomas' Solution (Control arm):

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:

- Donor weight 30-70 Kg: administer 1 litre of reconstituted SCfCI solution
- 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 depending on logistics and/or donor physiology.

The delivery pressure will be 60-90 mmHg and the heart will be stored in 2L of cold 0.9% sodium chloride solution, as is standard practice according to the UK NORS protocol.

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 are not directly involved in the transplant retrieval or implant procedures should not be informed of the treatment allocation.

The duration of treatment is from the point of perfusion via the aortic root at the donor hospital until the perfusate is washed out prior to transplantation into the recipient. The safety reporting will cover the 24-hour post-surgery upon admission to recovery from theatres. The patient will then be followed up until 30 days after surgery.

Discussion of the primary outcome:

The primary outcome will measure the proportion of eligible hearts randomised that receive the correct intervention. This is a composite outcome. For the purpose of this study, eligible hearts are defined as hearts from DBD donors, where an offer has been made to a recipient at a UK transplant centre. The composite outcome therefore includes the proportion of hearts where both donor family and recipient consent to take part in the study and where randomisation occurs according to the protocol and 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 of two-thirds will be considered reasonable, as it would indicate approximately 90 patients per year being recruited.

A power calculation for a superiority trial based on the development of primary graft dysfunction as the primary outcome, with an estimated effect size difference of 12% absolute risk reduction in PGD between the two solutions (or 15 cases of primary graft dysfunction prevented per year) gives a sample size of 450 for a power of 80%. Approximately 140 adult DBD heart transplants are performed in the UK each year. We therefore estimate the larger trial taking a maximum of 5 years to complete.

The primary endpoint will be analysed once recruitment ceases, after 50 patients have successfully been recruited. This is anticipated to be not more than 18 months from recruitment beginning.

**Intervention Type**

Drug

**Pharmaceutical study type(s)**

Not Applicable

**Phase**

Phase IV

**Drug/device/biological/vaccine name(s)**

St Thomas' solution, Custodiol-HTK

**Primary outcome measure**

The proportion of eligible hearts randomised that receive the correct intervention, once recruitment ceases after 50 patients have successfully been recruited. This is anticipated to be not more than 18 months from recruitment beginning.

**Secondary outcome measures**

The following secondary endpoints will be analysed 30 days after the final recruited patients undergoes their transplant:

1. Dataset completion rate
2. The development of Primary Graft Dysfunction, according to the 2014 ISHLT Consensus Definition
3. Cardiac Power Output Index at admission to ICU and at 6h post-operation
4. 30-day mortality
5. Time to death within the limits of the study
6. Development of postoperative complications: Dysrhythmias; myocardial infarction; stroke; transplant rejection; infection (from any source); venous thromboembolism; 30-day re-admission; hyponatraemia ( $\text{Na} < 125 \text{mEq/L}$ )
7. Length of ICU stay
8. Length of hospital stay

**Overall study start date**

08/09/2023

**Completion date**

01/03/2026

**Eligibility****Key inclusion criteria**

1. Age over 18 years old
2. Listed for a heart transplant in the UK
3. All categories of listing including urgent and super-urgent
4. All pathologies leading to the requirement for heart transplant
5. 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.

6. Patients who are simultaneously enrolled in other trials will be considered eligible to take part in this study

**Participant type(s)**

Patient

**Age group**

Mixed

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

50

**Key exclusion criteria**

1. Recipients under the age of 18 years old at the time of transplantation (patients listed when under the age of 18 will be eligible if their transplant is conducted on or after the date of their 18th birthday, provided that they have also provided consent to take part in the trial on or after the date of their 18th birthday)

2. Emergency re-transplant patients, where the re-transplant occurs within the same admission as the index transplant

3. 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

4. Patients who receive hearts from DBD donors procured using the organ care system device or normothermic regional perfusion (NRP). This rarely occurs

5. Patients receiving a heart-lung block or a multi-visceral transplant

**Date of first enrolment**

14/10/2024

**Date of final enrolment**

04/09/2025

**Locations****Countries of recruitment**

England

Scotland

United Kingdom

**Study participating centre**

**Queen Elizabeth Hospital**

Edgbaston

Birmingham

United Kingdom

B15 2TH

**Study participating centre**

**Golden Jubilee Hospital**

Agamemnon Street

Clydebank, near Glasgow

United Kingdom

G81 4DY

**Study participating centre**

**Wythenshawe Hospital**

Southmoor Road

Wythenshawe

Manchester

United Kingdom

M23 9LT

**Study participating centre**

**Harefield Hospital**

Hill End Road

Harefield

Uxbridge

United Kingdom

UB9 6JH

**Study participating centre**

**Freeman Hospital**

Freeman Road

High Heaton

Newcastle upon Tyne

United Kingdom

NE7 7DN



**Study participating centre**  
**Royal Papworth Hospital**  
Papworth Road  
Cambridge Biomedical Campus  
Cambridge  
United Kingdom  
CB2 0AY

## **Sponsor information**

### **Organisation**

Papworth Hospital NHS Foundation Trust

### **Sponsor details**

Heart and Lung Research Institute  
Cambridge Biomedical Campus  
Cambridge  
England  
United Kingdom  
CB2 0BB  
+44 (0)1223 638000  
papworth.randdenquiries@nhs.net

### **Sponsor type**

Hospital/treatment centre

### **Website**

<http://www.papworthhospital.nhs.uk/>

### **ROR**

<https://ror.org/01qbebb31>

## **Funder(s)**

### **Funder type**

Charity

### **Funder Name**

Heart Research UK

### **Alternative Name(s)**

### **Funding Body Type**

Private sector organisation

## Funding Body Subtype

Other non-profit organizations

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

1. Peer reviewed scientific journals
2. Conference presentation
3. Anonymous data will be made available to other researchers on written request to the Chief investigator.

## Intention to publish date

31/12/2025

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be available upon request from the Sponsor, Royal Papworth Hospital (Papworth.randdenquiries@nhs.net). Only anonymised data will be shared. The data requested will be reviewed by the Sponsor and released for a specified time period where reasonable applications are made by appropriate individuals or organisations.

## IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>	version 1.0	03/07/2023	25/09/2023	No	Yes