**HRA Protocol Development Tool**

**Hypothermic Oxygenated PErfusion for DCD KIDNEY Grafts: A Multi-centre Trial**

**HOPE for Kidneys**

* **This protocol has regard for the HRA guidance and order of content**

**RESEARCH REFERENCE NUMBERS TBC**

**TRIAL REGISTRY NUMBER AND DATE TBC**

**PROTOCOL VERSION NUMBER: 0.6**

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**OTHER RESEARCH REFERENCE NUMBERS TBC**

**SPONSOR / CO-SPONSORS / JOINT-SPONSORS: Leeds Teaching Hospitals, UK**

**RESEARCH REFERENCE NUMBERS**

|  |  |
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| **ISRCTN Number / Clinical trials.gov Number:** | TBC |
| **SPONSORS Number:** | TBC |
| **FUNDERS Number:** | O2LKT200LD/ZU-19/20 |
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# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed 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 publically 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):......................................................................................................  |  |  |
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#  KEY TRIAL CONTACTS

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**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

CA Competent Authority

CI Chief Investigator

CRF Case Report Form

CRO Contract Research Organisation

CS Cold Storage

CTA Clinical Trial Authorisation

CTIMP Clinical Trial of Investigational Medicinal Product

CTU Clinical Trials Unit

DCD Donation after Cardiac Death

DGF Delayed Graft Function

DMC Data Monitoring Committee

DSUR Development Safety Update Report

EC European Commission

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

GMP Good Manufacturing Practice

GS Graft Survival

HMP Hypothermic Machine Perfusion

HOPE Hypothermic Oxygenated Perfusion

IB Investigator Brochure

ICF Informed Consent Form

ICH International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

IMD Investigational Medicinal Device

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

KT Kidney Transplant

MA Marketing Authorisation

MHRA Medicines and Healthcare products Regulatory Agency

MS Member State

NHS R&D National Health Service Research & Development

NIMP Non-Investigational Medicinal Product

PI Principal Investigator

PIC Participant Identification Centre

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

QP Qualified Person

RCT Randomised Control Trial

REC Research Ethics Committee

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SDV Source Data Verification

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

UW University of Wisconsin perfusion fluid

WIT Warm Ischaemic Time

# iii. TRIAL SUMMARY

Kidney transplantation remains the therapy of choice for patients with end stage kidney failure. However, the number of patients waiting for a kidney continues to increase and far exceeds the availability of donors which has pushed transplant centres to consider less ideal organ donors, such as grafts from donors after circulatory death (DCD) i.e. cardiac arrest, currently representing 45% of deceased donors in the UK and 20% in Switzerland.

Due to the inevitable warm ischemia time after asystole followed by the no touch period till the start of cold perfusion, DCD kidneys are more prone to develop delayed graft function (DGF) which is defined as the need for dialysis within the first 7 days after transplantation. Up to date rates of DGF range between 55-60% in DCD kidney transplantation.

To overcome these side effects of DCD organs, new concepts of organ preservation such as machine perfusion have been introduced to recondition and assess these organs prior to transplantation. Cold machine perfusion without additional oxygen has demonstrated superiority over conventional cold storage being associated with lower DGF rates and improved 1 and 3 year survival rates following kidney transplantation. Furthermore the addition of oxygen to the perfusion solution, the so called hypothermic oxygenated perfusion (HOPE), could show significant advantages in a clinical setting of DCD liver transplantation as well as in pre-clinical studies of DCD kidney transplantation. The results suggest similar outcomes to HOPE in DCD liver transplantation. In this trial we aim to test HOPE vs. simple cold machine perfusion and static cold storage in DCD kidney grafts.

This study will take place across 2 sites; St. James’s University Hospital, Leeds and University Hospital, Zurich. It will involve 146 DCD kidney transplants and is expected to take 2 years. The participants will be consented and will require follow up over a period of 12 months post operatively including blood tests however this will not represent a deviation from the routine follow up protocol and the results will help shape the future of organ preservation.

|  |  |
| --- | --- |
| Trial Title | **H**ypothermic **O**xygenated **PE**rfusion (HOPE) for DCD KIDNEY Grafts: A Multi-centre Trial |
| Internal ref. no. (or short title) | HOPE for Kidneys |
| Clinical Phase  | Phase III (Ethical and Local R&I approvals pending) |
| Trial Design | Intervention Trial with Historical Cohort Controls |
| Trial Participants | Patients undergoing DCD Kidney Transplant |
| Planned Sample Size | 146 |
| Treatment duration | At least 1 hour of Hypothermic Oxygenated Perfusion of the kidney prior to implantation |
| Follow up duration | 12 months |
| Planned Trial Period | 2 years |
|  | Objectives | Outcome Measures |
| Primary | Investigating the benefit of combining Oxygenation and Hypothermic Machine Perfusion in DCD Kidney Transplant.  | Incidence of delayed graft function (DGF) |
| Secondary | Improving outcomes of DCD Kidney Transplants | -Duration of DGF & number of Dialysis sessions-Creatinine reduction ratio between Day 0 and Day 7 of less than 70 percent-Length of hospital stay in days-Rates of biopsy proven rejections -Incidence of complications-Clavien-Dindo Complication Classification-Measurement of renal function: Creatinine levels, glomerular filtration rate GFR-Graft function at 3,6 months and one year -CCI 30 and 90 days and 12 months after transplantation-Death censored graft survival -Analysis of Perfusion Fluidand histology for kidney injury  |

# iv. FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER(S)** | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
| Organ Recovery SystemsPeter De Muylder Director Clinical and Research SupportCorporate Village Business ParkDa Vincilaan 2 Box 61831 DiegemBelgiumE-mail: pdemuylder@organ-recovery.com | **Financial (£30000) and Hypothermic Perfusion Machines**  |
| **Leeds Cares** | **TBC** |

**v. ROLE OF TRIAL SPONSOR AND FUNDER**

Leeds Teaching Hospitals NHS Trust, as the main sponsor, will provide a site for the trial in the UK as well as indemnity and insurance for the clinical research activities taking place in this study.

Organ Recovery Systems, as a funder, will provide the machines required for the trial, onsite training session will be set up for all staff involved in handling the device and a 24/7 helpline in case immediate assistance is required during a clinical case. They will also provide financial support for the study. The training sessions will be offered by an experienced kidney perfusionist from the provider of the perfusion system. Setting up these training sessions will ensure that each staff member will feel comfortable handling the device before starting to perfuse any kidney for this study. A 24/7 helpline in case immediate assistance is required during a clinical case. They will also provide financial support for the study.

Leeds Cares TBC

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

Data Monitoring (and ethics) Committee

 Monitoring visits by an independent company at the investigators’ sites prior to the start and during the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors early point. Study protocol will be submitted to the Ethical Committees from both participating centres.

Trial Management Group

 The Chief Investigator along with the Principal Investigators will implement and maintain quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted, and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Monitoring and Audits will be conducted during the course of the study for quality assurance purposes. The Trial Management Group will meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

**vii. Protocol contributors**

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|  |  |
| --- | --- |
| **viii. KEY WORDS:** | Kidney Transplantation, Organ Preservation, Machine Perfusion, Hypothermic Oxygenated Perfusion (HOPE)  |

# ix. TRIAL FLOW CHART

**Low Clearance Nephrology Clinic** Patient identification as a candidate of Kidney transplant, worked up and referred to the Kidney Transplant Surgery Team.

**Kidney Transplant Consent Clinic**

Patient assessed kidney transplant. Risks and benefits of the operation and immune-suppression discussed in detail and placed on the Waiting List for a Kidney Transplant. **Patient approached, informed of the potential of involvement in the HOPE for KIDNEYS trial if a DCD kidney is offered and given information leaflets.**

**Admission for Kidney Transplant**

Once a DCD Kidney is offered for a patient within the inclusion criteria of the study. Routine pre-operative preparation for the procedure (Bloods, crossmatch, Chest X-ray, ECG … etc.) is done, patient is consented for the operation (or consent form is countersigned if already done in clinic) and **HOPE for KIDNEYS Consent is signed** if the patient agrees to take part. Baseline data will be documented on CRF

**HOPE Treatment**

Kidney is Prepared for transplant (Benched) and connected to the **HOPE machine for at least 1 hours** while the patient is anaesthetised and exposure of the implanting site (Dissection) is performed. At the end of the HOPE phase 2 samples of the perfusate will be obtained for analysis.

**Kidney Transplant**

Procedure is performed as per protocol in the transplanting centre and post-operative care is as standard not affected by the trial. Blood tests obtained during the admission will be used to assess kidney functions and will be logged on to CRF

**Follow Up**

Patient follow up for the trial will take place at **1, 3, 6 and 12 months** **in the post-transplant clinic** within the routine follow up schedule as per protocol in the transplanting centre, there will be no deviation from the standard clinical care. Blood tests during follow up will be documented on CRF for assessment of outcomes including kidney functions, complications, graft and patient survival. After 1 year review the study will conclude and patients will continue to receive the same follow up as those outside the trial.

# 1 BACKGROUND

Renal transplantation remains the therapy of choice for patients with end stage renal disease. However, the number of patients waiting for a kidney graft continues to increase and far exceeds the availability of donor grafts which has pushed transplant centres to expand their donor pools with less ideal organ donors. One such alternative donor organ pool are organs procured after donation of circulatory death (DCD) which currently represents about 45% of cadaveric organ donors in the UK and 20% in Switzerland.

Due to the inevitable period of warm ischemia time (WIT) between cardiac arrest and start of cold perfusion prior to procurement; DCD kidneys are more prone to develop delayed graft function (DGF). DGF is defined as the need for dialysis within the first 7 days after transplantation. Specific restrictions within the UK and Swiss DCD protocols (like prolonged agonal phase up to 3hrs and prohibition of administration of heparin in Switzerland and UK prior to declaration of death; the prolonged no touch time after cardiac arrest in Switzerland) have contributed to even higher risks for developing DGF. Participating centres in this study noticed that DGF rate in their recipients of a DCD kidney is still as high as 55-60%.

To overcome these disadvantages of DCD organs and to improve the quality of the grafts, new concepts of organ preservation have been introduced, e.g. machine perfusion instead of conventional cold storage. There are different perfusion techniques mainly differing by type of perfusate, temperature and timing (1-4).

# 2 RATIONALE

Evidence from randomized controlled trials and other studies have shown beneficial effects of hypothermic machine perfusion (HMP) before implantation on DGF in both DBD and ECD (extended criteria donor) kidney grafts (1, 5, 6). In the latter, investigators were able to show an improved 1 and 3 year survival after hypothermic perfusion (7, 8). Recent papers from Australia and Brazil recorded DCD kidneys with DGF to have significantly lower Graft Survival (GS) and could even show a link to the activation of the immune system, leading to a higher risk of rejection following kidney transplantation in humans (9, 10). The latest single centre retrospective analysis of over 2100 kidneys from the University of Wisconsin clearly indicated that DGF is leading to lower renal graft half-life by 3-5 yrs in DBD grafts as well as in DCD kidneys, irrespective of KDPI status (Kidney Donor Profile Index). Since the recognition of the association of DGF and inferior graft survival, higher rejection rates and the economic impact, strategies like HMP are en vogue to minimize these risks. In a recent Cochrane analysis HMP has proven to limit the risk of DGF in all types of donor kidneys is the use of Hypothermic machine perfusion (HMP) (11). HMP has clearly shown its benefits compared to simple cold storage in early graft function in a large UK retrospective analysis (12).

In DCD liver transplantation, hypothermic perfusion with **additional oxygen** is already well established, reducing the release of radical oxygen species (ROS) after reperfusion and ultimately improving outcomes after liver transplantation (13, 14). There is some existing evidence supporting the same mechanism in DCD kidney grafts as well (15). Our group has already extensive experience with hypothermic **oxygenated** perfusion in liver grafts, in animals (16, 17), humans (14, 18) as well as in DCD kidneys (15). Preclinical studies clearly showed in animal models that a short period of hypothermic oxygenated perfusion is able to boost the ATP levels resulting in a better renal function and is superior to perfusion without oxygen (15, 19). The use of a brief period of oxygenated HMP in a porcine auto-transplant model also resulted in lower expression of DAMP’s (Danger Associated molecular Patterns) and reduced innate immune response (lower levels recorded of HMGB and TLR4), (20) indicating the potential benefit of brief oxygenated HMP for reconditioning of the renal graft after cold storage and suggesting a crosstalk to potentially be able to reduce the risk of rejection. Kron et al. could show that oxygenated perfusion was able to significantly reduce the immune response in a rodent model of allogeneic kidney transplantation (19).

## **2.1 Assessment and management of risk**

Participants benefit from access to technology that has the potential, as suggested by pre-clinical trials, to improve the outcomes of their kidney transplants and contribute to a research project that could shape the future of organ preservation while the risk from being enrolled in the study is minimal as the clinical care pre-operatively, during surgery and on follow up is maintained to the standard and protocols of the transplanting centre.

This trial is categorised as:

 • Type A = No higher than the risk of standard medical care

See Appendix 1

# 3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of this study is to investigate, based on the promising pre- clinical data, the effect of additional oxygen on HMP of DCD kidney grafts. Therefore, we will compare the results of HOPE (HMP plus oxygen) treated DCD kidney grafts with a historical cohort of DCD Kidneys preserved using SCS as standard practice and a further historical cohort of HMP (without oxygen) treated DCD kidney grafts. Kidney transplantation and especially the DCD program is highly standardized. Therefore, these two treatment groups are ideal for comparison.

**3.1** **Primary objective**

The objective of this study is to assess the effects of additional oxygen in hypothermic machine perfusion applied in human DCD kidney grafts in comparison with alternative methods of organ preservation including CS and HMP.

Due to available evidence, we hypothesize that the application of oxygenated perfusion will significantly reduce the rate of DGF following DCD kidney transplantation.

**3.2 Secondary objectives**

Asses the effect of Hypothermic Oxygenated Perfusion on the outcomes of DCD Kidney Transplants including rate and severity of complications, rejection, and kidney function.

**3.3 Primary endpoint/outcome**

The primary outcome is the incidence of delayed graft function (DGF) of the kidney graft. Delayed graft function is defined as the need for dialysis during the first 7 days after kidney transplantation. If dialysis is necessary, the number of applications and their respective dates will be recorded in the CRF.

**3.4 Secondary endpoints/outcomes**

• Duration of DGF & number of Dialysis sessions

• Creatinine reduction ratio between Day 0 and Day 7 of less than 70 percent

• Length of hospital stay in days

• Rates of biopsy proven rejections

• Incidence of complications

• Clavien-Dindo Complication Classification

• Measurement of renal function

• Creatinine levels, glomerular filtration rate GFR

• CCI 30 and 90 days and 12 months after transplantation

• Death-censored graft survival and patient death

• Analysis of Perfusion Fluid for Kidney Injury

**3.5 Table of endpoints/outcomes**

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures**  | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective**Assessment of the benefit of HOPE in DCD kidney transplant | Incidence of DGF | Requirement of dialysis within the first 7 days of transplantation |
| **Secondary Objectives**Effect of Hypothermic Oxygenated Perfusion on the outcomes of DCD Kidney Transplants | * Complications
* Rejection
* Kidney Functions
* Effects of HOPE in reducing kidney injury
 | • Duration of DGF & number of Dialysis sessions• Creatinine reduction ratio between Day 0 and Day 7 of less than 70 percent• Length of hospital stay in days• Rates of biopsy proven rejections • Incidence of complications• Clavien-Dindo Complication Classification• Creatinine levels and glomerular filtration rate (GFR)• CCI 30 and 90 days and 12 months after transplantation• Death-censored graft survival and patient death• Analysis of Perfusion Fluid for markers of Kidney injury |

# 4 TRIAL DESIGN

This is an intervention study comprised primarily of **two arms**: a prospectively recruited group of patients undergoing HOPE a historical cohort where kidneys were preserved using SCS a **third arm** of historical cohorts undergoing simple HMP is added to further investigate the benefit of Oxygenation in HMP. Therefore, this study will not influence any post-operative treatment policy of the individual transplant centre.

Study Group (HOPE):

146 Kidneys initially stored on ice will be put on the machine perfusion device as soon as possible upon arrival in the study centre. Cold storage time well as start of perfusion time will be recorded.

Historically matched Cohorts:

For comparing the primary end point of DGF, historically matched cohorts from both participating centres will be used: One historically matched cohort will consist of 146 kidneys with HMP without oxygen another of 146 DCD kidneys with CS.

# 5 TRIAL SETTING

The Proof of Concept Study will be conducted as a prospective, multicentre trial which will run simultaneously across 2 sites (St. James’s University Hospital in Leeds, UK and University Hospital Zurich, Switzerland.) both of which will be recruiting treating and follow up centres.

All kidneys will be allocated following standard allocation procedure as established by NHSBT (Leeds) or Swisstransplant (Zurich) and the interventions such as connecting the kidney to the perfusion machine and kidney transplantation will be undertaken by members of the research team and/or from members of the Renal Transplant Surgery Team.

Upon arrival at transplant centre all consecutive, accepted DCD grafts which comply with the inclusion criteria of the study will immediately be placed on the perfusion device undergoing graft reconditioning via oxygenated HMP. All kidneys will be perfused with UW-MP perfusion solution. HOPE treatment is planned for 1-2 hours which is normally the time taken from benching to implantation of the graft in practice so there will be no delays caused by the trial.

Outcomes will be compared to historical matched cohorts of DCD kidneys being preserved by simple cold storage or non- oxygenated perfusion at both participating centres.

To estimate the potential impact at a national scale, outcome will also be compared with the data from the recently published UK retrospective DCD cohorts in which kidneys were cold stored or machine perfused subsequently to CS.

General management of the recipient (including rejection episodes, medical and surgical complications) remains the responsibility of the surgeons/nephrologists. This study does not impose unnecessary restrictions on such clinical management decisions.

**6 PARTICIPANT ELIGIBILITY CRITERIA**

All adult patients (≥18 years) undergoing primary single kidney transplantation from DCD donors (Maastricht III) are eligible for study inclusion. The criteria listed below further specify the different inclusion and exclusion criteria.

**6.1 Inclusion criteria**

* Age ≥ 18 years
* DCD grafts
* Primary kidney transplantation
* Single kidney transplantation
* Signed informed Consent

**6.2 Exclusion criteria**

* DBD graft
* Dual kidney transplantation
* Kidney re-transplantation
* Multi-organ transplantation
* Perfusion of the organ not possible due to technical problems

# 7 TRIAL PROCEDURES

* Patients are admitted on the day of the kidney transplant once an offer is confirmed where the standard pre-operative preparation is done as per protocol in the transplanting centre (see 7.1.2 Screening) and baseline data (see 7.3) is collected.
* The patients are consented for the procedure and for involvement in the trial (see 7.2 Consent)
* The kidney is connected to the HOPE Machine after back table preparation (benching) as per protocol (see 8 Trial Treatment)
* The surgical procedure is performed as standard in the transplanting centre and the trial will not affect the technical aspects and surgeon preference of side or method of implantation.
* Post-operative care is managed by the Transplant Surgery Team and the Nephrologists as per protocol in the transplanting centre and the trial will not cause any deviation in the standard of patient care from a clinical perspective.
* Outpatient Follow up is as standard on the Post-Transplant Clinic in the transplanting centre and results of the blood tests routinely taken during these visits will be included in the study (see 7.5 Long term follow up assessments).

**7.1 Recruitment**

**7.1.1 Participant identification**

Patients who are on the transplant list and who are eligible for the trial based on the inclusion and the exclusion criteria will be identified and recruited for the trial. The final inclusion will be made by the Kidney Transplant team on an offer of a DCD kidney.

Controls of for the SCS and HMP arms will be historical cohorts identified from the transplanting centre databases and will be subject to the same inclusion and exclusion criteria.

**7.1.2 Screening**

The screening process will take place on admission for the kidney transplant in accordance with the protocol of pre-operative preparation of the transplanting centre and will include:

Full clinical history and physical examination.

Baseline blood tests (FBC and U&Es).

Chest X-ray.

ECG.

**7.1.3 Payment**

There are no payments or incentives to participants associated with this trial.

**7.2 Consent**

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant data)

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this. Any intention to utilise such data should be outlined in the consent literature.The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant’s behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment), or requesting an interpreter as per hospital protocol to overcome language barriers.

The process of giving informed consent for participation in the trial will include the following:

* A discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation including:
* Information regarding the handling and storage of personal details and medical records including access for members of the clinical and research teams, monitoring committees, and sharing with GPs.
* Information regarding the collection, transport, export, storage and analysis of collected blood and perfusate samples and their use in further studies.
* The presentation of written material (e.g., information leaflet and consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements
* The opportunity for potential participants to ask questions
* An assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
	+ understand the purpose and nature of the research
	+ understand what the research involves, its benefits (or lack of benefits), risks and burdens
	+ understand the alternatives to taking part
	+ be able to retain the information long enough to make an effective decision.
	+ be able to make a free choice
	+ be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
	+ where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain.

This trial does not include children (defined as a person under the age of 16 years of age) or participants who lack the capacity to consent for themselves.

Where a participant is able to consent but later becomes incapacitated, the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

**7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable**

The perfusate collected at the end of HOPE treatment will be transported to University Hospitals Zurich for further analysis and data obtained from these samples may be used in further studies supporting the topic of organ preservation and machine perfusion.

These samples will be coded and stored at a tissue bank with links to the database at the main research site but will not carry any identifiable information.

**7.3 Baseline data**

Data will be recorded on CRF as follows:

* Baseline values and parameters at inclusion will be measured before transplantation, i.e. Patient demographics (age, gender, weight, height) and patient medical history including and transplantation indication for KT.
* Donor and kidney graft demographics (age, gender, weight, height, cause of death, serum creatinine and GFR, donor risk index, etc.) will be documented.
* The surgical technique of transplantation including technical difficulties, and anatomical abnormalities e.g. two arteries, the cold and warm ischemia time and the total preservation time (SCS + HOPE) will be documented.

**7.4 Trial assessments**

Assessments will be recorded on CRF as follows:

* Parameters measured during HOPE perfusion are:

Perfusion pressure, flow, temperature, duration of the perfusion, partial pressure of O2 and CO2 in the perfusion solution. These values are assessed at standardized time points during the perfusion procedure. (For further information please refer to the SOP)

* The donor kidney biopsy is routinely performed after reperfusion and a pathological work-up will be performed including specific staining for immunological and tissue markers.
* Other parameters of transplantation will be measured as follows: transplantation duration, blood transfusions (RBC, FFP, TC, others), circulatory support by anaesthesiology will be documented (noradrenaline at the end of transplantation).
* Lab values after transplantation will include kidney function markers (Serum Creatinine, GFR, urine output, urine samples, proteinuria), coagulation parameters (haemoglobin, INR, Quick, Platelet count) and inflammation parameters (white blood cell count, CRP levels). These values are checked regularly, starting from admission till the day of discharge.
* A duplex ultrasound of the DCD kidney grafts will be performed within 24 hours after transplantation, verifying the proper and adequate perfusion of the kidney graft.
* Complications will be recorded daily and graded according to the Clavien-Dindo classification.
* Primary non-function, defined as a never working graft
* Biopsy proven episodes of acute rejection

**7.5 Long term follow-up assessments**

* After hospital discharge the patients will be followed up in the outpatient clinic of the Department of Nephrology. Follow-up will not differ from usual.
* Complications will be recorded at discharge, 30 days and 90 days
* Death censored graft survival at 3, 6 and 12 months
* Patient survival at 3, 6 and 12 months

**7.6 Withdrawal criteria**

Patients who lose mental capacity to give consent will be withdrawn from the trial. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

**7.7 Storage and analysis of clinical samples**

Blood samples will be collected and analysed in the laboratory at the transplanting centre as per local protocols

For perfusate samples PO2 & PCO2 measurements:

A 1ml perfusate sample will be taken from the sample port in the perfusion circuit at following time points: 15min, 30min, 1h, 2hr and at end of perfusion time.

1 or 2 ml syringes could be used to draw the perfusate sample.

This sample should be analyzed ASAP by a blood-gas analyzer capable to handle acellular (Hb-free) samples. Ideally the gas analyzer should also allow for temperature correction in order to obtain a read-out of the PO2 & PCO2 result at ± 4°C. (Availability of such analyser to be checked).

Printouts of the results should be logged into the CRF for further data control & validation.

Sample can be destroyed after analysis.

Additional perfusate samples for FMN analysis:

Since FMN has been recently identified as potential marker for viability assessment in livers, it would make sense to look whether this marker would also have any predictive value in kidneys.

Since FMN during the first two hrs of HMP might reflect the degree of mitochondrial damage, we would suggest taking an extra 1ml perfusate sample at 15 min, 30 min, 1 and 2 hr of perfusion.

Since FMN analysis can be done by simple fluorescence measurement, all FMN samples will be stored at the transplanting centre then transported en masse to University Hospital Zurich for analysis of kidney function and tubular injury analyzed with NGAL and creatinine in plasma samples. Oxidative damage of DNA will be analyzed in perfusate and plasma by 8-hydroxy-2-deoxy Guanosine (8-OHdG). Nuclear injury will be measured by release of high mobility group box protein-1. Quantitative real-time polymerase chain reaction (PCR) will be performed idf possible (TaqMan gene expression assays) for Toll-like receptor (TLR)-4, tumor necrosis factor-alpha (TNF-[alpha]), high mobility group box-1 protein (HMGB-1), von Willebrand factor (vWF), endothelin 1 (Edn-1), Hepatocyte growth factor and if possible hitological assessment will be performed: Haematoxylin-Eosin (H&E)-staining (tubular injury), TLR-4-staining (Macrophage and tubuli activation), and vWF (endothelial activation).

## **7.8 End of trial**

The trial will end with the completion of the 12 months follow up of the last recruited patient.

# 8 TRIAL TREATMENTS

**8.1 Perfusion Machine**

The perfusion will be performed with the Life Port from Organ Recovery. This is a custom-made machine for kidney perfusion and is CE certified for human use, commercially available and already used for hypothermic perfusion of DCD organs routinely worldwide.

In the product information, the machine is described as follows:

The self-contained Perfusion Circuit cradles the organ in cold physiologic solution. It provides a sealed, sterile environment in which the perfusate is pumped through the kidney in a pulsatile manner at a pressure of 30 mmHg at 4 °C. It is portable and allows continuous perfusion from organ recovery until transplantation. During preservation, data such as temperature, flow, vascular resistance, and pressure can be recorded every 10 s. Pulsatile HMP with Belzer MPS® solution at 4 °C is already well established clinically. A custom-made disposable cannula, comfortably supported by an adjustable mount, allows swift connection of the kidney, even for organs with the most challenging anatomies. The entire disposable apparatus set – complete with organ cassette, pressure sensor and preservation solution – loads and unloads in one easy motion.

**8.2 Perfusion fluid**

We will use the standardand certified perfusion solution in human kidney transplantation Bridge to life® . The components of the perfusion solution is : 5% HES, 10 mM hepes, 100 mM sodium, 25 mM potassium, 5 mM magnesium, 0.5 mM calcium, 1mM chloride, 30 mM mannitol, 10 mM glucose, 85 mM gluconate, 0.5 ribose, 25 mM hydrogenphosphate.

Oxygen will be supplied in the operating room through the medical approved oxygen supplier. Oxygen will directly go to the perfusion solution through a specific designed input on the Life Port.



**8.3 Machine operation**

Kidneys will be benched prior to being placed on the device. This will allow keeping the kidney on the machine perfusion device until the recipient vessels have been exposed and dissected for implantation of the organ. If applicable, cross-match testing will be performed during machine perfusion, which is expected to allow a minimum perfusion time of at least 1-2 hours. Use of machine preservation may not result in prolonging the total cold ischemia time. Total perfusion time as well as total cold ischemia time will be recorded.

During the set-up of the perfusion circuit, 0.5l/min of O2 will be administered via the submerged bubble line for uploading of the perfusate with O2. Once the kidney has been connected to the circuit and both lids of the organ chamber have been closed again, perfusate surface O2 supplementation with 0.5l/min of O2 will be continued until implantation of the graft. Kidneys will be perfused with a systolic pressure fixed at 30mmHg. Perfusion parameters will not be used for accepting/ discarding kidneys. To verify whether the kidney is being adequately perfused, perfusion flow and RR at 15 minutes after initiation of perfusion will be recorded. Any necessary corrective actions will be recorded (check for leakages, obstructions, re-cannulation, etc.). At the end of perfusion, final flow, RR and temperature will be manually recorded. Also, at the start, after 1hr of perfusion and at the end of perfusion time, a perfusate sample will be taken for pO2 measurement. All machine perfusion data will be downloaded at the end of each case; flow & RR will be used for retrospective analysis.

Since currently no objective, scientific data support discarding DCD kidneys based on MP parameters; discarding kidneys based on poor renal flow or resistance on the machine cannot be justified. After acceptance, the kidney can only be considered as non-transplantable based on standard procurement data and anatomical appearance. MP data cannot be used in the decision process of accepting/discarding a kidney for transplantation. Retrospectively, MP data will be analysed for associations with post-op outcome.

Two additional perfusate sample will be taken at the end of perfusion time for additional analyses (e.g. anaerobic or mitochondrial injury markers like lactate, succinate, hypoxanthine, FMN, Kidney Injury markers etc.)

# 9 SAFETY AND INCIDENT REPORTING

**9.1 Definitions**

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.NOTE 1: This includes events related to the investigational device or the comparator.NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).NOTE 3: For users or other persons this is restricted to events related to the investigational medical device. |
| **Adverse Device Effect** **(ADE)** | Adverse event related to the use of an investigational medical device.NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.NOTE 2- This includes any event that is a result of a use error or intentional misuse. |
| **Device deficiency** | Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling. |
| **Serious Adverse Event (SAE)** | Adverse event that:• results in death, • is life-threatening, • results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, • any important medical event and any event which, though not included in the above, may jeopardise the participant or may require intervention to prevent one of the outcomes listed above.NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event. |
| **Serious Adverse** **Device Effect (SADE)** | Any Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| **Unexpected Adverse Drug Reaction** | An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | Suspected adverse reaction which is related to an IMP (the tested investigational medicinal product and comparator) that is both unexpected and serious and subject to expedited reporting). |
| **Unanticipated Serious Adverse Device Effect (USADE)** | Includes any serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Includes also anticipated effects: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. |

**9.2 Operational definitions for (S)AEs**

During the entire duration of the study, all serious adverse events (SAEs) are collected and documented in source documents. Reportable events are recorded in the electronic case report form CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures.

Assessment and Recording of Adverse Events

Clinical study subjects will be routinely questioned about SAE/AEs at study visits. The well-being of the subjects will be ascertained by neutral questioning ("How are you?"). The investigator is responsible for reporting all AEs occurring during the study

All observed or volunteered adverse drug events (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational drug or study treatment(s) will be recorded in the CRF.

AEs or abnormal test findings felt to be associated with the study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an AE if one or more of the following criteria are met:

• The test finding is accompanied by clinical symptoms.

• The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.

• The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

All AEs, serious and non-serious, will be fully documented on the appropriate CRF. For each AE, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the investigational product.

The intensity of AEs will be assessed as being

• Mild (hardly noticeable, negligible impairment of well-being),

• Moderate (marked discomfort, but tolerable without immediate relief), or

• Severe (overwhelming discomfort, calling for immediate relief).

The principal investigator will determine the relationship of the investigational device to all AEs

Assessment of Serious Adverse Events

An unexpected SAE refers to any AE, the nature or severity of which is not consistent with the applicable product information.

The investigator will promptly review SAEs to determine if the SAE meets the criteria for a SUSAR.

The assessment by the investigator with regard to the study drug relation is done according to the following definitions:

|  |  |
| --- | --- |
| Unrelated | * The event started in no temporal relationship to medicinal product applied and
* The event can be definitely explained by underlying diseases or other situations.
 |
| Related | * The event started in a plausible temporal relationship to medicinal product applied and
* The event cannot be definitely explained by underlying diseases or other situations.
 |

**9.3 Recording and reporting of SAEs, SARs AND SUSARs**

Clinical investigators and ultimately the Principal Investigator (PI) have the primary responsibility for SAE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention.

Based on the definitions above, the following events are considered reportable events:

* any SAE,
* any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate
* new findings/updates in relation to already reported events.

All SAEs will be fully documented in the appropriate CRF. For each SAE, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the investigational product.

The Investigator is responsible for SAE reporting to the CEC according to the following details:

* Reporting to CEC any SAE which resulted in death: without delay, and no later than 7 calendar days.
* Reporting to CEC of fatal SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR) without delay and no later than 7 calendar days following awareness that event meets criteria for an SUSAR.
* Reporting to CEC of non-fatal SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR): promptly and no later than 15 calendar days following awareness that event meets criteria for a SUSAR.

All other SAEs will be summed up in the annual safety report (ASR), containing:

* A summary of the safety profile of the drug studied as well as the safety issues that have arisen;
* A listing of all SUSARs that have occurred in Switzerland
* The accompanying letter provided with the Annual Safety Report should contain a short summary of the status of the clinical trial in Switzerland (number of centres open/closed, number of patients recruited/recruitment closed, and number of SADR/SUSAR.

The Sponsor is responsible for the reporting of unexpected ADRs in according to the normal pharmacovigilance practice.

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so-called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the local Ethics Committee (local event via local Investigator).

**9.4 Responsibilities**

 “Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated [in Phase III and late Phase II CTIMPs] using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated [in Phase I and early Phase II CTIMPs] using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

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. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information [in Phase I and early Phase II CTIMPs].
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.

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 (Data Monitoring Committee (DMC) and / or Trial Steering Committee (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 (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
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.
8. Providing indemnity and insurance to meet potential legal liabilities

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, 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

Deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate.

**9.6 The type and duration of the follow-up of participants after adverse reactions.**

Participants terminating the study (either regularly or prematurely) with

* reported ongoing SAE, or
* any ongoing AEs of laboratory values or of vital signs being beyond the alert limit

Will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective AE page in the CRF. All other information must be documented in the source documents. Source data must be available upon request.

In case of participants lost to follow-up, efforts should be made and documented to contact the participant to encourage him/her to continue study participation as scheduled.

All new SAE or pregnancies that the investigators will be notified of within 30 days after discontinuation of study medication have to be reported in appropriate report forms and in the CRF if required.

Follow-up investigations may also be necessary according to the investigator’s medical judgment even if the participant has no SAE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documents.

# 10 STATISTICS AND DATA ANALYSIS

**10.1 Sample size calculation**

In regards to the primary end point comparing incidence of DGF in all cohorts in both participating centres:

Latest incidence rate of DGF after non-oxygenated end-ischemic HMP or CSS in DCD kidneys reported upon by both participating centres is about 45% in Leeds and 60% in Zurich.

* + Based on a cautious impact of 35% reduction for DGF (OR of 0.7), we would estimate DGF rate to be reduced from 45% to 29.2% which would require a study group sample size of 146 patients to reach significance ( p= 0.05) with a study power of 80%.
	+ Based on current DCD transplant activity, it is expected that 106 recipients could be enrolled by Leeds and 40 by Zurich between December 2020 and November 2021.

**10.2 Planned recruitment rate**

Recruitment will take place in the 2 centres involved in this study St. James’s University Hospital, Leeds and University Hospital Zurich. DCD kidney transplant activity over the past year is supports the required number of patients and the trial set-up will allow for a high consent rate as there is no additional risk, clinical or logistical burden compared to routine kidney transplant outside the trial.

**10.3 Statistical analysis plan**

We will conduct propensity score matching to reduce the selection bias between the groups. Potential variables for calculating the Propensity scores are preservation time (cold ischemic time = CIT), length of WIT, donor and recipient age, final donor serum creatinine, donor co-morbidities like AHT or Diabetes and patients will be matched with a 1:1 ratio using the 'MatchIt' package in 'R' for propensity matching, using the "Nearest neighbour" method. Unmatched patients will be excluded from the subsequent analysis. We will assess balance before and after matching by comparing the means/proportions for each matching variable between the groups.

Normality of distribution will be determined by the Kolmogorov-Smirnov test and quantile - quantile plots of dependent variables for all continuous variables.

Comparisons: the Mann-Whitney U tests and ANOVA will be used to compare continuous variables were appropriate. Difference among proportions will be determined by the Fisher’s exact test. Correlations will be determined by the Spearman’s or the Pearson’s Correlation Coefficient tests where appropriate. The prognostic efficacy and weighted cut-off points will be determined by the ROC curves. The logistic regression model will be used to identify independent predicting factors of a complication Grade ≥ I.

General linear multivariate regression analysis methods will be used with dependent variables being the creatinine levels, donor and recipient age, cold ischemia time.

**10.3.1 Summary of baseline data and flow of patients**

All data will be prospectively collected in Case Report Forma (CRFs) specifically designed for the purpose and needs of this study. The reason for this is to ensure a standardized data collection technique and to avoid missing data. This software will be stored in an encrypted folder of the hospital server and access will be provided only to the investigators.

Statistical analysis of demographic donor and recipient characteristics will be carried out to check whether adequate historical cohorts match with study arm or whether relevant differences are being detected.

To verify whether all prognostic factors are being equally distributed between the cohorts, a posteriori stratification will be performed, implying a modelling of the data using the appropriate multivariate analysis technique. The following preservation, donor and recipient factors are associated with early renal graft dysfunction and thus will be included in the stratification: preservation time (cold ischemic time = CIT), length of WIT, length of agonal phase, functional WIT, number of HLA mismatches, recent PRA level, 1st/re-transplant, length of time on dialysis, donor and recipient age, final donor serum creatinine, donor co-morbidities like AHT or Diabetes and cause of death.

**10.3.2 Primary outcome analysis**

Primary analysis will be univariate comparing the difference in proportion of DGF (No DGF vs. DGF) within the study groups (HOPE vs HMP and CS) with the Fischer’s exact 2-sided test.

**10.3.3 Secondary outcome analysis**

Comparison of Quantitative data; Duration of DGF in days, number of Dialysis sessions, Length of hospital stay in days, Creatinine levels and glomerular filtration rate (GFR), CCI 30 and 90 days and 12 months after transplantation and Analysis of Perfusion Fluid for markers of Kidney injury will be tested using ANOVA

Categorical data such as Rates of biopsy proven rejections, Incidence of complications, Clavien-Dindo Complication Classification, Death-censored graft survival and patient death will be compared using the Fischer’s exact 2-sided test.

**10.4 Interim analysis and criteria for the premature termination of the trial**

Regular block interim analysis could be performed after each 20 enrolments which might lead to early termination of the study once statistical significance achieved.

**10.5 Participant population**

This is an intention to treat analysis and consequently data from all included kidneys for HOPE will be analysed and outcomes will be compared to HMP and CS (see 5 Trial Setting) using the aforementioned statistical tests (see 10.3)

# 11 DATA MANAGEMENT

## **11.1 Data collection tools and source document identification**

## **Electronic Case Report Forms**

## All planned visits, examinations as well as all parameters and data described in the study protocol will be recorded in a CRF to ensure the correct conduct of the clinical trial.

## We will use paper case report forms (CRF), one for each enrolled study participant, which will be filled in with all relevant data pertaining to the participant during the study. The investigator will document the participation of each study participant on the Enrolment Log.

## For data and query management, monitoring, reporting and coding a CRF system developed in agreement to the Good Clinical Practice (GCP) guidelines will be used for this study. It is the responsibility of the investigator to assure that all data in the course of the study will be entered completely and correctly in the respective data base. Corrections in the CRF may only be done by the investigator or by other authorised persons. In case of corrections the original data entries will be archived in the system and can be made visible. For all data entries and corrections date, time of day and person who is performing the entries will be documented.

## CRFs must be kept current to reflect participant status at each phase during the course of study. Participants are not to be identified in the CRF/CRF by name but an appropriate coded identification (e.g. Participant Number) will be used. Please note: Initials will not be used in combination with the date of birth in the CRF for identification of the study participant.

## It will be assured that any authorised person, who may perform data entries and changes in the CRF, can be identified. A list with signatures and initials of all authorised persons will be filed in the study site file and the trial master file, respectively.

## Documented medical histories and narrative statements relative to the participant’s progress during the study will be maintained. These records will also include the following: originals or copies of laboratory and other medical test results (e.g. ECGs, etc.) which must be kept on file with the individual participant’s CRF.

## The investigators assure to perform a complete and accurate documentation of the participant data in the CRF. All data entered into is also be available in the individual participant file either as print-outs or as notes taken by either the investigator or another responsible person assigned by the investigator.

## Essential documents must be retained for at least 8 years after the regular end or a premature termination of the respective study

**Specification of Source Documents**

The following documents are considered source data, including but not limited to:

• SAE worksheets

• Nurse records, records of clinical coordinators, and

• Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if participant visited any during the study period and the post study period.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) will be included in the source documents:

• Demographic data (age, sex)

• Inclusion and Exclusion Criteria details

• Participation in study and signed and dated Informed Consent Forms

• Visit dates

• Medical history and physical examination details

• Key efficacy and safety data (as specified in the protocol)

• AEs and concomitant medication

• Results of relevant examinations

• Laboratory printouts

• Dispensing and return of study drug details

• Reason for premature discontinuation

## **11.2 Data handling and record keeping**

Data will be recorded in a paper CRF in the data-management-system designed specifically for the study

Information on CRF will be extracted to secure software systems on the hospital sites and is available in numerous data formats allowing for statistical analysis and through plausibility checks, data is immediately checked at recording in the CRF. Potential errors are immediately notified to ensure a rapid correction.*By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis. By introducing the data in the eCRF an immediate storage in an online database is performed. The data can be extracted directly and is available in numerous data formats allowing for statistical analysis.*

## **11.3 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.

11.4 Archiving

All study data will be archived for a minimum of 8 years after study termination or premature termination of the clinical trial.

### 12 MONITORING, AUDIT & INSPECTION

**Monitoring** visits at the investigator’s site by an independent organisation prior to the start and during the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors early point. The Sponsor-Investigator organises professional independent monitoring for the study.

All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the CRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

A quality assurance **audit/inspection** of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

# 13 ETHICAL AND REGULATORY CONSIDERATIONS

**13.1 Research Ethics Committee (REC) review& reports**

Study protocol will be submitted to the Ethical Committees from both participating centres.

It is being estimated that there will be no increased risk for the recipient by participating in this study. On the contrary, based on previous findings, recipients might benefit from participating in this trial since it could lead to improved renal graft function.

Nevertheless, informed consent from the recipient will be required to obtain approval to participate in this study as well as for post-op data collection.

**13.2 Protocol compliance**

* There are no prospective, planned deviations or waivers to the protocol
* Any accidental protocol deviations will 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.

###

### 13.3 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 –

* 1. the safety or physical or mental integrity of the participants of the trial; or
	2. 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 a clinical trial will notify the licensing authority in writing of any serious breach of
	1. the conditions and principles of GCP in connection with that trial; or
	2. the protocol relating to that trial, as amended from time to time,

Within 7 days of becoming aware of that breach

**13.4 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.

Data will be maintained in secure CRF kept on site and on hospital computers which is encrypted and password protected (see 11.2 Data handling and Record keeping)

13.5 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

There are no ownership interests, commercial ties or non-commercial conflicts to disclose oin relation to this study.

13.6 Indemnity

Arrangements for insurance and indemnity will be made by Leeds Teaching Hospitals as the sponsor of the trial in accordance with the NHS indemnity scheme.

Aim: to fully describe indemnity arrangements for the trial

13.7 Amendments

Any amendments to the protocol will be communicated to the CI and PIs and substantial amendments will be reported to the sponsor.

Amendment history can be tracked using the version and date (see 16.6 Appendix 6)

**13.8 Post-trial care**

Patients continue follow up in the Post-Transplant Clinic as per protocol in the transplanting centre. This is standard practice for all kidney transplant patients.

**13.9 Access to the final trial dataset**

The PI and CI at both recruiting centres will have access to the final data set for analysis and research purposes.

### 14 DISSEMINIATION POLICY

**Authorship eligibility guidelines and any intended use of professional writers**

Draft copies of any manuscripts will be provided to all local lead investigators and study sponsors for review prior to their submission for publication. Papers will be written in the name of the study group with each individual investigator named personally at the end of the report (or to comply with medical journal requirements). First and last authorship of the main paper concerning primary and secondary endpoints will be reserved for the coordinating CI and the PIs. Further authorship positions will be evaluated by the scientific steering committee taking into account the number of inclusions and the scientific input.

Each participating centre has the right to submit amendments. These will be discussed by the scientific steering committee. First and last authorship of manuscripts resulting from these amendments will be reserved for members of the centre submitting the amendment.

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### 16. APPENDICIES

**16.1 Appendix 1-Risk**

|  |
| --- |
| Risks associated with trial interventionsA ≡ Comparable to the risk of standard medical care. |
| Justification: There is no additional risk to the organ included in the study as the handling and connection to the machine will be carried out at the same standard of retrieval, transport, benching and implantation.There is no additional risk to the patients involved in the study as the surgical procedure, pre and post-operative and follow up is as standard and follows the protocols of the transplanting centre. |

**16.3** **Appendix 4 – Schedule of Procedures**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Study Periods*** | ***Listing Clinic***  | ***Admission and hospital stay for Transplantation*** | ***Follow-up period (( 1 year after KT)*** |  |
| ***Type of visit*** |  | ***Admission***  |  | ***KT+ HOPE*** | ***Hospital stay*** | ***Discharge***  | ***1st follow-up visit*** |  ***Follow-up visits*** |
| ***Kidney Transplant Consent Clinic***  | ***Kidney benching***  | ***until 1 year after transplantation*** |
| *Screening (exclusion/inclusion criteria)* | *X* | X |   |  |  |  |  |  |
| *Informed Consent* | *X* | X |   |  |  |  |  |  |
| *Demographics* | *X* | X |   |  |  |  |  |  |
| *Medical History* | *X* | X |   |  |  |  |  |  |
| *Laboratory Tests (Inflammation markers, Kidney function, urine samples, coagulation, platelets)* | *X* | X |   | *X* | *X* | *X* | *X* | *X* |
| *definitive inclusion*  |  |   | X |  |  |  |  |  |
| *Kidney US* |  |   |   |  | *X* |  |  | *X\** |
| *Assessment of DGF* |  |   |   | *X* | *X* |  |  |  |
| *Assessment of Secondary outcome measures*  |  |   |   | *X* | *X* | *X* | *X* | *X* |
| *Adverse Events/Serious Adverse Events* |  | *X* |  | *X* | *X* | *X* | *X* | *X* |
|  |  |   |   |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |

**16.4** **Appendix 6 – Amendment History**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
| 0 | Version 0.1 | 28/08/2019 | P. Kron | First Draft |
| 1 | Version 0.2 | 29/10/2019 | P. Kron, A. Ghoneima | Protocol draft modified to fit HRA Protocol Development Tool |
| 2 | Version 0.3 | 18/11/2019 | A. Ghoneima, P. Kron | ix TRIAL FLOW CHART8.1 Machine Perfusion (details added)8.2 Perfusion Solution (details added)8.3 Machine operation (previously 8.2)Additional information regarding Perfusate samples added to 7.2.1 and 7.7 |
| 3 | Version 0.4 | 13/07/2020 | A. Ghoneima |  |
| 4 | Version 0.5 | 06/09/2020 | A. GhoneimaD. Keane | 3.4/3.5 Secondary Outcomes (further outcomes added as per reviewers’ request)4 Trail design (Two arms+Third arm design)10.1 Sample Size Calculation (recalculated according to the most recent rates in LTH 2019) 10.3.3 Secondary Outcomes (details of statistical tests added) |
| 5 | Version 0.6 | 24/10/2020 | A. Ghoneima | Changes within Research Team (Mr. Adam Barlow as Chief Investigator with Dr med Philipp Kron)Updated Schedule of Procedures |
| 6 | Version 0.7 | 02/12/2020 | A. Ghoneima | Logo Update11.1/11.4 Data storage for 8 years |