Trial Title: Oxygenated Hypothermic Machine Perfusion in Pancreas Preservation for Transplantation, a phase 1 safety and feasibility trial.

Internal Reference Number / Short title: Hypothermic Oxygenated Pancreas Perfusion - The HOPP Study

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Conflicts of Interest

Professor Rutger Ploeg has received paid consultancy income from the distributor and industry collaborator Bridge to Life Ltd. (B2L) for preservation solution development advice. He will not be involved in approaching, consenting, recruiting, or in the clinical management of patients in this study.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

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1 KEY TRIAL CONTACTS

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2 LAY SUMMARY

Pancreas transplantation is an effective treatment for patients with the most severe complications of diabetes. It improves quality-of-life and life-expectancy by returning blood sugar levels to normal and removing the need for insulin. Most pancreas transplants are performed at the same time as a kidney transplant for patients with kidney failure due to diabetes.

When a donor pancreas is removed from the body it is stored in specialist fluid in an ice box. This simple method slows down cell activity and reduces the need for oxygen and energy. Recent clinical trials in kidney and liver transplantation have shown that continuously pumping the organ with cold preservation fluid enriched with oxygen provides improved protection and better clinical outcomes. This technique has increased donor organ utilisation (defined as the proportion of organs donated which result in a transplant) but has not been tested in pancreas transplantation.

This study will investigate the application of the above-mentioned technique in pancreas transplantation.

The study will recruit 30 patients who are receiving a simultaneous pancreas and kidney transplant in Oxford. The donor organs will be transported from the donor hospital as usual in an ice box. While the kidney is being transplanted, the pancreas will be pumped with oxygenated fluid for 2 hours. The pancreas will then be transplanted as standard.

Outcomes in these 30 patients will be compared to 60 recent patients who have had the same type of transplant without pumping of oxygenated fluid. Outcomes will be assessed including the function and survival of both pancreas and kidney, post-transplant complications (particularly any inflammation of the pancreas), the need for additional surgery and the length of hospital stay.

This research has the potential to reduce injury to the donor pancreas, increasing the number of pancreases safely and successfully used for transplant. The results will also be valuable to the design of larger clinical trials in the future.

3 SYNOPSIS

Trial Title	Oxygenated Hypothermic Machine Perfusion in Pancreas Preservation for Transplantation, a phase 1 safety and feasibility trial.		
Internal ref. no. (or short title)	Hypothermic Oxygenated Pancreas Perfusion - HOPP		
Trial registration	International Standard Randomised Controlled Trial Number (ISRCTN) ISRCTN Number: Insert Date of Registration: Insert		
Sponsor	University of Oxford		
Funder	NIHR Invention for Innovation i4i Challenge Awards (NIHR204643)		
Clinical Phase	Phase I (IDEAL 2a)		
Trial Design	Single centre prospective cohort study		
Trial Participants	Adult recipients of deceased donor simultaneous pancreas kidney transplants, where pancreases have been perfused.		
Sample Size	30 perfused, transplanted pancreases		
Planned Trial Period	36 months total trial period		
Planned Recruitment period	18 months (01/03/2024 to 30/09/2025)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Demonstrate safety and feasibility of end-ischaemic $HMPO_2$ of pancreas grafts prior to transplantation in clinical practice.	Pancreas graft survival	90 days
Secondary	Produce preliminary efficacy data for end-	• Perfused pancreas organ utilisation	Inpatient stay (visit 1)

	ischaemic $HMPO_2$ of pancreas grafts prior to transplantation to inform the size, design, and clinical endpoints of a future efficacy trial.	● Incidence of post-transplantation graft pancreatitis	Inpatient stay (visit 1)
		● Incidence of pancreas graft intravascular thrombosis	Inpatient stay (visit 1)
		● Incidence of graft loss related to transplant vascular thrombosis.	90 days
		● Clinically suspected & treat episodes of acute rejection of pancreas graft	3-month visit (visit 3)
		● Patient survival	All 3 study visits
		● Number of post-operative interventions (surgical/endoscopic/radiological)	1-month follow up (visit 2)
		● Incidence of ureteric complications	All 3 study visits
		● Incidence of bowel complications	All 3 study visits
		● Incidence of vascular complications	All 3 study visits
		● Re-admission rates	3-month visit (visit 3)
		● Length of hospital and ICU stay postoperatively.	3-month visit (visit 3)
		● Serum C-reactive protein (CRP)	All 3 study visits
		● Recipient infection (defined as a clinically diagnosed and treated infection)	All 3 study visits

		• Serum Glucose (on daily laboratory tests)	All 3 study visits
		• Blood Glucose (point-of-care) measurements twice daily.	Inpatient stay (visit 1)
		• Glycated haemoglobin ($HbA1_C$) in mmol/mol	3-month visit (visit 3)
		• Oral glucose tolerance test (OGTT) as detailed in section 9.7.1	Discharge and 3-month visit (visit 3)
		• Kidney-specific secondary outcomes will include: – Delayed kidney graft function (DGF) – Acute rejection (Biopsy proven) – Early kidney graft loss – Kidney graft function (Serum creatinine & eGFR)	3-month visit (visit 3)
		• Full Blood Count	All 3 study visits
		• Serum Amylase and Lipase	All 3 study visits
		• Drain Amylase (when available)	Inpatient stay (visit 1)
		• During $HMPO_2$ the following will be recorded: – Perfusate flow – Pancreatic resistance – Extent of oedema	Inpatient stay (visit 1)
	Identification of possible viability markers during preservation	• During $HMPO_2$ samples will be collected to measure markers of damage in the perfusate:	Inpatient stay (visit 1)

		– Amylase – Lipase – Cell-free DNA (cfDNA)	
Intervention(s)	120 minutes of oxygenated hypothermic machine perfusion of the pancreas graft at the end of the cold ischaemia time.		
Comparator	60 (2:1) hierarchically matched historical controls of SPK recipients from the same centre since 1st of March 2018		

4 ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATP	Adenosine triphosphate
CI	Chief Investigator
CIT	Cold ischaemia time
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DBD	Donation after Brainstem Death
DCD	Donation after Circulatory Death
DD	Device Deficiency
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HMP	Hypothermic machine perfusion
$HMPO_2$	Oxygenated Hypothermic Machine Perfusion
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRI	Ischaemia/reperfusion injury
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NMP	Normothermic Machine Perfusion
NR	Normothermic Reperfusion
OTC	Oxford Transplant Centre

PI	Principal Investigator
PIS	Participant Information Sheet
PTx	Solid organ pancreas transplantation
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
ROS	Reactive Oxygen Species
RSI	Reference Safety Information
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SCS	Static Cold Storage
SNOD	Specialist Nurse in Organ Donation
T1DM	Type 1 Diabetes Mellitus
TMF	Trial Master File
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
UKTR	UK Transplant Registry

5 BACKGROUND AND RATIONALE

5.1 Diabetes and its treatment options

Diabetes is a progressive disease which significantly reduces both quality-of-life and life expectancy. It causes complications including, but not limited to blindness; renal failure; neuropathy; limb loss and cardiovascular disease. Diabetes is caused by the failure of the beta cells of the pancreas to produce adequate levels of insulin which may be a complete failure due to autoimmune disease (Type 1) or a partial failure due to other metabolic factors (Type 2). Insulin, an anabolic hormone, has vital functions in the metabolism of carbohydrates, fats, and proteins, and the medical management of diabetes is centred on the provision of physiological insulin levels. In the UK, 3.9 million people were living with diabetes in 2019. Approximately 400,000 patients have type 1 diabetes (T1DM), expected to reach 650,000 by 2035. (1)

Delivering the right level of insulin by injection is a major challenge and even the most assiduous patient cannot achieve perfectly physiological levels of blood glucose control. The occurrence and progression of long-term secondary complications of diabetes are known to correlate with the quality of blood glucose control (2). In patients with progressive complications of diabetes (typically renal failure), or those in whom adequate blood glucose control is impossible to achieve consistently (especially if leading to episodes of hypoglycaemia-unawareness), the establishment of physiological levels of control is a vital benefit: pancreatic transplantation may be the only means to achieve this intention (3).

5.2 Pancreas transplantation

Solid organ pancreas transplantation (PTx) was shown to achieve insulin independence in the 1960s (4). During the ensuing decades, the discipline of organ transplantation evolved greatly with the development of safer, and more effective immunosuppressive medications and improved surgical techniques. This has translated to a substantial improvement in graft and recipient outcomes, such that pancreas transplantation is now an approved and NHS-funded therapeutic option for patients with life-threatening complications of diabetes (most commonly that of renal failure).

Pancreas transplantation in the UK has internationally competitive outcomes, with pancreas graft survival of 93% at one year and 80% at 5 years (5). However, utilisation (defined as the proportion of pancreases donated which result in a transplant) is the lowest amongst solid abdominal organs. Currently, 50% of pancreases removed for the purpose of transplant are not used. The reason for this is primarily clinician uncertainty about organ quality and fear of postoperative complications (6).

5.3 Ischaemia/reperfusion (IRI) and pancreas transplantation

The pancreas is extremely vulnerable to ischaemia/reperfusion injury (IRI), which is a key factor in the pathophysiology of early post-operative morbidity and mortality associated with PTx, particularly transplant pancreatitis. The severity of pancreatitis varies from sub-clinical (i.e., identified by imaging or biochemistry) through to severe graft inflammation, necrosis, and a life-threatening systemic

inflammatory response. Previous work by our group has shown evidence of a degree of pancreatitis in almost half of all transplanted pancreases (7).

This has important clinical implications: re-operation following pancreas transplant is needed in around 20-25% of patients, and pancreatitis remains the major cause of early graft loss (8,9).

During cold storage, ATP is depleted, and the toxic by-products of anaerobic respiration, succinate and lactate accumulate. When the pancreas is transplanted the severity of this cold ischaemic injury is unmasked. This results in the inflammatory cascade known as ischaemia/reperfusion injury (IRI). In the case of transplanted pancreases, this is characterised by acinar necrosis, oedema, and endothelial disruption (10–12) (graft pancreatitis), which may be complicated by vascular thrombosis and/or sepsis.

5.4 Mechanism of IRI in pancreas grafts

During ischaemia, the pancreas is deprived of oxygen and nutrient-rich blood resulting in depletion of ATP, which causes cell-membrane ionic pumps to fail and leads to acidosis, enzyme activation and reactive oxygen species (ROS) production. Ionic pumps located across the cell-membrane require ATP to maintain intracellular sodium, potassium, and calcium levels. ATP depletion prevents the pumps actively transporting ions and leads to the movement of sodium into the cell, resulting in cellular oedema. To maintain ATP in the absence of oxygen, anaerobic respiration is initiated, causing lactic acid accumulation, cellular acidosis, and enzymatic activation. These activated enzymes leak into the tissues and accumulate as there is no mechanism for removal in the nonperfused organ (13). ROS are produced at the time of reperfusion following ischaemia, in particular as a consequence of succinate accumulation in the mitochondria which result in cellular and tissue injury (14).

Reperfusion injury is an insult which paradoxically occurs when the ischaemic organ is reperfused with the recipient's blood. This instigates an acute inflammatory response and the severity of such a response is determined by the quality of the individual donor organ and the injury sustained during the preservation period (15). A long period of Static Cold Storage (SCS) increases the severity of the reperfusion injury, and this is compounded by older donor age and fatty infiltration of the gland.

This insult causes injury to the endothelial cells resulting in:

- Release of vasoactive compounds such as endothelin-1 which reduces microcirculatory blood flow.
- Degradation and shedding of endothelial glycocalyx leading to hyperpermeability and interstitial oedema.
- Activation of polymorphonuclear leukocytes which adhere to endothelium occluding venules and impairing microcirculatory blood flow.
- Activation of coagulation pathways leading to intravascular micro-thrombosis.
- Reactive oxygen species resulting in direct damage to cell membrane, DNA, and proteins.

5.5 Vulnerability of the pancreas to microcirculatory failure

The anatomy and physiology of the pancreas underpins its vulnerability to microcirculatory failure, which is one of the key features of the pathophysiology of IRI in the pancreas, resulting in acute pancreatitis (16–18). The parenchyma of the pancreas is made up of individual lobules, which consist of acinar exocrine cells amongst which the highly vascularised endocrine 'Islets of Langerhans' are embedded. Each lobule is supplied by an end-artery which preferentially supplies the islets before reaching the exocrine capillary bed (19). These capillaries are fenestrated, and thus, highly susceptible to extravasation which results in interstitial oedema and occurs following IRI. Arteriovenous shunting is a physiological phenomenon, which causes about 10% of the blood supply to bypass the capillary bed altogether. During reperfusion shunting of blood away from the capillary bed reduces perfusion of exocrine tissue and further accentuates ischaemia in the exocrine part of the pancreatic lobule (2).

These pathophysiological features that occur during IRI cause microcirculatory failure and graft pancreatitis. Oxygenated Hypothermic Machine Perfusion ($HMPO_2$) is a preservation technique designed to counter the pathophysiology of the ischaemic injury sustained during preservation. $HMPO_2$ is the delivery of oxygenated perfusion solution through the organ under hypothermic conditions (temperature <12°C). This technology combines the safety of hypothermia and the benefits of dynamic machine perfusion which reduce IRI by flushing-out metabolic products and avoiding the accumulation of mitochondrial succinate and resulting creation of ROS. (15,20,21)

5.6 $HMPO_2$ as a preservation technology

The current standard for storage and transport of the donor pancreas is static cold storage (SCS): the organ is flushed with preservation solution, cooled to ice temperature, and placed in a sterile bag in an icebox. This simple and cost-effective technique was historically used for all organs; however, recent years have seen the introduction of machine perfusion technology in liver and kidney preservation. 'Perfusion' describes the continuous pumping of a solution through the vasculature of the organ: this is performed at low temperature (hypothermic machine perfusion, HMP) or normal body temperature (normothermic machine perfusion, NMP). The primary objectives of this technology are: (i) improving preservation; (ii) functional testing/viability assessment; (iii) organ repair/reconditioning (20). The demonstration that simple non-oxygenated HMP is beneficial in higher-risk kidney grafts (22) led to this becoming standard of care in the Netherlands (23) and Belgium(24). The presumed mechanism is thought to be the flushing-out of metabolic products and enzymes with the maintenance of the microvasculature and reduction of vascular resistance. The addition of oxygenation to the perfusate, $HMPO_2$, has been shown to add further value, demonstrated in multi-centre randomised controlled trials in liver (25) and Donation after Circulatory Death (DCD) kidney (20), both demonstrating a significant reduction in ischaemia/reperfusion injury. The purported mechanism of action relates to the maintenance of aerobic mitochondrial metabolism and the avoidance of succinate accumulation, which otherwise triggers the generation of damaging ROS at the time of transplant reperfusion (26).

This is evidenced by the reduction in episodes of acute rejection in kidneys preserved by $HMPO_2$, thought to be due to reducing IRI (20). There is no published evidence describing the use of machine perfusion in clinical pancreas transplantation, although the evidence base is now strong enough to support clinical trial evaluation (21,27,28).

Branchereau et al. reported that pulsatile HMP (non-oxygenated) was feasible for a period of 24 hours perfusion in marginal human pancreases (n=7) declined for clinical transplantation. This conclusion was based on macroscopic and histological assessment: there was minimal or no oedema and normal histological features of the pancreatic parenchyma and duodenal villi at 24 hours perfusion. Insulin, glucagon, and somatostatin staining appearances were normal at 12 hours of perfusion (29). The Nantes group also reported successful pancreas allotransplantation in a diabetic porcine model after HMP (non-oxygenated) preservation for up to 6 hours without occurrence of pancreas graft thrombosis (30). The same group reported that HMP was feasible for up to 24 hours on healthy non-human primate pancreases. Oedema was only evident after 12 hours of perfusion, and immunostaining for insulin, glucagon and somatostatin was comparable to controls. The apoptosis index was <1% in both groups at 24 hours indicating minimal cellular injury (31).

Oxygenated HMP of the pancreas has been tested in human pancreases (n=5) declined for transplant. Homogeneous perfusion was confirmed by Acridin Orange staining and an increase in ATP concentration was shown, supporting the hypothesis that oxygen delivery restores cellular energy stores under hypothermic conditions. Tissue analysis showed no evidence of cellular injury, oedema or increased ROS after 6 hours of perfusion, following which two pancreases underwent islet isolation and in vitro assessment which confirmed islet viability and function (21). To test the ability of $HMPO_2$ to recondition organs, Hamaoui et al. treated porcine pancreases (n=3) with 5-hour perfusion following 26 hours of SCS followed by normothermic reperfusion (NR) with whole blood as a viability assessment. These were compared with pancreases preserved by SCS alone (n=3). Two pancreases in the SCS + HMP group demonstrated an insulin response to glucose stimulation in contrast to none in the SCS-alone group (32). Doppenberg et al. preserved human pancreases (n=5) for 6 hours of $HMPO_2$ at a pressure of 25mmHg after an average period of cold ischaemia of 13 hours. There was no evidence of oedema or apoptosis on biopsy at the end of $HMPO_2$, and subsequent islet isolation produced similar yield, purity and function of islets compared to SCS controls and other studies (27).

Our group has demonstrated that $HMPO_2$ of porcine pancreas grafts for up to 120 minutes results in superior perfusion characteristics, lower lactate and improved glucose stimulated insulin secretion compared to the SCS group (33). Our ongoing (unpublished) pre-clinical porcine and human pancreas perfusion work establishes a feasible reproducible model for pancreas $HMPO_2$.

6 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures and timepoint(s)
Primary Objective Demonstrate safety and feasibility of end-ischaemic $HMPO_2$ of pancreas grafts prior to transplantation in clinical practice.	• 90-day pancreas graft survival, defined as the absence of insulin requirement 90 days postoperatively. (*1ry outcome*)
Secondary Objectives Produce preliminary efficacy data for end-ischaemic $HMPO_2$ of pancreas grafts prior to transplantation to inform the size, design, and clinical endpoints of a future efficacy trial.	● Perfused pancreas organ utilisation. ● Incidence of post-transplantation graft pancreatitis, defined as evidence of pancreatitis on contrast enhanced CT scan of the abdomen (performed between day 2 & 10 post-op). ● Incidence of pancreas graft intravascular thrombosis (detected on CT scan, day 2-10 post-op) requiring anticoagulation. ● Clinically suspected & treated episodes of acute rejection of pancreas graft during the 3 months follow-up period. ● Patient survival at 90 days. ● Length of hospital and ICU stay postoperatively (a surrogate marker for burden of post-operative complications). ● Incidence of ureteric, bowel, and vascular complications during the 3 months follow-up period. ● Number of interventions (surgical/endoscopic/radiological) in the first 30 days after transplantation, classified by Clavien-Dindo grade (34). ● Re-admission rates during the 3 months follow-up period. ● Recipient infection (defined as a clinically diagnosed and treated infection) during the 3 months follow-up period. ● Full Blood Count, Serum Glucose, Serum C-reactive protein (CRP), Serum Amylase and Lipase during inpatient stay, 1-month and 3-month follow-up visits. ● Blood Glucose (point-of-care) during inpatient stay. ● Drain Amylase (when available) during inpatient stay. ● Glycated haemoglobin (HbA1C) at 90 days. ● Oral glucose tolerance test (OGTT) at discharge and at 90 days. Presented in three categories: normal, pre-diabetic and diabetic. As defined in section 9.7.1. ● Incidence of 90-day graft loss related to transplant vascular thrombosis. ● Kidney-specific secondary outcomes will include:

Identification of possible viability markers during preservation	- Delayed kidney graft function (DGF), defined as the need for dialysis in the first week after transplantation. - Acute rejection in the first 90 days after transplantation, defined as an episode of rejection (Banff 1a or greater) confirmed by graft biopsy. - Early kidney graft loss, defined as surgical removal of the kidney. - Serum Creatinine - Kidney graft function, defined as estimated glomerular filtration rate (eGFR) at 90 days in ml/min/1.73m^2 using the CKD-EPI formula (35). See Appendix A3. • During $HMPO_2$ the following will be recorded: - Perfusate flow in the circuit as recorded by the investigator. - Pancreatic resistance as recorded by the investigator. - Extent of oedema using macroscopic oedema scale (36). - Markers of damage in the perfusate at 0, 15 and 60 minutes and end of perfusion: i. Amylase ii. Lipase iii. Cell-free DNA (cfDNA)

7 TRIAL DESIGN

This will be a single centre, prospective Phase 1/IDEAL 2a cohort study (37), investigating the safety and feasibility of end-ischaemic oxygenated hypothermic machine perfusion of pancreas grafts prior to transplantation. Upon offer of an eligible deceased donor pancreas and kidney, recipient eligibility will be confirmed, and consent will be sought. The pancreas and kidney will be transported to the Oxford Transplant Centre (OTC) under static hypothermic conditions, as per standard practice.

Upon arrival at the OTC, the pancreas and kidney will be prepared on the back-table and if suitable for perfusion the pancreas will be placed on the Vitasmart™ device and enrolled in the study. The duration of preservation will be a minimum of 90 minutes and a maximum of 150 minutes, with a target perfusion of 120 minutes.

As a 'first-in-human' trial there is an inherent risk associated with performing a new intervention. Therefore, an interim safety report will be prepared for the DMC following discharge of participant number 6 (or after 30 days in the event of a prolonged index admission), there will be a pause in recruitment until the report is reviewed to ensure that no safety concerns are identified.

Furthermore, if any of the initial 6 grafts is lost or if any device related SAE occurs, the event will be reviewed by the DMC/TSC. These added reviews would not stop recruitment unless a safety concern was identified. Any additional interim or ad-hoc analyses, as stated in the DMC Charter or requested by the DMC, will be fulfilled.

In addition, reports for the DMC will be drawn up after recruitment of patients 10 and 20. These reports will be prepared and reviewed by the time of recruitment of patients 12 and 22. The trial will not proceed further before being authorised to do so by the DMC and TSC. Furthermore, should any two out of six consecutive recipients experience graft loss in the first 30 postoperative days, recruitment will be paused to allow for investigation and consideration by the DMC.

The intervention group will comprise of deceased donor pancreas grafts, preserved with $HMPO_2$ at the end of their cold ischaemic time, accepted for transplantation in adult recipients as part of a simultaneous pancreas and kidney (SPK) transplant. This will continue to achieve the target of **30** adult recipients of deceased donor SPK transplants.

Enrolled participants will participate in the study for 90 days, starting from the day of intervention until the 90-day follow-up visit. All the samples and data will be collected during the inpatient admission, the 30-day and the 90-day follow up visits which will coincide with normal clinic visits as best as possible. Data will be collected into a secure central online electronic database using electronic case report forms and national registry data (UKTR) will be collected up to 12 months after transplantation.

A historical control cohort will be employed to elicit the preliminary evidence of efficacy and this control cohort will comprise **60** deceased donor simultaneous pancreas kidney (SPK) transplant recipients from the Oxford Transplant Centre transplanted since 1st of March 2018. Control patients will be matched 2:1 to study participants hierarchically (see Appendix A2) based on:

i. DBD/DCD donor status
ii. Donor age

iii. Cold ischaemia time (CIT).

Anticipated flow of patients through the trial is depicted in appendix A1.

8 PARTICIPANT IDENTIFICATION

8.1 Trial Participants

Participants will be adult patients active on the waiting list for simultaneous pancreas kidney transplantation at the OTC.

All eligibility criteria must be met prior to enrolment.

8.2 Inclusion Criteria

8.2.1 Organ offer criteria

- Simultaneous pancreas and kidney from deceased donors, including both Donation after Circulatory Death (DCD) or Donation after Brain Death (DBD) donors.
- Accepted for transplantation according to local criteria.
- Cold ischaemia time (CIT), prior to start of $HMPO_2$, no greater than 10 hours.
- Both donor organs, kidney and pancreas, transported in SCS prior to start of $HMPO_2$.
- Donor/family/next of kin consent for research.

8.2.2 *Recipient criteria*

- Participant is able to give informed consent for participation in the trial.
- Participant has had at least 24 hours to consider written information sent to them.
- 18 years or older.
- On waiting list for simultaneous pancreas kidney transplantation at Oxford Transplant Centre.
- Able to comply with all study requirements (in opinion of Investigator or deputy).
- Fit to proceed with simultaneous pancreas kidney transplantation.

8.3 Exclusion Criteria

8.3.1 *Organ offer criteria*

- Donor organs accepted for pancreas-only transplants (pancreas after kidney or pancreas transplant alone)
- Donors subjected to Normothermic Regional Perfusion (NRP).

8.3.2 *Recipient criteria*

- Participation in an investigational study likely to affect interpretation of the trial data.
- Recipients of pancreas-alone or pancreas after kidney transplants will be excluded.
- Other significant disease or disorder which, in the opinion of the Investigator, may: (i) put the participant at risk by participating in the study; (ii) affect the participant's ability to participate in the study.

9 TRIAL PROCEDURES

A schedule of activities attached as appendix C.

9.1 Recruitment

All pancreas organ offers accepted at OTC which meet the inclusion criteria will be eligible for consideration. Offers are managed by NHS Blood and Transplant Hub Operations using the electronic offering system. Following NHSBT standard practice potential donors are identified by the donor hospital ITU staff and referred to the specialist nurse for organ donation (SNOD). The SNOD will obtain donor family consent for donation and research samples, arrange any necessary investigations and register the donor with Hub Operations as per standard practice.

Pancreas organ offering will follow standard NHSBT policy, and offering will not be altered in any way by participation in the study.

The emergency nature of pancreas transplantation means that once a potential recruit is called in for a transplant there will only be a 3–6-hour window for the consent and screening process to take place. This does not allow sufficient time for the potential participant to consider the implications of participating in the study.

For this reason, all patients who fulfil the recipient eligibility criteria and who are on the waiting list or being assessed to join the waiting list for simultaneous pancreas kidney transplantation at the OTC will be approached in advance of the study. Further details are provided in the relevant sections below.

Screening and Eligibility Assessment

9.1.1 Recipient Eligibility Assessment

Screening will take place at the OTC by delegated members of the research team and will be restricted to an assessment of the inclusion and exclusion criteria and obtaining informed consent and recording ethnicity information held locally.

The inclusion criteria stating that the patient must be fit to proceed with simultaneous pancreas kidney transplantation will be determined by the standard care assessment performed on admission to hospital and according to standard local procedures. This is not a trial-specific assessment.

If a recipient is deemed unfit for transplant at the time of admission, they will no longer remain active on the transplant waiting list and as such will be excluded from the trial.

Should a recipient who has been deemed unfit for transplant subsequently becomes fit, be re-activated on the transplant waiting list, and be called in again for transplant, they would be eligible to join the trial as any other recipient.

9.1.2 Donor organ offer assessment

The role of the transplant recipient co-ordinator is to facilitate calls for organ offers and co-ordinate most aspects of the transplant process. On receiving an organ offer, the local recipient co-ordinator and on-call transplant surgical team will ascertain baseline demographic information from the NHSBT electronic offering system (EOS) to assess eligibility of the pancreas for inclusion in the trial.

9.2 Informed Consent

9.2.1 Recipient Approach

All patients who fulfil the recipient eligibility criteria and who are on the waiting list or being assessed to join the waiting list for simultaneous pancreas kidney transplantation at the OTC will be approached in advance of the study in person or by post or electronic means accompanied by an initial cover letter and Participant Information Sheet.

This approach will be followed by provision of information verbally at either a routine clinic appointment, during inpatient admission, or by telephone. Detailed information will, therefore, be given both verbally and in writing in the form of a Participant Information Sheet. A delegated member of the research team will provide the information.

A screening sheet encompassing a list of patients who have received the Participant Information Sheet and who have had a verbal discussion about the trial will be maintained at the OTC by the members of the research team. To aid recruitment this list will be accessible to the pancreas transplant recipient coordinators.

9.2.2 Recipient Informed Consent

Written informed consent will be obtained when patients attend the hospital for transplant. Patients will only be eligible if they have had at least 24 hours to consider the written trial information sent to them.

When a suitable donor organ becomes available and is allocated to a recipient who has been deemed to be fit to proceed with simultaneous pancreas kidney transplantation, the recipient will be approached by a member of the research team and the study will again be discussed. Written and verbal versions of the Participant Information Sheet and Informed Consent Form will be presented to the recipient, detailing the exact nature of the study, the implications and constraints of the protocol, the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The recipient will be allowed as much time as possible to consider the information, as well as the opportunity to question the investigator or other members of the clinical or research team, to decide whether to participate in the study.

The recipient will be asked if they would like to take part in the study; if so, they will be asked to sign and date the Informed Consent Form. This will include optional consent points for sample collection and storage in a suitable biobank (section 9.11.2). Each subject must also give consent for the Sponsor

and regulator's representatives to review their hospital records for safety monitoring or auditing purposes if required.

If the recipient is not willing to participate in the study at this stage, then organ preservation will be carried out using conventional procedures and transplanted in accordance with local protocol (no change from standard practice). In addition to trial consent, a consenting recipient will also be required to complete a surgical consent form for the transplant procedure in accordance with standard local policy (taken by the primary clinical team).

No study specific procedures will be performed until the recipient has signed and dated the latest approved version of the Informed Consent Form.

Written informed consent will be taken and documented by means of dated signatures from both the participant and the member of the research team who obtained the informed consent. The person who obtains consent must be:

1. GCP Trained, suitably qualified and capable of providing information about the study.
2. capable of answering questions about the study or ensuring that such questions are answered by a suitably qualified individual.
3. authorised to do so by the Chief Investigator.

A copy of the signed and dated Informed Consent Form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy will be placed in the patient's medical notes.

Subjects are free to withdraw consent at any time, irrespective of their initial consent. All participants who receive a perfused pancreas will be followed up for safety endpoints as far as possible; however, no new study-specific samples would be taken following withdrawal of consent.

The participant's general practitioner/family doctor will be informed of their participation in the study. A letter to the participant's GP will be produced and sent out after they have consented to join the study and undergone transplantation.

There is a small risk that participants in this study may lose capacity to consent to continued involvement in this study. It is standard practice in Oxford for patients to be cared for on an intensive care unit (ICU) for a short period of time (24 – 48 hours) following a simultaneous pancreas kidney transplant. They would occasionally remain sedated following their surgery as part of this higher- level care. We would continue to take blood samples in accordance with the protocol whilst their capacity is impaired in this manner, in the immediate post-operative period. In the event of a prolonged loss of capacity to consent to continued involvement in the trial, we would provide their designated next of kin with information about the study (as the Patient Information Sheet) and satisfy any questions or queries which could arise.

Should a consented participant subsequently not receive the perfused pancreas transplant they can be re-approached at a later date (dependent on whether they continue to meet the eligibility criteria). In these situations, original study consent remains valid, however this should be reaffirmed prior to

receiving the intervention. This discussion and reaffirmation should be clearly recorded in the participant's medical notes.

9.2.3 Donor consent

Consent for organ donation and research samples from the donor family will be obtained and recorded by the SNOD as per NHSBT standard practice.

Explicit consent from the donor family is required for participation in research, but not trial-specific consent as the donation process is unaltered by participation in the trial (no intervention occurs prior to donation).

During the course of the study, donor details will be kept anonymous (specific study identification codes will be used for each study pancreas). Anonymised donor data will only be made available to authorised staff of the study sponsor, its authorised representatives, and regulatory authorities.

9.2.4 Registration / Enrolment

The point of enrolment for the pancreas graft into this study occurs at the point that the use of the intervention is given the green light by the lead transplant surgeon clinically responsible for the participant's care and perfusion begins.

The point of enrolment for the participant (potential recipient) into this study occurs at the point that the perfused pancreas graft is implanted into recipient (time of reperfusion with recipient blood).

Randomisation does not occur in this study because it is a cohort (single intervention prospective group) phase 1 clinical trial.

9.3 Blinding and code-breaking

The treatment/intervention in this study is not blinded, therefore a code-breaking procedure is not required.

9.4 Baseline Assessments

The data detailed in this section will be collected after admission for transplantation and informed consent has been obtained (study visit 1).

9.4.1 Organ offer donor demographics

Donor demographics to be recorded will include the following:

- Age
- Sex
- Ethnicity
- Cause of death (CVA, hypoxia, trauma, other)
- Type of donor (DBD, DCD)
- Donor height
- Donor weight and girth

- Donor history of hypertension
- Donor inotrope use
- Number of days in hospital prior to retrieval
- Donor risk index (DRI)
- Last and peak serum creatinine
- Last and peak eGFR
- Donor glycated haemoglobin (HbA1c), when available.
- Donor reported blood/serum glucose measurements.
- CMV status
- Cold preservation solution (e.g., University of Wisconsin, HTK)

9.4.2 Recipient demographics

Recipient demographics to be recorded will include the following:

- Initials
- ODT number
- Age
- Sex
- Ethnicity
- Type of diabetes and year of diagnosis
- Current hypoglycaemic treatment and dose
- Aetiology of renal failure
- Native urine output (unimpaired/ reduced (10-500ml)/ absent)
- Dialysis status/type/duration
- History of hypertension
- Height and weight
- Number of previous transplants
- Calculated reaction frequency (CRF, %)
- HLA mismatches (A, B, DR)
- Matchability
- CMV status

9.4.3 Recipient baseline biochemical parameters

The results of blood tests taken on admission for transplant in line with departmental protocol/routine clinical care will be recorded, including:

- Serum creatinine
- eGFR (if pre-dialysis)
- Haemoglobin concentration
- White cell count
- Lymphocyte count
- Neutrophil count
- Platelet count

9.5 Oxygenated Hypothermic Machine Perfusion ($HMPO_2$)

Following the routine retrieval procedure at the donor hospital the pancreas and kidney will be placed in SCS and transported to the OTC under hypothermic conditions as per standard NHSBT practice.

On arrival at the OTC, the kidney and pancreas will be removed from storage and prepared for transplantation as per standard unit practice, including a Y-graft vascular reconstruction. General guidance for preparing the device for use is described in the VitaSmart™ User Manual and Disposable Set for Kidney Perfusion IFU. The detailed perfusion protocol is described in the IB. $HMPO_2$ will be performed using Belzer UW Machine Perfusion Solution®, the perfusion will be monitored at all times by a research fellow or member of the surgical team.

Meanwhile, the participant will be anaesthetised, and the laparotomy started, and then the kidney implanted and reperfused first. Once the intended surgical site for pancreas implantation is ready and the perfusion is over 90 mins in duration, the pancreas can then be implanted and reperfused as per usual local practice. The procedure for removing the pancreas from the device is also described in the IB. The targeted duration of machine perfusion will be 120 minutes with a minimum of 90 minutes and a maximum of 150 mins in a temperature range of 2-10°C.

It is not the intention of this trial to use $HMPO_2$ as an assessment tool, however it is acknowledged that it is possible that adverse parameters (e.g., flow or calculated resistance index) or gross morphological changes observed during perfusion may cast doubt on the suitability of an organ for transplant. In the event of concerns arising, technical issues such as dissection of the arterial supply; mal-positioning or kinking of cannulae; vascular occlusion; sensor dysfunction or device malfunction will be rapidly ruled out by the investigator. If it is not attributable to a technical complication a decision will be reached in conjunction with the *implanting surgeon* as to whether the organ is transplantable or should be discarded/offered for reallocation. If other perfusion issues are encountered, such as leak from the set; software problems, device failure, and these cannot be resolved rapidly, the pancreas will remain in the cooled organ chamber without continuous perfusion until implantation. In this circumstance the duration of perfusion and reasons for failure to perfuse will be recorded and reported as a device deficiency (refer to Section 11.5) and detailed in the final Data Analysis Report.

The approach to perfusion will be determined by the anatomical configuration and implantation plan. The options include back table reconstruction to create a single inflow, and then, cannulate the donor common iliac artery (if available length allows trimming after the perfusion is complete) or suture the end of the donor common iliac artery to a vascular graft. If perfusion is not technically possible, the pancreas will be preserved using standard static cold storage and transplanted as soon as is logistically possible. In this circumstance the reasons for failure to perfuse will be recorded and detailed in the final data analysis report. For the purposes of the trial sample & data collection, the perfusion will be replaced by recruiting a further pancreas.

9.6 Recording of operative and perfusion parameters

The following data will be collected from the NHSBT HTA form B and the implanting surgical team:

Donor timings

The times to be recorded for DBD donors are as follows:

- Cessation of donor circulation (cross clamp).
- Start of cold perfusion (should be the same unless technical problem).
- Pancreas removal and placement on ice.
- Kidney removal and placement on ice.
- Arrival time at OTC.
- Time pancreas removed from storage to bench.
- Time kidney removed from storage to bench.
- Initiation of oxygenated hypothermic machine preservation.
- Cessation of oxygenated hypothermic machine preservation.
- Time of removal from ice for implant for both pancreas and kidney.
- Time of reperfusion in recipient for both pancreas and kidney.
- Perfused pancreas organ utilisation, defined as the percentage of organs transplanted after perfusion. Presented as 3 categories: (i) Discarded before perfusion, (ii) Discarded after perfusion and (iii)Transplanted.

The times to be recorded for DCD donors are as follows:

- Withdrawal of life sustaining treatment.
- Onset of functional warm ischaemia (SBP < 50 mmHg).
- Cessation of donor circulation (asystole).
- Start of cold perfusion.
- Pancreas removal and placement on ice.
- Kidney removal and placement on ice.
- Arrival time at OTC.
- Time pancreas removed from storage to bench.
- Time kidney removed from storage to bench.
- Initiation of oxygenated hypothermic machine preservation.
- Cessation of oxygenated hypothermic machine preservation.
- Time of removal from ice for implant for both pancreas and kidney.
- Time of reperfusion in recipient for both pancreas and kidney.

- Perfused pancreas organ utilisation, defined as the percentage of organs transplanted after perfusion. Presented as 3 categories: (i) Discarded before perfusion, (ii) Discarded after perfusion and (iii)Transplanted.

Preservation parameters

- In addition to timings, several other preservation parameters will be recorded. These will include:
- Quality of in-situ perfusion of pancreas (graded as is there any concern about in-situ perfusion: yes/No by donor surgeon)
- Quality of bench perfusion of the pancreas (graded poor, moderate, good by recipient surgeon)
- Weight of the pancreas at start and end of perfusion ($HMPO_2$).
- Perfusion parameters:
    - Perfusate pressure (in mmHg).
    - Perfusate flow rate (in ml/min).
    - Perfusate temperature (°C).
    - Pancreatic resistance index as calculate by device.
    - Extent of oedema using a macroscopic oedema scale (36), previously described in pre-clinical pancreas perfusion studies. This is going to be assessed at three timepoints (start, 60 minutes of perfusion and end of perfusion) independently by two pancreas transplantation surgeons who will be blinded to the timepoints using photography and grading the pancreases using a scale of 0 to 3; 0 refers to no oedema, 1 to mild oedema, 2 to moderate and 3 to severe oedema.
- Perfusion solution used for donor aortic perfusion.
- Perfusion solution used for organ transport, both pancreas and kidney.
- Method of donor arterial connection.

Perfusate samples (5mls) will be taken prior to connection of the organ, at 0, 15 and 60 minutes and end of $HMPO_2$ duration to assess:

- Amylase
- Lipase
- Cell-free DNA (cfDNA)

In addition to these pre-specified outcomes, additional perfusate samples will be taken for storage in a suitable biobank at the same prespecified timepoints. At the end of preservation, a sample of perfusate/storage solution will be taken for microbiological culture.

Operative parameters

These will include:

- Total operative duration: defined as time from knife-to-skin to skin closure.
- Anastomotic duration (secondary warm ischaemia): defined as time between removal of each organ from ice to each organ reperfusion.

- Use of vasopressors prior to and after reperfusion of both organs.
- Intraoperative transfusion of blood products measured in units.
- Number of arterial, venous, bowel and ureteric anastomoses.
- Details of any vascular reconstruction performed for the pancreas graft.

9.7 Concomitant care

All other aspects of the retrieval procedure will be carried out according to local policies and national guidelines. Recipient management including the implantation procedure, postoperative care, immunosuppression and other medications, and post-transplant monitoring will follow local protocols.

9.8 Matched controls

The heterogeneous nature of the donor population and the relatively small number of patients in this trial means that a contemporary randomised control cohort would be poorly matched. For this reason, we will identify two matched historical control patients for each study patient, drawn from patients who have undergone deceased donor simultaneous pancreas kidney transplantation since 01/03/2018 at the Oxford Transplant Centre. The matching of cases to controls (see Appendix A2) will be based, hierarchically, on:

(i) DBD/DCD donor status, followed by,
(ii) Donor age, then,
(iii) Cold ischaemia time (CIT).

The database of matched controls will be drawn from follow-up data held locally for research and audit purposes at the OTC. The data on matched controls used for the trial will include no patient identifiable data and will contain data required for matching as detailed in section 9.4 alongside the specified endpoints.

9.9 Subsequent Visits

9.9.1 Study visit 1 – 'Inpatient stay' (continued)

Patients will be assessed daily by the clinical team and managed according to normal local protocols.

Outcome assessment

The following post-operative daily biochemical outcomes, which are standard of care unless marked to indicate otherwise, will be recorded:

- Serum C-reactive protein
- Serum Glucose
- Serum creatinine
- eGFR (using the CKD-EPI formula)
- Full blood count

- Blood Glucose (point-of-care) measurements twice daily.
- Drain Amylase will be recorded when available but not sampled for the trial specifically.

On the post-operative days 0,1,3,7 &10, the following tests will be added:

- Amylase
- Lipase *

Blood samples for storage in a biobank for use in future research on the post-operative days 0,1,7,8,9,10 & on the day of discharge. (section 9.11.2) **

The first measurements should be taken as close to 24 hours post-transplant as possible. For subsequent measurements, sample taken closest to the specified time-point should be used. (Refer to Trial specific Sample Management Manual for further information)

* Trial specific test which will be performed on a standard of care sample and does not require research specific sampling.

** Trial specific samples which will only be biobanked but not tested as part of the trial.

Other outcomes to be recorded include:

- Daily Insulin requirements, presented as number of units required daily as reported by patient during visit and what date insulin administration started. **(Primary outcome)**
- Contrast enhanced CT scan of the abdomen between day 5 and day 10. This will be conducted as part of the protocol unless one or more clinically indicated CT scans are performed, excluding scans done in the first 24 post-operative hours (postoperative CT scanning is currently performed for clinical indications in about 68.6% of SPK transplant recipients in our centre). If multiple scans are performed as part of standard clinical care, they will all be considered and any scan performed between days 2 and 10 post-operatively (inclusive), which demonstrates pancreatitis or vascular thrombosis would be considered a positive result. CT evidence of pancreatitis includes enlargement and heterogeneity of the gland at imaging +/-surrounding fluid or mural thickening of adjacent bowel loops. Presence or absence of graft pancreatitis on CT will be determined by an experienced radiologist and validated by a second independent radiologist.
- Total length of intensive care unit (ICU) stay (days).
- Total length of hospital stay (days).

- Requirement for renal replacement therapy i.e., DGF & early graft loss (haemodialysis (HD), haemodiafiltration (HDF), haemofiltration (HF).
- Incidence of intra vascular thrombosis (detected on CT scan during between day 2 and 10 post-operatively) requiring therapeutic anticoagulation.
- Incidence of 90-day graft loss related to transplant vascular thrombosis.
- Oral glucose tolerance test (OGTT) at discharge.
    - Measurement of fasting plasma glucose, oral administration of 75g of glucose, samples every 30 to 60 minutes including an accurate 2-hour sample (+/- 5 minutes).
    - The results will be presented in 3 categories: **Normal** if fasting is under 6 mmol/L and at 2 hours is under 7.8 mmol/L, **impaired glucose tolerance** if fasting is 6.0 to 6.9 mmol/L and at 2 hours is 7.9 to 11.0 mmol/L or **diabetic** – as per current WHO diagnostic criteria – if fasting is over or equal 7.0 mmol/L and/or at 2 hours is over or equal 11.1 mmol/L.

<u>Further safety outcomes</u>

- Recipient infection (defined as a clinically diagnosed and treated infection).
- Biopsy-proven acute rejection episodes (for kidney), and clinically suspected and treated for the pancreas.
- Ureteric complications (ureteric strictures - anastomotic and non-anastomotic, urine leak).
- Bowel complications (leak, bleeding, bowel obstruction, post-operative ileus).
- Vascular complications (bleeding, transplant renal or pancreatic artery stenosis, artery thrombosis, or vein thrombosis).
- Tissue samples of explanted pancreas are routinely sent for histopathological assessment, with recipient consent further samples will be taken after explantation for biobanking.
- Any other adverse event – Severity will be graded according to the Clavien-Dindo classification (34) as described in appendix A4.

<u>Immunosuppression</u>

Details of induction immunosuppression and maintenance immunosuppression on discharge from hospital will be recorded.

9.9.2 Study visit 2 – '1 month post-transplant'

This visit will, where possible, coincide with a routine outpatient appointment. If the recipient is an inpatient, assessment will be made in hospital where appropriate. Follow up will be as close to 30-days post-operative as possible; dates 30 days ± 1 week from the date of operation will be acceptable.

Outcome assessment

The following biochemical outcomes, which are standard of care unless marked to indicate otherwise, will be recorded at study visit 2:

- Serum C-reactive protein
- Serum Glucose
- Serum creatinine
- eGFR (using the CKD-EPI formula)
- Full blood count
- Blood Glucose (point-of-care) measurements
- Amylase*
- Lipase

Samples for storage in a biobank for use in future research (section 9.11.2) **

* Trial specific test which will be performed on a standard of care sample and does not require research specific sampling.

** Trial specific samples which will only be biobanked but not tested as part of the trial.

Other outcomes to be recorded include:

- Daily Insulin requirements, presented as number of units required daily as reported by patient during visit and what date insulin administration started. **(Primary outcome)**
- Graft and patient survival at day 30 post-transplant.
- Requirement for renal replacement therapy i.e., DGF & early graft loss (haemodialysis (HD), haemodiafiltration (HDF), haemofiltration (HF))

Further safety outcomes

- Recipient infection (defined as a clinically diagnosed and treated infection)
- Biopsy-proven acute rejection episodes (for kidney), and clinically suspected and treated for the pancreas.

- Ureteric complications (ureteric strictures - anastomotic and non-anastomotic, urine leak)
- Bowel complications (leak, bleeding, bowel obstruction, postoperative ileus)
- Vascular complications (bleeding, transplant renal or pancreatic artery stenosis, artery thrombosis, or vein thrombosis)
- Number of postoperative intervention (surgical/endoscopic/radiological) in the first 30 days after transplantation
- Any other adverse event.

Severity will be graded according to the Clavien-Dindo classification (34) as described in appendix A4.

Immunosuppression

Immunosuppression will follow the local protocol; details of maintenance immunosuppression at 1 month post-transplant will be recorded.

9.9.3 Study visit 3 – '3 months post-transplant'

This visit will, where possible, coincide with a routine outpatient appointment. If the recipient is an inpatient, assessment will be made in hospital where appropriate. Follow up will be as close to 3 months post-operative as possible; dates 90 days ± 2 weeks from the date of operation will be acceptable.

Outcome assessment

The following biochemical outcomes, which are standard of care unless marked to indicate otherwise, will be recorded during study visit 3:

- Serum C-reactive protein
- Serum Glucose
- Serum creatinine
- eGFR (using the CKD-EPI formula)
- Full blood count
- Blood Glucose (point-of-care) measurements
- Glycated haemoglobin (HbA1C)
- Amylase*
- Lipase

Samples for storage in a biobank for use in future research (section 9.11.2) **

* Trial specific test which will be performed on a standard of care sample and does not require research specific sampling.

** Trial specific samples which will only be biobanked but not tested as part of the trial.

Other outcomes to be recorded include:

- Daily Insulin requirements, presented as number of units required daily as reported by patient during visit and what date insulin administration started, i.e., Pancreas graft survival. **(Primary outcome)**
- Requirement for renal replacement therapy i.e., DGF & early graft loss (haemodialysis (HD), haemodiafiltration (HDF), haemofiltration (HF))
- Patient survival.
- Oral glucose tolerance test (OGTT) ***
    - Measurement of fasting plasma glucose, oral administration of 75g of glucose, samples every 30 to 60 minutes including an accurate 2-hour sample (+/- 5 minutes).
    - The results will be presented in 3 categories: **Normal** if fasting is under 6 mmol/L and at 2 hours is under 7.8 mmol/L, **impaired glucose tolerance** if fasting is 6.0 to 6.9 mmol/L and at 2 hours is 7.9 to 11.0 mmol/L or **diabetic** – as per current WHO diagnostic criteria – if fasting is over or equal 7.0 mmol/L and/or at 2 hours is over or equal 11.0 mmol/L

*** Trial specific test that requires research specific sampling. If there is clinical concern over graft function, this is considered standard of care.

Further safety outcomes

- Recipient infection (defined as a clinically diagnosed and treated infection)
- Biopsy-proven acute rejection episodes (for kidney), and clinically suspected and treated for the pancreas.
- Ureteric complications (ureteric strictures - anastomotic and non-anastomotic, urine leak)
- Bowel complications (leak, bleeding, bowel obstruction, post-operative ileus)
- Vascular complications (bleeding, transplant renal or pancreatic artery stenosis, artery thrombosis, or vein thrombosis)
- Re-admission rates
- Any other adverse event

Severity will be graded according to the Clavien-Dindo classification (34) as described in appendix A4.

Immunosuppression

Immunosuppression will follow the local protocol; details of maintenance immunosuppression at 3 months post-transplant will be recorded.

9.9.4 Later outcomes

Beyond study visit 3, only data from the NHSBT UKTR is to be collected at 12 month after transplantation, namely:

- Graft survival
- Patient survival

9.10 Sample Management

For detailed information on the sampling schedule, handling, collection, storage, and processing of samples collected during the trial please refer to the Sample Management Manual. A summary schedule and is provided in Appendix B5.

9.10.1 Sample handling for standard of care and added trial purposes:

Informed consent to participate in the study includes consent for the following trial samples:

- Donor families are consented for: Regular samples of perfusate during the process of hypothermic perfusion
- Recipients are consented for: Trial-specific blood tests up to 10ml (total) per day on the day of transplant (pre-reperfusion of the pancreas with recipient blood and post-reperfusion); on post-operative days 1, 7, 8 and 10, and on the day of discharge; as well as, any day that the patient has a CT scan, and study visits 2 and 3 (as indicated in appendix B5 and the Trial specific Sample Management Manual). Trial-specific sampling will usually only be required for OGTT on study visit 3 and biobanking throughout all study visits; all other blood-based biochemical trial endpoints are anticipated to be met through routine blood samples which are required as part of standard patient care. A total volume of 10ml is sufficient for all required trial measurements and biobanking (section 9.11.2) in the event that bloods are not taken for routine clinical care, and therefore represents a maximum amount that would be required.

9.10.2 Biobank Samples

In addition to the collection of trial-specific samples, additional biological samples will be obtained to be stored for use in future studies of the mechanism of action of oxygenated hypothermic perfusion, utilising a suitable existing biobank infrastructure.

We will obtain perfusate samples during perfusion. We will also obtain blood (total up to 10ml), including that required for trial-specific investigations from the participant, starting with the sample taken following the induction of anaesthesia for transplantation (day 0). The schedule for collection of blood from participants post-operatively, and amounts to be taken, are detailed in appendix B5 and the trial Sample Handling Manual. The schedule for collection of specimens during perfusion is detailed in appendix B5 and the trial Sample Handling Manual. Any pancreas graft removed (explantation) as clinically indicated after transplantation will be biopsied after explantation and biobanked in addition to histopathological assessment (clinical standard).

Patients are required to authorise these procedures by reviewing the relevant section of the Participant Information Sheet and initialling the associated additional points on the Informed Consent form. The consent form will identify them by name and Trial ID number and a copy will be sent to the biobank along with their samples, this includes any restrictions on the use of the samples provided e.g. commercial studies. Participants can withdraw permission to use their samples for biobanking, at any time, without affecting their participation in the study. Biobanked samples will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

9.11 Early Discontinuation/Withdrawal of Participants

All enrolled participants completing the 3-month follow-up assessment will be regarded as having completed the primary objective of the study. All participants will be encouraged to complete study follow-up, and all reasonable efforts will be made to ensure completeness of follow-up. Measures include ensuring that assessments are made, where possible, at routine hospital visits rather than additional study-specific appointments, and that participants do not incur extra financial costs (e.g., travelling costs) as a result of study participation.

It is understood that participants may withdraw consent for study participation at any time irrespective of their reasons. In the event of a participant choosing to withdraw from the trial, the reason for withdrawal, if provided, should be documented on the withdrawal eCRF. Such participants will be asked whether they wish to withdraw from future trial procedures only, or trial procedures and remote data collection. The options available to participants wishing to withdraw consent will be:

a) In the event that perfusion has begun but transplantation is yet to take place – participant withdraws consent for the pancreas to be perfused further and wishes to undergo transplant as soon as feasible but agrees to continue with follow-up as per protocol.

b) Post-transplant – participant has requested to withdraw from active participation in the trial including future trial-specific tests but agrees to continued remote data collection and data linkage as per protocol. In this instance we would continue to collect safety data (instances of adverse events) and data on graft function as recorded during routine clinic reviews, from routine laboratory tests, and as recorded by the NHSBT UKTR and the referring centre up to 3 months post-transplant; samples collected to the point of withdrawal will be retained for the study and may be used in analysis. This may include samples and data taken for use in future research.

c) Pre- or post-transplant – participant withdraws consent for both further tests/trial-specific procedures and the future collection of data. In this instance we would continue to collect safety data (instances of adverse events) and data regarding pancreas function as recorded during routine clinic reviews and by NHSBT up to 3 months post-transplant; samples collected to the point of withdrawal will be retained for the study and may be used in analysis. The scope of the data collected would be agreed on a case-by-case basis with the participant, documented in their medical record.

Follow up of participants who have withdrawn beyond the intervention (the initial inpatient stay) will revert to standard clinical follow-up.

The investigators will not seek to withdraw any participant from study follow up who has received a pancreas which has undergone $HMPO_2$; as far as is possible, all protocol-stipulated follow-up information will be collected. In the event of loss to follow-up, all available information will be used in the study analysis.

The investigators may withdraw a recipient from the study to protect their safety and/or if they are unwilling or unable to comply with the required study procedures. We will keep all data accrued to the point of withdrawal, as is stipulated in the trial Participant Information Sheet.

Possible reasons for investigator-led withdrawal of a participant from the trial include:

i. Ineligibility for transplantation overlooked at screening or arising before transplantation (for example, positive crossmatch)
ii. Significant perfusion protocol deviation precluding transplantation.

In this early phase study, analysis of sufficient numbers of participants who adhered to all important aspects of the protocol is vital. Recruitment will continue as long as authorised by TSC and DMC to achieve the aim of 30 perfused pancreases transplanted in suitable participants as part of a SPK transplant.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

Procedure in the event of organ reallocation after the start of perfusion: It is possible that due to the detection of a last-minute contraindication to proceeding with transplantation such as an unexpected positive crossmatch result, or recipient issue encountered during anaesthesia or surgery, the pancreas will have to be reallocated to a different recipient after consent has been taken and perfusion has been started. In this very uncommon eventuality, the pancreas may be reallocated either locally or nationally. If the pancreas is reallocated to a local recipient, it will be offered to that patient as a pancreas which has already begun perfusion as part of the trial. The patient will be provided with three options: (1) to accept the pancreas but not consent to joining the trial (in which case their data will not be collected for the purposes of the trial, and this perfusion will be replaced), (2) to accept the pancreas and consent to join the trial, (3) to decline the pancreas in this event the pancreas is re-allocated nationally. If the pancreas is reallocated nationally, it will be offered as a pancreas that has undergone a period of hypothermic machine preservation. If it is accepted by an alternative transplant

centre, perfusion will be terminated, and the pancreas will be statically cold stored from the point of acceptance (see section 3.3 of the Investigator brochure for further information).

9.12 Definition of End of Trial

Data will be collected from participants for 3 months follow-up (Study visit 3) post-transplant. Once all data from all participants has been collated, entered, and cleaned, and all sample analyses have been completed then the database will be locked, and the trial will end.

Longer-term (12-month) follow-up data (beyond the end of the trial) will be collected from the UKTR.

The procedures for the early termination/suspension of the study in light of safety or compliance concerns are detailed in section 11.8.

10 TRIAL INTERVENTIONS

10.1 Medical Device System Description

The VitaSmart™ perfusion system is a hypothermic preservation system for use in human kidney and liver transplantation. It perfuses the donor organ with oxygenated perfusate in hypothermic conditions. This system is comprised of the following devices:

I. A reusable Base Unit which controls the perfusion – VitaSmart™ Base Unit.
II. A single-use, disposable Perfusion Kit which provides the path for fluid circulation.
III. A single-use Oxygenator.
IV. The consumable solution required for perfusion - Belzer UW Machine Perfusion Solution®.

Full details on all device aspects can be found in the Investigator's Brochure.

10.1.1 The VitaSmart ™ Base Unit

The VitaSmart™ Base Unit consists of electromechanical components and software housed in a polyurethane enclosure and provides all safety-critical control and monitoring functions. It also includes a pump unit that interfaces with the disposable tubing set to deliver the perfusate. The external console provides additional status information transmitted from the pump unit via a communication cable. It perfuses the donor organ with oxygenated perfusate in hypothermic conditions. The device provides information as to the flow dynamics providing substrates for cellular metabolism, such as oxygen.

The VitaSmart™ Base Unit is a class IIb hypothermic preservation device and is CE-marked for the purpose of the preservation of kidney or liver organs in accordance with the associated models. The model designed for kidney perfusion will be utilised within the HOPP Study for pancreas perfusion which is therefore an 'off-label' use.

10.1.2 Perfusion Kit

The disposable Perfusion Kit used with the core base unit of the VitaSmart™ device contains all the components used with each organ perfusion on the device. The Kidney Perfusion Kit will be utilised within the HOPP Study and is comprised of the following individually packaged components:

- Single line for kidney perfusion - STERILE (composed of perfusion line, klemmer, clips for fixing line, arterial filter)
- Instructions For Use – kidney perfusion
- Bluetooth temperature sensor - STERILE
- C-Arm Bonnets (Ice Cap)
- Oxy Tube with gas filter – STERILE
- Instructions For Use – Oxy Tube
- RFID Tag accessory for kidney perfusion
- Kidney Artery Adapter

The single line interfaces to the Pump Unit pump and sensors and incorporates an arterial filter, a dampening chamber, and connections for an Oxygenator. The temperature sensor is a small waterproof disk that is placed in the perfusion bowl over the ice, perfusate, and organ and transmits temperature readings via wireless signals to the Base Unit. Additional accessories provided in the kit include tubing, plastic clamps and forceps, and an RFID Tag that constrains use of the Perfusion Kit to a single use.

The Perfusion Kit is a contains class IIa, IIB and Is devices and is CE-marked for the purpose of kidney preservation. The use of the kidney Perfusion Kit within the HOPP Study for pancreas perfusion is therefore an 'off-label' use.

10.1.3 Oxygenator

The Oxygenator mounts on the Base Unit and is connected to the oxy tube. This is a Class IIa medical device and is CE-marked for the oxygenation of fluid/blood components. Therefore, the use of this device for the HOPP Study is within its current CE-marked indication.

Belzer UW Machine Perfusion Solution®

The Belzer UW Machine Perfusion Solution® is provided in a 1000mL bag and is a straw-coloured solution. The solution is CE marked for organ perfusion and will be used within such CE mark for the HOPP Study. It used commercially in Europe for hypothermic liver and kidney perfusion and is also FDA cleared in the USA for kidney perfusion.

10.1.4 Device Manufacturer

A full listing of all component manufacturers is provided in the IB. Manufacturer details for the VitaSmart™ Base Unit and Perfusion kit is provided below.

Manufacturer	**Medica S.p.A.** via degli Artigiani 7 Medolla, Modena 41036, IT
UK Responsible Person	MedEnvoy Global 85, Great Portland Street, First Floor London, W1W 7LT United Kingdom +44 20 3970 1258 https://medenvoyglobal.com/contact-us/
UK Device Distributor	**Bridge to Life (Europe) Ltd.** (a subsidiary of Bridge to Life Ltd.) LU 311 The Light Bulb 1 Filament Walk London SW18 4GQ Phone: +44(0)20 3411 8326

10.2 Device Safety

Since the VitaSmart™ is implemented in the operating room of the transplant centre, it does not affect the current practices of organ retrieval and minimizes workflow changes by transplant teams. From a

regulatory standpoint, it is important to note that the VitaSmart™ is an organ perfusion system and its use does not involve direct connection to either the donor or recipient at any time.

The device has been designed according to ISO 13485, the standard that stipulates the requirements for a comprehensive management system for the design and manufacture of medical devices. In addition, ISO 14971 specifies a process for a manufacturer to identify the hazards associated with medical devices to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. As part of the development of the device an extensive risk analysis has been undertaken and the risks identified and minimised in accordance with this standard.

The device is CE marked for use in both kidney and liver preservation and it has demonstrated safety, feasibility & benefit in clinical trials in both kidney and liver preservation.(38,39) A search on the Gov.uk website for alerts, recalls and safety information on medical devices at the time of writing returned no results related to the VitaSmart™ Base Unit or Perfusion Kit produced no results for these devices.

10.3 Device Labelling

Full details of the device labelling is included in the IB.

The VitaSmart™ Base Unit and Perfusion Kits are provided to the Investigators by Bridge to Life Ltd. and will be clearly labelled as investigational devices.

The Oxygenator and Belzer UW Machine Perfusion Solution® will maintain the standard labelling as provided by the manufacturers.

10.4 Device Training

Bridge to Life Ltd. will conduct structured training of investigational site staff on proper usage of the investigational device and its components. Initial staff training will take place after delivery and successful installation and verification of the device by Bridge to Life Ltd. and prior to the start of study subject recruitment. All training will be documented, and provision of certification is required prior to any device-related research activities. Resources used as part of the training and for user reference are:

- The VitaSmart™ user manual
- The Instructions for Use for the Disposable set for kidney perfusion
- The perfusion protocol in the IB

Device Accountability

Device accountability will be undertaken at the OTC throughout the study for the reusable unit(s) and disposable sets (sterilisation/assembly batch number and disposable set number). The manufacturer and lot number for each perfusion solution will also be recorded on the case report forms (CRFs).

The local research team will maintain an accountability log of usage of both the retained unit, disposable set, and perfusion solutions used throughout the study recording the lot number used against each subject (on the CRF).

10.5 All investigational device components should be stored in a secure area to prevent unauthorized access or use, and maintained by the investigator according to labelling, the user manual and the study protocol. (see section 4 of the Investigator brochure for further information). Device Maintenance

Device cleaning and routine maintenance will be the responsibility of the Investigator storing the device. Full details for cleaning and routine maintenance required is provided in the User Manual. Preventative maintenance will be performed by Bridge to Life Ltd. on a minimum annual basis.

10.6 Device Logistics

10.6.1 Logistical considerations

A VitaSmart™ machine will always be available to the research team. It will be stored securely at the Churchill Hospital, Oxford according to storage conditions stipulated in the IB and user manual. Perfusions will take place in the operating theatre suite at the Churchill Hospital, with back-table preparation of the graft and connection to the machine performed under sterile conditions in the operating theatre. When taken out of storage for interventional use, it will remain in the theatre suite and always supervised by the Clinical Research Fellow.

10.6.2 Procedure for the re-supply and return of unused, expired or malfunctioning device

Bridge to Life Ltd. will be contacted for device issues and troubleshooting. Engineering expertise is available at all times. Response time is rapid as the technical support team is available for clinical support of use in kidney and liver clinical perfusion. The support line can be contacted 24-hours at +44 33047202287 and requesting the UK clinical support. In addition to this, key members of the site team will be added to a 24-hour centralised communication platform.

An initial supply of disposable sets and perfusion solution will be provided prior to study start; additional product may be ordered by contacting Bridge to Life Ltd.

In the event that the base unit or a component of the disposable set malfunctions Bridge to Life Ltd. will be contacted as soon as possible to support troubleshooting and repair or replacement if appropriate.

10.7 Certification

Full details of the CE-marks for all devices is stated in the IB. The VitaSmart™ Base Unit and Perfusion Kit will be used ‘off-label’ within this study. The Oxygenator and Belzer UW Machine Perfusion Solution® will be used within their CE-marked indication.

10.8 Other Treatments (non-IMPS)

There are no non-IMPs in the trial design.

10.9 Other Interventions

There are no additional interventions in the trial design.

11 SAFETY REPORTING

11.1 Routine Safety Monitoring in Pancreas Transplantation

The procedure of pancreas transplantation is associated with serious risks to the recipient, such as infection, rejection of the organ, IRI particularly graft pancreatitis and potentially death. Recipients of pancreas transplantation are therefore intensively monitored. In alignment with national standards, Oxford University Hospitals NHS Foundation Trust performs comprehensive clinical monitoring of pancreas transplant recipients according to local policy. Multidisciplinary team meetings occur daily between the Transplant Surgeon, Nephrologist and Registrar to review each associated patient case and weekly departmental meetings are held involving the Microbiology team, Anaesthetics, Nephrology, clinical Pharmacists and Transplant Surgeons.

Transplantation

The transplantation procedure is performed by a team of at least one Anaesthetist, one Operating Department Practitioner, a minimum of two Surgeons and a full scrub team. All vitals and extensive biochemical parameters are closely monitored which includes but is not limited to general anaesthesia, oxygen saturation, respiration rate, ventilation, carbon dioxide, the monitoring of blood pressure invasively, glucose, insulin requirements, blood gas, coagulation function TEG and urine output. Any changing requirements are acted upon immediately and as required clinically.

Inpatient Admission

Following transplantation, all patients are transferred to intensive care for approximately 12-25 hours, which is extended as required. Patients are continued to be monitored as described above and are seen daily by the Registrar. Daily blood tests and clinical/medication reviews are performed, and immunosuppression assays are analysed 3 times weekly.

Patients are moved to a ward when deemed fit, where they are seen daily by a Physician and a Surgeon. Nursing care is provided continuously to the ratio of one nurse to every four patients.

Patients are then discharged after approximately 7-14 days depending on their recovery.

Outpatient Activities

All patients have 24hr telephone access to the Surgeon and Physician on call. Weekly visits to the Hospital occur for the first postoperative month and then two-weekly onwards, which can be changed according to clinical need and condition These visits include but are not limited to blood tests and clinical/medication reviews.

HTA Licence Requirements

It is a statutory condition of a licence for procurement or transplantation activity to rapidly report to NHSBT (acting on behalf of the HTA), relevant and necessary information concerning adverse events which may influence the quality and safety of organs. Further information regarding the regulations of the quality and safety of organs Intended for transplantation can be found here: https://www.odt.nhs.uk/odt-structures-and-standards/regulation/quality-and-safety-of-organs-intended-for-transplantation/

Any incident which may have an adverse effect on organ donation and/or transplantation will be reported according to standard ODT Clinical Governance incident reporting processes; the study site will therefore follow their usual procedures for reporting the relevant and necessary information concerning adverse events by completing an NHSBT incident submission form:

https://safe.nhsbt.nhs.uk/IncidentSubmission/Pages/IncidentSubmissionForm.aspx

if the incident is deemed urgent this will also be reported via telephone to the ODT Hub Operations, as described on the ODT clinical governance website:

https://www.odt.nhs.uk/odt-structures-and-standards/governance-and-quality/tell-us-about-an-incident/

11.2 Potential Risks of Oxygenated Hypothermic Machine Perfusion using VitaSmart™

Use of VitaSmart™ for end-ischemic $HMPO_2$ adds some potential risk, but these risks are similar relative to the current standard of care (SCS). The additional manipulation of the pancreas during organ connection to the device and perfusion represents potential risk to graft integrity; however, this risk is mitigated by organ cannulation and device operation by experienced clinicians following hands-on training by a Bridge to Life Ltd. perfusionist. Preparation of kidney and pancreas for transplantation will be completed prior to start of perfusion to minimize organ manipulation while using the device. The pancreas will undergo $HMPO_2$ during the time period when the graft routinely would be in SCS; any additional time during $HMPO_2$ does not contribute to cold ischemia time since the pancreas is being perfused with oxygen.

VitaSmart™ has multiple features that mitigate the potential risk of organ injury during $HMPO_2$. The device will be set to a maximum pressure of 25mmHg for each procedure. The system will stop automatically (i.e., the pump turns off) if the pressure during $HMPO_2$ exceeds the user-defined threshold or the system detects air bubbles in the line, thereby converting the treatment to SCS. Additionally, the risk of exceeding the target perfusate temperature is no different for $HMPO_2$ than for SCS, and the system provides an additional visual alarm when the temperature sensor detects a

threshold breach. In the event that a $HMPO_2$ procedure is stopped and cannot be resumed due to a malfunction of the device, the existing set-up can be used to preserve the pancreas (e.g. static cold storage per standard of care) until the graft can be transplanted.

11.3 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Event of Special Interest (AESI)	An adverse event of scientific and medical concern specific to the clinical trial, for which ongoing monitoring and reporting by the Investigator could be appropriate.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. NOTE 1: This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: a) led to death b) led to serious deterioration in the health of the subject, that either resulted in: - a life-threatening illness or injury, or - a permanent impairment of a body structure or body function; - in-patient hospitalisation or prolonged existing hospitalisation; c) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;

	d) led to foetal distress, foetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. 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 the circumstances had been less fortunate. These are handled under the SAE reporting system. Note 2: A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a SAE for example transplant ureteric stent removal and haemodialysis catheter removal.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	For the purpose of the HOPP Study, all serious adverse device effects will be classified as Unanticipated (see section 15.1 of IB).
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.
Use error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

11.3.1 Severity definitions

The following definitions will be used to determine the severity rating of all adverse events:

Mild: awareness of signs or symptoms that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae.

Moderate: a sign or symptom, which interferes with the subject's usual activity.

Severe: incapacity with inability to do work or perform usual activities.

Severity will additionally be graded according to the Clavien-Dindo classification (34) (detailed in appendix A4).

NB: To avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

11.3.2 Assessment of Causality

The relationship of each adverse event to the device must be determined by a medically qualified individual according to the following definitions:

Relationship	Description
Unrelated	There is no evidence of any causal relationship to the medical device
Unlikely	The relationship with the use of the investigational medical device seems not relevant and/or the event can be reasonably explained by another cause.
Possible	The relationship with the use of the device is weak but cannot be ruled out completely
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot be reasonably be explained by another cause
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt.

11.4 Procedures for Reporting Adverse Events / Adverse Device Effects

As pancreas transplant recipients, all patients recruited to the HOPP Study are at high risk of experiencing AEs due to the complexity of their condition and the associated standard clinical interventions. Many of these events are anticipated as a result of the patient’s medical condition and standard treatment received in hospital. Given the intensive monitoring of pancreas transplant recipients in routine clinical care described in section 11.1 and the favourable safety profile of the device in liver and kidney transplantation (refer to section 10.2), the HOPP study will only record AEs if they fulfil at least one of the following criteria;

a) in the opinion of the Investigator, they are likely to be associated with the device,
b) the AE is **not** anticipated (see section 11.3.1)
c) the AE is an Adverse Event of Special Interest (see Section 11.3.2)

It is the responsibility of the local Investigator to ensure that all ADEs and AEs (within the criteria listed above) that are observed or reported by the participant to occur from the initiation of the perfusion intervention until the end of the follow-up period (3 months post-transplant visit) are recorded. The

local Investigator must record all of these occurrences immediately, but not later than **7 calendar days** after becoming aware of the event.

Occurrences are to be recorded using the electronic Safety Event Reporting form via a purposely designed OpenClinica database (access via https://nhsbt.openclinica.io). This CRF will include but not be limited to:

- A description of the event
- The dates of the onset and resolution
- Action taken
- Outcome
- Assessment of relatedness to the device
- Whether the AE is serious or not
- Whether the AE arises from device deficiency
- Whether the AE arises from user error

The relationship of AEs to the device (causality) will be assessed by a medically qualified Investigator and will be followed up until resolution or the event is considered stable. All ADEs that result in a participant's withdrawal from the study or are ongoing at the end of the study, should be followed up until a satisfactory resolution occurs.

All submitted electronic Safety Event Reporting forms will be reviewed by the CI and NHSBT CTU on behalf of the Sponsor and follow-up information should be provided as necessary by the local Investigator. Listings of these reports will be provided to the DMC according to the DMC Charter or as requested by the DMC.

AEs that occur during the course of the study should be treated by established standards of care that will protect the life and health of the study subjects.

11.4.1 Anticipated Adverse Events

Specific events are anticipated due to the comorbidities of the participant population and transplantation procedures. These anticipated Adverse Events, that are unlikely to be associated with use of the device, are defined as the following:

- Infection (chest, urine, blood, bile, wound, abdominal)
- Renal dysfunction
- Cardiac failure
- Bleeding
- Urine leak
- Ureteric stricture
- Deep venous thrombosis and /or pulmonary embolism
- Injury to surrounding structures e.g., bowel, liver, native blood vessels, native ureters, etc.
- Rejection*
- Delayed graft function of either graft*
- Admission for suspected rejection of either graft*

- Occurrence and treatment of abdominal or wound infection
- Occurrence and treatment of lymphocele/seroma
- Respiratory failure requiring mechanical ventilation.
- Pre-existing medical conditions and hospitalisation for pre-existing condition that has deteriorated.
- New illnesses or conditions not requiring concomitant medication or medical intervention/procedures
- Clinically significant abnormal laboratory finding or other abnormal assessments that is associated with the condition being studied (unless judged by the investigator as more severe than expected for the patient's condition).

*The events listed above that will be recorded as trial data for the primary or secondary outcomes are indicated.

11.4.2 Adverse Events of Special Interest (AESI)

AEs of scientific and medical concern specific to this study and are therefore defined as AESIs are as follows:

Return to theatre and/or endoscopic/radiological intervention due to any of the following;

- Graft pancreatitis, including infection, sepsis and fluid collection secondary to the condition.
- Graft vascular thrombosis of the pancreas, including graft pancreatitis and its sequelae as stated above secondary to it.
- Enteric leak.

11.5 Procedures for Reporting all Serious Adverse Events / Serious Adverse Device Effects

All AEs meeting the definition of SAE and all ADEs meeting the definition of SADE according to section 11.2 will be recorded using the electronic Safety Event Reporting form. If the eCRF is unavailable for any reason, a paper version of the form should be completed, scanned and emailed to HOPP@nhsbt.nhs.uk. Reporting by email will provide a backup system in the event that the online data collection tool is unavailable. Paper electronic Safety Event Reporting forms will be supplied to the site and filed in the ISF.

It is the responsibility of the local Investigator to ensure that all SAEs, SADEs and DDs that may have led to an SAE if any of the following statements are correct, are recorded as soon as possible after becoming aware of the event but not later than **within 3 calendar days** after the occurrence of the event.

a) suitable action had not been taken
b) intervention had not been made
c) if circumstances had been less fortunate

SAE reporting will begin at initiation of the perfusion intervention until the end of the follow-up period (3 months post-transplant visit). Participant ID cards will be provided to all participants of the study,

with a contact telephone number (research nurse / researcher) to inform regarding the occurrence of SAEs.

On submission of an electronic Safety Event Reporting form, the NHSBT CTU and all of the clinical reviewers will be immediately notified by email. The clinical reviewers are the Chief Investigator and co-investigators. They will review the report and, if they feel it poses an immediate risk to patient health or safety, then they will report them to the DMC immediately and to the device manufacturer, competent authority and the REC.

The site study team will provide additional, missing or follow up information in a timely fashion. The site study team may be required to provide additional information on the electronic Safety Event Reporting form in the form of a written narrative. This should include any other diagnostic or relevant information that will assist the understanding of the event. Significant new information on ongoing SAE/SADEs should be provided promptly to the NHSBT CTU and clinical reviewers using the same electronic Safety Event Reporting form.

All SAEs will be followed up to resolution or until the event is considered stable. The DMC will review the accumulating data at regular intervals as described in the DMC Charter or as requested by the DMC. Bridge to Life Ltd. will be provided with unblinded DMC reports on behalf of the UK Responsible Person and the Manufacturer.

11.5.1 Safety Reporting to the Competent Authority (MHRA)

The MHRA will be notified of all SAE/SADEs according to MEDDEV 2.7/3 via via the online MORE portal (https://more.mhra.gov.uk/login) by a designated Sponsor representative at NHSBT CTU.

An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons will be reported immediately, but **not later than 2 calendar days** after awareness by the NHSBT CTU.
Any other reportable events will be submitted immediately, but **not later than 7 calendar days** following the date of awareness by the NHSBT CTU.

11.5.2 Safety Reporting to the Research Ethics Committee (REC)

The REC will be notified of SAEs via email using the *Non-CTIMP safety report to REC form* within 15 days of the Chief Investigator becoming aware of the event. Only reports of SAEs that are related to the study (ie they resulted from administration of any of the research procedures) and unexpected (ie not listed in the protocol as an expected occurrence) will be reported to the REC.

11.5.3 Safety Notification to the Manufacturer

Reports of all SADE/USADEs will be notified to Bridge to Life Ltd. for onward reporting to the UK Responsible Person and Manufacturer as required to comply with device vigilance reporting.

11.6 Procedures for Reporting Device Deficiencies and Use Errors

All DDs and use errors, as defined in section 11.2, should be recorded via the online Device Deficiency Reporting form and will be collected by NHSBT CTU for investigation by Bridge to Life Ltd. If the eCRF is unavailable for any reason, a paper version of the form should be completed, scanned and emailed to HOPP@nhsbt.nhs.uk.

It is the responsibility of the local Investigator to ensure that all DDs and user errors are recorded as soon as possible after becoming aware of the event but not later than **within 2 business days** after the occurrence of the event.

If necessary, a service technician from Bridge to Life Ltd. will evaluate and determine whether service or replacement is necessary. A qualified Bridge to Life Ltd. representative will investigate and determine troubleshooting steps and corrective actions (e.g., staff re-training on proper use of an investigational device component, service, replacement) as applicable, and directives will be provided to the site as warranted.

Examples of device deficiencies warranting reporting include the following:

- Any situation where the device or component to the device physically breaks for any reason.
- Any situation where a component of the device fails to perform as it is specified in the study protocol or user manual (e.g., perfusion procedure is stopped and cannot be resumed due to a malfunction of the device or component).
- Potential manufacturing or shipping failures where device contamination, potential for device contamination, or a break in sterility or sterile barrier upon opening the device packaging is identified.
- Other situations in which the device or component fails to meet expectations, including labelling issues and missing components.

11.6.1 Onward notification to Manufacturer and UK Responsible Person

All Device Deficiency Reporting forms will be provided to Bridge to Life Ltd. who will perform onward reporting to the UK Responsible Person and Manufacturer. Bridge to Life Ltd. will support the UKRP and Manufacturer's investigation and root cause analysis of device deficiencies as well as reporting to MHRA by NHSBT when required.

11.6.2 Device Deficiency Reporting to the Competent Authority (MHRA)

The MHRA will be notified of all DDs according to MEDDEV 2.12/1 via the online MORE portal (https://more.mhra.gov.uk/login) by the UKRP in accordance with the MHRA device vigilance reporting process.

11.7 Urgent Safety Measures

The Investigators have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the NHSBT CTU, MHRA and REC within three calendar days of the occurrence. This may be reported verbally in the first instance but must be supported by a written report as soon as information is available.

11.8 Assessment results outside of normal parameters as AEs and SAEs

The investigator will exercise his/her medical judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. However, if in the opinion of the investigator, the frequency or severity of the event is greater than would be expected then it must be reported via the electronic Safety Event Reporting form.

11.9 Annual Reports

The CI will submit (in addition to the expedited reporting above) an Annual Progress Report (APR) once a year throughout the study, or on request, to the REC.

The CI shall submit throughout the study, or on request, any reports as required by the Competent Authority (MHRA), HRA, Host NHS Trust, ODT research, Funder and Sponsor.

11.10 Study Suspension or Early Termination

The DMC or Sponsor may recommend suspension or termination of the study for significant and documented reasons. If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by a regulatory authority, the Sponsor shall suspend the study while the risk is assessed. The Sponsor shall terminate the study if an unacceptable risk is confirmed.

The Sponsor shall consider terminating or suspending the participation of an Investigator in the study if monitoring or auditing identifies serious or repeated deviations on the part of the Investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The CI and Sponsor shall keep each other informed of any communication received.

If suspension or premature termination occurs,

a) the Sponsor shall remain responsible for providing resources to fulfil the obligations from the study protocol and existing agreements for following up the subjects enrolled in the study, and
b) the chief investigator or authorized designee shall promptly inform the enrolled subjects at his/her study site, if appropriate.

12 STATISTICS

12.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a separate statistical analysis plan.

12.2 Description of Statistical Methods

Baseline characteristics of the donors and recipients will be summarised in each treatment group to assess comparability across treatment groups. A CONSORT diagram will be produced to show the flow of pancreases and participants in the $HMPO_2$ group through the study.

12.2.1 Primary objective

To demonstrate safety and feasibility of end-ischaemic $HMPO_2$ of pancreas grafts prior to transplantation in clinical practice, 90-day pancreas graft survival, defined as the absence of insulin requirement 90 days post-operatively will be assessed as the primary outcome.

This will be analysed in a time-to-event manner where the failure-event is defined as any use of insulin. Any need for insulin in the first 24 hours or the use of insulin for continued support during surgery will not be treated as a failure event. Patients who have died in the first 90 days post-operatively and not received insulin prior to death will be censored at time of death. If the pancreas fails and requires removal, this will be considered as an event as the participant would require insulin in this case.

Graft survival at 90 days will be estimated for each treatment group separately using the Kaplan-Meier method and presented with a 95% confidence interval. The relative difference between treatment groups will be assessed using a Cox Proportional hazards model where a hazard ratio and 95% confidence interval along with the p-value will be presented.

12.2.2 Secondary outcomes

Since this study is not powered to detect any differences, the analysis of secondary outcomes will be largely descriptive with no hypothesis tests conducted. Continuous outcomes will be summarised using means and standard deviations if the data is normally distributed or medians and inter quartile ranges if the data is non-normal. These will be summarised by treatment group. Categorical outcomes will be summarised by number and percentage in each category, by treatment group. Time to event secondary outcomes will be analysed using Kaplan-Meier estimates by treatment group. Odds ratios, hazard ratios and other measures of treatment difference will be presented with 95% confidence intervals where appropriate. Outcomes measured over several timepoints will be summarised using minimum, maximum, change or average as appropriate and as specified in the SAP.

<u>Sample Size Determination</u>

This is a safety/feasibility trial, which may inform the design of a subsequent efficacy study, and therefore no formal power calculation has been undertaken. The group size of 30 perfused and

transplanted SPKs represents a compromise between feasibility, precision, clinical considerations and is based on data from other phase I device trials. During the recruitment for this study, any pancreas perfused using the study intervention, but not transplanted will be included in the study. Data on these pancreases will be collected to assess organ discard rate, however, recruitment will only end once 30 perfused pancreases have been transplanted.

Previous phase I studies in organ perfusion have recruited between 20 (40) and 36 (41)patients, which is in keeping with FDA guidance and published recommendations (42). The proposed recruitment is feasible within an 18-month recruitment window (expecting recruitment of 50% of the eligible patients - Oxford Transplant Centre typically performs 50 simultaneous kidney-pancreas transplants per year).

The intervention group will comprise **30** adult recipients of deceased donor simultaneous pancreas and kidney (SPK) transplants. The organs must have been successfully perfused and transplanted to be included in this cohort. A historical control cohort will be employed to elicit the preliminary evidence of efficacy and this control cohort will comprise **60** deceased donor simultaneous pancreas kidney (SPK) transplant recipients from the Oxford Transplant Centre transplanted since 1st of March 2018.

12.3 Analysis Populations

Analysis of all outcomes (excluding organ discard rate) will be performed on a modified intention to treat (mITT) basis where organs that were not transplanted are excluded. Organs which were perfused and transplanted will form our mITT population. Assessment of organ discard rate will use an intention to treat approach, whereby any pancreas perfused, using the study intervention, will form the intervention group.

Withdrawn patients will remain in the analysis up to the point of withdrawal.

12.4 Decision Points

As a 'first-in-human' trial there is an inherent risk associated with performing a new intervention. Therefore, an initial safety report will be prepared for the DMC following discharge of participant number 6 (or after 30 days in the event of a prolonged index admission) to ensure the trial can safely proceed.

In addition, reports for the DMC will be drawn up after recruitment of patients 10 and 20. These reports will be prepared and reviewed by the time of recruitment of patients 12 and 22. The trial will not proceed further before being authorised to do so by the DMC and TSC.

In addition, should any two out of six consecutive recipients experience graft loss in the first 30 postoperative days, recruitment will be paused to allow for investigation and consideration by the DMC.

12.5 Stopping Rules

The decision points in section 12.4 (above) would dictate stopping if a decision is reached by TSC and DMC. There are no other stopping rules in the study design.

12.6 The Level of Statistical Significance

One formal statistical test will be performed on the primary outcome. The level of statistical significance will be 5%, i.e., a p-value less than 0.05 will be considered statistically significant.

12.7 Procedure for Accounting for Missing, Unused, and Spurious Data.

For the primary analysis, any missing data for the primary and secondary outcome measures will be treated as missing data and not be imputed. If an outcome has data missing for more than 25% of participants in either arm, then the analysis will not be undertaken for that arm. All missing primary and secondary outcome data will be summarised.

Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the original statistical analysis plan will be reported in the final report along with the justification for deviation.

12.8 Health Economics Analysis

Health economic analysis will not be conducted in this phase 1 study.

13 DATA MANAGEMENT

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

13.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, participant's medical records, device accountability records, recorded data from automated instruments, and records from medico-technical departments involved in the clinical investigation.

eCRF entries will be considered source data where the eCRF is the site of original recording (i.e. there is no other written or electronic record of the data), and where it's not possible to capture data directly into eCRF, paper source data form will be provided (e.g. data recorded during perfusion and transplantation). Full details will be provided in the Data Management Plan.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the pancreas trial ID, not by name.

13.2 Access to Data

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

13.3 Data Recording and Record Keeping

The Principal Investigator has overall responsibility for data collection at site. Participant data will be entered onto the trial database designed and administered by the NHSBT CTU data management team using the Electronic Data Capture system (EDC) OpenClinica which is a commercially available FDA 21 Code of Federal Regulations (CFR) Part 11 compliant clinical trial database system. Following completion of analysis, the study database will be archived in accordance with NHSBT policy.

Training and instructions for completion of eCRFs will be given to the site at site activation. All case report forms will be electronic. The NHSBT CTU office will grant the site access to the EDC system following approval of all site registration documentation and completion of training. The site must adhere to the instructions and submission schedule outlined in the protocol. The eCRFs must be completed directly onto the EDC system (i.e. database).

The study team must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g. locked filing cabinets in a room with restricted access). All data must be accessible to the competent authorities and the Sponsor with suitable notice for inspection.

All trial documentation must be retained for at least 5 years after trial completion or termination. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by NHSBT.

14 QUALITY ASSURANCE PROCEDURES

14.1 Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and Monitoring Plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2 Monitoring

Regular monitoring will be performed according to the trial specific Risk assessment and Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.3 Trial committees

14.3.1 Trial Management Group:

A TMG comprising the CI, other lead investigators, local principal investigators and members of the CTU. The TMG will be responsible for the day to day running and management of the trial. It will meet at least twice a year, more often during set up and close down phases of the trial.

14.3.2 Trial Steering Committee:

A Trial Steering Committee (TSC) with an independent Chair, clinicians, and patient representative has been appointed and will be responsible for overseeing the progress of the trial. The TSC will convene at least annually. The TSC will focus on progress of the trial, patient safety, and the consideration of new information relevant to the research question. The TSC Charter includes details of membership as well as roles and responsibilities of the committees' members.

14.3.3 Data Monitoring Committee

The trial has a data monitoring committee (DMC) which consists of at least three independent members, including clinicians with relevant expertise and a statistical expert, independent from the Investigators and the funding source. The DMC will periodically review accruing data to safeguard the interests of the trial participants, potential participants and future patients and assess the safety of the interventions. As a result of the reviews the DMC may make recommendations to the TSC, including premature termination of the trial, should they feel it is indicated. A separate DMC charter will contain full details of the committee and its roles and reporting structure.

14.3.4 Adjudication of Radiological findings

For the interpretation of the CT scan(s) performed as part of this trial or held for the matched control cohort in relation to secondary outcomes: (i) Incidence of post-transplantation graft pancreatitis, (ii) Incidence of intravascular thrombosis, and (iii) graft loss related to vascular thrombosis. A departmental radiologist will initially report the scan and then all the scans will be verified by a second blinded independent radiologist after the end of visit 1 for all participants.

15 PROTOCOL DEVIATIONS

The investigators shall conduct this trial in accordance with this protocol or other trial document or process, Good Clinical Practice (GCP), any applicable regulatory requirements and any conditions of approval/notification imposed by the Research Ethics Committee and Competent Authority.

A "protocol deviation" is a failure to adhere to the requirements specified in this study protocol without adequate justification.

15.1 Reporting of Protocol Deviations

All protocol deviations, unless listed section 15.1.1, must be recorded via a Protocol Deviation Reporting Form and submitted to the NIHR CTU for review and onward reporting. All protocol deviation reports will be filed in the Trial Master File and reported to the DMC. The DMC will review all deviations and assess their impact on patient safety.

Protocol deviations will be monitored by NHSBT CTU and those which are found to recur will not be accepted and will require immediate action and could potentially be classified as a serious breach. Serious breaches must be reported as per section 16.

15.1.1 Non-reportable protocol deviations

Protocol deviations will be reported to the regulatory authorities as requested, however, missed blood tests and other clinical assessments (e.g. height) are to be considered non-reportable.

16 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

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

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

16.1 Reporting of serious breaches

In the event that a serious breach is suspected, the NHSBT CTU must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by NHSBT CTU and, if appropriate, NHSBT CTU in conjunction with the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3 Approvals

Following Sponsor approval the protocol, Informed Consent Form, Participant Information Sheet and templates of any proposed advertising materials, these documents will be submitted to an appropriate Research Ethics Committee (REC), the HRA, competent authority (MHRA in the UK), and host institution for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4 Other Ethical Considerations

It is possible that, through participation in this trial, incidental findings may be made that are unrelated to a participant's transplantation or involvement in the trial but are of relevance to their health or wellbeing. If this does happen, the patient will be informed of the findings and, with their consent, so too will their GP and other relevant members of their local health team, as per local procedures.

Participation in this trial will not affect a patient's position on the transplant waiting list or their likelihood or receiving a transplant. Similarly, withdrawal of a participant from the trial at any point and for any reason will not affect their position on the transplant waiting list or their likelihood or receiving a transplant.

17.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, NIHR (as per agreed reporting schedule) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

Other reports (such as protocol deviations) will be submitted as required.

17.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on the publicly accessible database, the ISRCTN.

The results will be published in peer-review journals and uploaded to ISRCTN registry if not published within 12 months of the end of the trial declaration.

17.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique pancreas study number only on all study documents and any electronic database(s. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

17.8 Expenses and Benefits

Where possible, study visits and investigations will be conducted during routine hospital attendances, occurring within the permitted visit windows. Therefore, there will be no added travel or financial

burden expected in addition to normal care and thus no expenses or reimbursements are expected for participants.

18 FINANCE AND INSURANCE

18.1 Funding

This study is funded by an NIHR Invention for Innovation (i4i) award (NIHR204643). Funding will be managed through the Nuffield Department of Surgical Sciences (NDS) finance office. Funding payments to collaborators is detailed in the Collaboration Agreement.

18.2 Insurance

As Sponsor, The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

19 CONTRACTUAL ARRANGEMENTS

Appropriate contractual arrangements will be put in place with all third parties.

20 PUBLICATION POLICY

The Clinical Trial results will be published in a peer reviewed journal, irrespective of the outcome of the research. This is inline with the NIHR, University of Oxford and NHSBT CTU policy.

Further information on the NHSBT CTU policy can be found here (accessed 03Nov2023):

https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16779/nhsbt-ctu-publication-policy-v1-29th-jul-2019.pdf

The study and its results may also be presented and/or displayed at conferences around the UK and abroad.

21 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by this study is governed by the Research Contract between the Funder (NIHR - Secretary of State for Health and Social Care) and the Sponsor (The Chancellor Masters and Scholars of the University of Oxford).

Further detail regarding the IP arrangements are documented in the Collaboration Agreement between the Sponsor, Oxford University Hospitals NHS Foundation Trust, NHSBT and Bridge to Life Ltd.

22 ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. The TMF including all essential documents will be retained for at least 5 years after the completion of the study.

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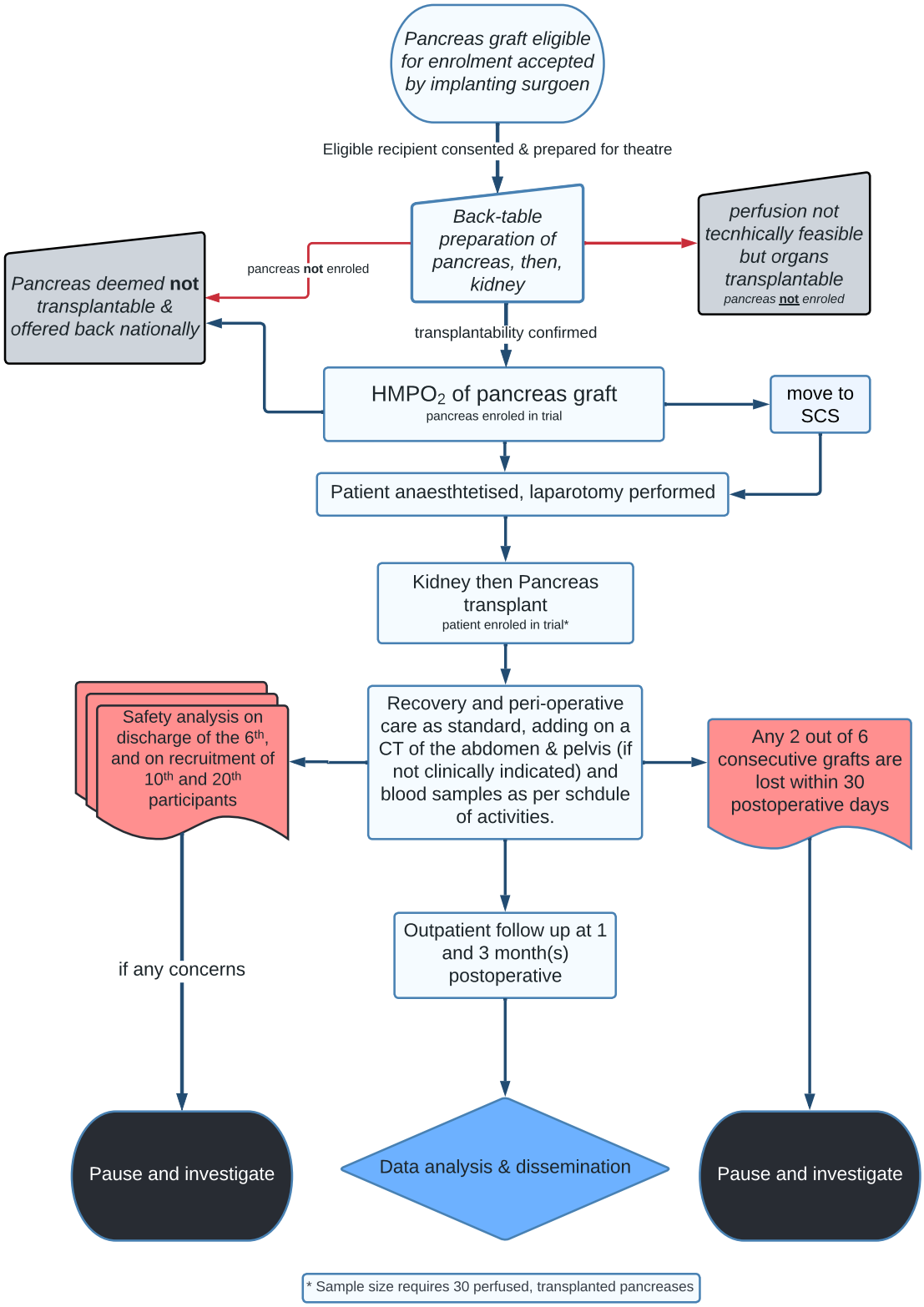
24 APPENDICES

24.1 APPENDIX A1: TRIAL FLOW CHART



24.2 APPENDIX A2 – MATCHING ALGORITHM

Historical matched controls will be drawn from a pool of all simultaneous pancreas-kidney (SPK) transplants performed at the Oxford Transplant Centre, conducted from 1st of March 2018 to the start of the trial, not including those transplants where 1ry outcome (date of death or graft failure) is not available.

A matching algorithm has been developed, and validated by simulation, that matches each case to two controls drawn from this pool. Cases are matched to controls strictly on DBD/DCD donor status and then by minimising the summed percentage difference ('match score') in Donor age and cold ischaemia time (CIT)):

$$Match\ score = \frac{CIT_{case} - CIT_{control}}{CIT_{case}} + \frac{Donor\ age_{case} - Donor\ age_{control}}{Donor\ age_{case}}$$

Match scores are computed for all possible case-control pairs. The final case-control allocation is then defined as that which minimises the total match score summed across all cases. This is computed by the Hungarian method (37) implemented in R, as below.

Matching algorithm – R code

```
Hoppmatchfunc = function(db=db, m_dtype, m_cit, m_donorage, nmatch=2) {

  require(dplyr)
  require(clue)
  as_tibble(db) -> pool
  pool[0,] -> controls
  tibble(nmp_dtype = m_dtype, hmp_cit = m_cit, hmp_donorage = m_donorage) -> cases
  cases[rep(seq_len(nrow(cases)), each = nmatch), ] -> cases

    matrix = matrix(nrow=nrow(cases), ncol=nrow(pool))
    for (i in 1:nrow(cases)){
      for (j in 1:nrow(pool)){
        abs((cases[i,]$hmp_cit - pool[j,]$cit_mins)/cases[i,]$hmp_cit) +
        abs((cases[i,]$hmp_donorage - pool[j,]$dri)/cases[i,]$hmp_dri) +
        (if(cases[i,]$hmp_dtype==pool[j,]$dtype) 0 else 1000) -> matrix[i,j]
      }
    }

    solve_LSAP(matrix) -> solution
    for (i in 1:length(solution)){
      rbind(controls, pool[solution[i],]) -> controls
    }

  return(cbind(cases, controls))
}
```

24.3 APPENDIX A3: DEFINITIONS OF eGFR

CKD-EPI formula for estimation of GFR

Throughout this trial, wherever eGFR is referred to it will be computed by the CKD-EPI formula:

$$eGFR = 141 \times \min(\frac{SCr}{\kappa}, 1)^{\alpha} \times \max(\frac{SCr}{\kappa}, 1)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159[if\ black]$$

24.4 APPENDIX A4: CLAVIEN-DINDO CLASSIFICATION

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention.
IIIa	Intervention not under general anaesthesia.
IIIb	Intervention under general anaesthesia.
IV	Life-threatening complications (including CNS complications) requiring HDU/ITU management.
IVa	Single organ dysfunction (including dialysis).
IVb	Multi-organ dysfunction.
V	Death of a patient.
Suffix 'd'	If the patient suffers from a complication at the time of discharge, the suffix 'd' (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

24.5 APPENDIX B: BIOLOGICAL SAMPLES

Below is a brief description of samples collected during the HOPP trial, however, individuals should refer to the Trial Sample Management Manual for detailed information regarding the collection, handling and processing of all samples within the study.

B1 ROUTINE CLINICAL SPECIMENS

All specimens collected as part of the recipient's routine clinical care, such as pre- and postoperative blood samples for routine laboratory analysis, will be analysed and stored locally as per normal local procedure.

B2 TRIAL SPECIMENS – PRE-TRANSPLANT

A single blood sample will be taken from the recipient for biobanking (consent dependent), of up to 10ml, following induction of anaesthesia.

B3 TRIAL SPECIMENS – DURING $HMPO_2$

Perfusate samples will be collected during hypothermic machine perfusion and exocrine samples at the end of perfusion if the duodenum is shortened.

B4 TRIAL SPECIMENS – POST-TRANSPLANT

Blood samples
A single blood sample will be taken from the recipient for biobanking (consent dependent), of up to 10ml, while under general anaesthesia.

Biopsies from explanted pancreas
If a pancreas is to be explanted due to clinical indication. The standard biopsy technique will be 3 wedge biopsies from explanted specimen (one from the head of the pancreas, one from the body and one from the tail) after removal from recipient.

Timing of samples

- The first samples will be taken within 24 hours post-transplant, with subsequent samples at as close to 24-hour intervals as feasible.
- On attending clinic appointments at 1-month, and at 3-month post-transplant visits (as detailed in appendix B5).

Regulatory aspects
All samples will be collected in accordance with national regulations and requirements including local standard operating procedures for logistics and infrastructure. Samples will be taken in appropriately licensed premises, stored, and transported in accordance with the HTA guidelines and local trust policies. Samples for long-term storage will be kept in suitable biobank.

B5 Sampling Schedule

Donor Sampling schedule

VISITS	0												
		During perfusion											
SAMPLING	Pre-Reperfusion	T0	T15	T30	T45	T60	T75	T90	T105	T120	T135	T150	Post-reperfusion
Perfusate samples ≈5 mL		X	X	X	X	X	X	X	X	X	X	X	
Biobank perfusate samples ≈2.5 mL		X	X	X	X	X	X	X	X	X	X	X	

Recipient Sampling schedule

VISITS	0		1															2	3	
SAMPLING	Pre-reperfusion	Post-reperfusion	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	Discharge	30 days (± 1 week)	90 days (± 2 weeks)	Unscheduled
Biobank blood sample 10 mL*	X	X	X	X	O	O	O	O	X	X	X	X						X	X	X	
OGTT (2 x 3 mL blood sample)																		X		X	
Biobank biopsy (explanted pancreas – head)																					X
Biobank biopsy (explanted pancreas – body)																					X
Biobank biopsy (explanted pancreas – tail)																					X

Highlighted samples are trial-specific, all other samples are standard of care.

*In the event that patients are discharged before day 15, daily follow-up will cease at the point of discharge. Patients are commonly brought back to clinic within the first week after discharge – if a standard care clinic appointment falls within 15 days of transplant this may be used as an opportunity to acquire clinical and biochemical data as if the patient were still an inpatient.

24.6 APPENDIX C: SCHEDULE OF ACTIVITIES

VISITS	Screening	0	1[a]																2	3	Unscheduled
ACTIVITY		Baseline (Transplant)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	Discharge	30 days (± 1 week)	90 days (± 2 weeks)	
Recipient Consent	X																				
Recipient Eligibility	X																				
Donor Eligibility	X																				
Donor Demographics		X																			
Recipient Demographics		X																			
Recipient Baseline biochemical parameters		X																			
Biobank blood samples[b, c]		X	X	X	O	O	O	O	X	X	X	X						X	X	X	
Perfusion ($HMPO_2$)		X																			
Operative and perfusion parameters		X																			
Perfusate samples		X																			
Outcome assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Outcomes			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Post-operative biochemical parameters			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT scan[d]				O	O	O	O	O	O	O	O	O									
Oral glucose tolerance test (OGTT)																		X		X	
Immunosuppression																		X	X	X	
AE/SAE/ADE/SADE reporting			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Device Deficiency reporting		X																			X
Explanted pancreas biopsies																					X
Drain amylase level CRF																			X		
Withdrawal																					X

Key:

X = planned activity

O = activity may occur

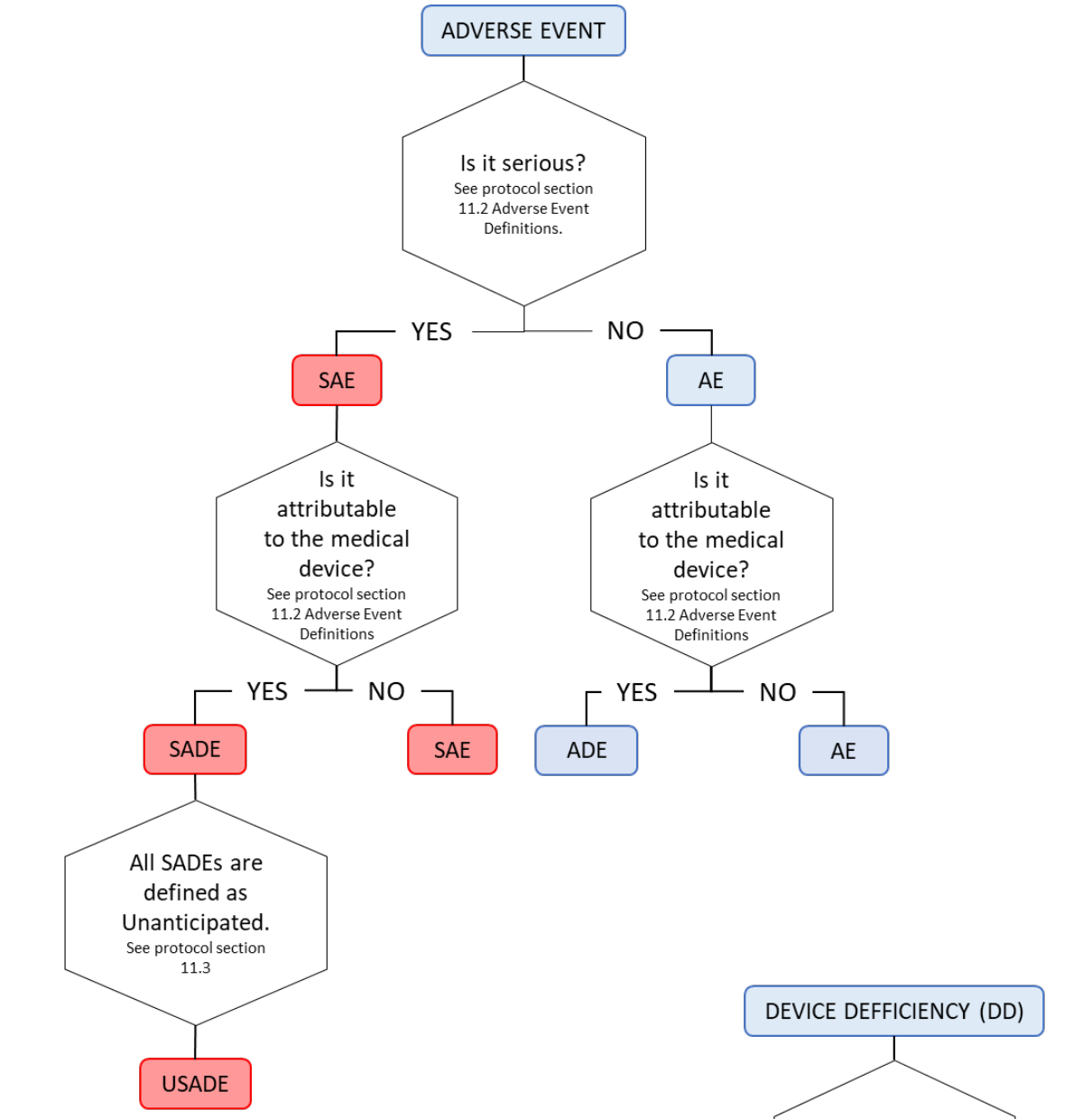
[a] In the event that patients are discharged before day 15, daily follow-up will cease at the point of discharge. Patients are commonly brought back to clinic within the first week after discharge – if a standard care clinic appointment falls within 15 days of transplant this may be used as an opportunity to acquire clinical and biochemical data as if the patient were still an inpatient.

[b] Where possible, samples will be collected at the time of routine sample collection and if discharged prior to day 15, sampling for visit 1 will stop on the day of discharge.

[c] When a CT scan occurs, an additional biobank blood sample is required if the CT scan does not fall on one of the planned biobank blood sample days.

[d] CT scan between day 5 and day 10 will be conducted as part of the protocol unless one or more clinically indicated CT scans are performed. If multiple scans are performed as part of standard clinical care, they will all be considered. Refer to protocol section 9.10.1 for further detail.

24.7 APPENDIX D: SAFETY REPORTING FLOW CHART



Reporting timelines:

Report by PI to NHSBT CTU
The reporting of events will be provided in acceptable timely conditions, but not later than **within 3 calendar days** after the occurrence of the event.

Report from NHSBT CTU to MHRA
The sponsor must report to the MHRA:

- an SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons immediately, but **not later than 2 calendar days** after awareness by sponsor
- any other reportable events immediately, but **not later than 7 calendar days** following the date of awareness by the sponsor

24.8 APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	1.0	Protocol Date: Date	N/A	N/A