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Does normothermic machine preservation increase the availability of livers for transplantation without compromising outcome?

Submission date 01/10/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 16/11/2021	**Overall study status** Ongoing	
Last Edited 22/11/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims

Liver transplantation is a highly effective treatment, but the supply of suitable donor organs is greatly exceeded by the number of patients who would benefit. More than 10% of patients on the waiting list die before receiving a transplant and many others are never placed on the list because access is restricted to patients with the best chance of success.

Less than 2/3 of deceased donors in the UK result in a liver transplant, because the livers from many donors are less suitable, due to older age, medical conditions or circumstances of death, and are much more likely to cause complications. To use these higher-risk livers safely, we need to find better ways to preserve, repair and test livers so that more of the available donor organs can be transplanted without compromising the survival rate.

Normothermic machine perfusion (NMP) is a novel method of organ preservation which replaces the conventional icebox, using a machine which restores the flow of blood at body temperature allowing the liver to function during storage. This results in (i) better preservation of the liver (less injury), (ii) repair of the donor organ (reconditioning), and (iii) assessment of the organ's functional state (viability assessment).

Previous studies, from the UK and elsewhere, showed a substantial reduction in injury. They also suggested that transplant surgeons could accept higher risk organs with confidence, mainly due to the ability to assess function prior to transplant. However, these studies were not primarily designed to test the effects of NMP on organ use, and there remains a crucial need for high-quality evidence as to whether this more complex and expensive technology should become the standard of care.

The UK-designed and manufactured NMP device proposed in this study has already been used in small numbers of transplants in all of the UK's seven liver transplant units. This has mostly relied upon charitable funding, because this technology has not yet been funded by NHS commissioners.

In this study, we will identify offers of those donor livers less likely to be used and make the NMP machine available for storage and assessment. We will compare the proportion resulting in successful transplants with a group of offers where NMP was not used to see if a pre-defined

threshold for increased use is met. We will also collect information about the overall cost of the new technology compared to the old, so that the NHS can decide whether NMP is good value for money.

Who can participate?
Liver transplant recipients 18 years of age or above

What does the study involve for participants?
Eligible livers will be preserved using the NMP machine. The transplant surgeon will use information about the donor and the appearance of the liver, as well as information from the NMP machine, to make a decision as to whether the liver is safe to transplant.
We will ask for consent to collect information and outcomes from recipients during the transplant operation, during hospital stay and at routine hospital appointments 3 and 12 months after the transplant. We will also ask permission to continue to use the information routinely collected in the UK Transplant Registry to check the health status and care of recipients for up to 5 years after enrolment in the study.
All scans and blood tests will be the same as normal care after a transplant, however, participants will be asked to consent to optional additional samples of blood from the NMP machine during perfusion and a small biopsy sample after the liver has been transplanted at the end of the operation.
When assessing whether a new treatment is cost-effective, it is important that we understand quality of life. Will we ask participants to complete a short quality-of-life questionnaire (EQ5D-5L) before their transplant and at 3 and 12 months afterwards. This questionnaire includes questions about mobility, self-care, activity levels, pain levels and symptoms of anxiety and depression.

What are the possible benefits and risks of participating?
The allocated liver will only be transplanted if the transplant surgeon feels that it is safe to do so, given all of the information available. We will not be using any livers that would not normally have been offered. It is possible that the additional information from the NMP device may improve the confidence of surgeons in deciding whether to transplant the liver, and/or improve the condition of the liver. However, the reason that we are undertaking this study is that this effect is uncertain, so no benefit can be promised. The study may help us understand how we can increase the availability of donor organs and may benefit other people in the future.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2020 to September 2026

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
Simon Knight, plus@nhsbt.nhs.uk

Study website
https://www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/plus

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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
283200

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50567, NIHR201003, IRAS 283200, PID 15694

Study information

Scientific Title
Utilisation of normothermic machine preservation in extended criteria livers - a national threshold-crossing study

Acronym
PLUS

Study objectives
Does normothermic machine perfusion increase the availability of livers for transplantation without compromising outcome?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/11/2021, South Central - Oxford C Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8041; oxfordc.rec@hra.nhs.uk), ref: 21/SC/0297

Study design
Threshold-crossing design with a prospectively-defined efficacy threshold

Primary study design
Observational

Secondary study design
Threshold crossing design

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
https://www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/plus

Health condition(s) or problem(s) studied
Preservation of donor liver before transplant

Interventions
Study cohort (normothermic machine perfusion; NMP):
Prospectively identified, consecutive liver offers with a donor utilisation index (DUI) > 0.27, in which NMP is made available
NMP with oxygenated blood, using the OrganOx metra, prior to implantation, for a minimum of 4 hours and maximum of 24 hours. Device-to-donor or back-to-base at the discretion of the accepting centre.

Control cohort (static cold storage; SCS):
A priori defined real-world control cohort meeting study inclusion criteria, identified from the NHSBT registry, in which NMP was not used.

Intervention Type
Other

Primary outcome measure
Functional utilisation defined as the defined as the number of livers transplanted where the patient is alive, without the need for a re-transplant, 12 months postoperatively. This is a binary outcome extracted from records held by the UK Transplant Registry (UKTR).

Secondary outcome measures
1. Graft survival defined as a functioning transplant in the absence of death and re-transplantation (death censored). These are measured at 7 days, 3 and 12 months and 5 years following re-transplantation. These are time to event outcomes and are also based on records held by the UK Transplant Registry (UKTR).
2. Graft loss including death or re-transplantation. These are measured at 7 days, 3 and 12 months and 5 years following transplantation. These are time to event outcomes and are also based on records held by the UK Transplant Registry (UKTR).
3. Patient survival at 7 days, 3 and 12 months and 5 years following transplantation. These are time to event outcomes and are also based on records held by the UK Transplant Registry (UKTR).
4. Primary non-function, defined as irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation, in the absence of technical or immunological causes. This is a binary outcome extracted from records held by the UK Transplant Registry (UKTR).
5. NHS resource use based on published data and hospital episode statistics on the number of inpatient and outpatients' episodes and treatments at 7 days, 3 and 12 months from Hospital Episode Statistics (HES) data. These will be valued using standard NHS unit costs.
6. Health-related quality of life for patients on the waiting list and post-transplant at 3 and 12 months, assessed by completion of the EQ-5D-5L questionnaire.
7. Post-operative resource use and quality of life (comparative and collected for both the study and historical cohort from data extracted from records held by the UK Transplant Registry)
7.1. Length of stay in high level (HDU/ITU) care post-transplant (days).
7.2. Length of initial hospital stay post-transplant (days).
7.3. Need for renal replacement therapy (haemodialysis, haemofiltration, haemodiafiltration) measured during transplant admission. The data indicate transient filtration, short or long-term dialysis.
7.4. Presence of transplant related renal dysfunction at 12 months
7.5. Number of re-admissions during the 12 months post-transplant and reason for re-admission
7.6. Lifestyle activity score post-transplant and at 12 months. This is a 5-scale categorical outcome, reflecting the recipient's ability to carry out daily activity at different levels.
8. Safety measured by
8.1. Organ discard. Binary outcome data extracted from records held by the UK Transplant Registry (UKTR), for both cohorts. These are also tracked in study CRFs for the study cohort.
8.2. Recipient infection : Data on presence of CVM infection, fungal infection and sepsis including site of sepsis (sputum, blood, urine) are extracted from records held by the UK Transplant Registry (UKTR). These are available post-operatively, for both cohorts.
8.3. Biopsy proven rejections. Categorical variable denoting the presence and acute or chronic

rejection during the first year of follow-up. Data at the 12-month routine visit are extracted from records held by the UK Transplant Registry (UKTR) and available for both cohorts.
8.4. Presence of biliary complications, their type (biliary strictures and bile duct leaks), and whether these required intervention along with type of intervention are collected post-transplant, at 3 months and 12 months through study CRFs for the study cohort. These are only available post-transplant for the historical cohort.
8.5. Presence of vascular complications requiring intervention, their type (bleeding, hepatic artery stenosis, hepatic artery thrombosis, portal vein thrombosis, portal vein stenosis), and whether these required intervention, along with type of intervention are collected post-transplant, at 3 months and 12 months through study CRFs for the study cohort. These are only available post-transplant for the historical cohort.
9. Safety (Study cohort only)
9.1. Presence of any adverse event rates, expectancy and relatedness to study intervention and severity, graded according to the Clavien-Dindo classification system. These are collected by study CRFs, for the prospective cohort at any time they may present.
9.2. Presence of any technical complications/device failures, binary indicatory collected through study CRFs for the study cohort at organ retrieval and when NRP is used.
10. Concomitant care: Details of induction and maintenance immunosuppression in total dosage in mg will be collected at day 7, 3 months and 12 months for the study cohort. This is available only post-transplant and at 12 months for the historical cohort.
11. Biochemical liver function (Study cohort only)
11.1. Biochemical liver function (ALT (IU/L), GGT (IU/L), INR, Bilirubin(umol/L)) (Days 1-7 post-transplant)
11.2. Daily serum lactate (mmol/L) (whilst on ITU/HDU)
11.3. Model for Early Allograft Function predictive score (MEAF). This is a composite score based upon the maximum values of ALT, INR and bilirubin during the first 3 days postoperatively. (Areja E, Cortes M, Hervás D et al. A score model for the continuous grading of early allograft dysfunction severity. Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2015; 21 (1): 38.)
12. Value of perfusion parameters to predict clinical outcomes and support clinical decision making (Study cohort only)
12.2. Perfusion parameters (logged automatically by the device):
Arterial and caval pressures (in mmHg)
Arterial, portal and caval flow rates (in mmHg)
pO2, pCO2 and pH
Blood temperature (oC), Glucose (mmol/L) and bile production (ml/h)
12.3. Perfusate lactate (mmol/lL) at 5 minutes, 1, 2 and 4 hours and end of NMP
12.4. Perfusate ALT (IU/L) at 2 and 4 hours and end of NMP
12.5. Perfusate glucose (mmol/L) at 2 and 4 hours and end of NMP
12.6. Bile pH at 2 and 4 hours and end of NMP
12.7. Bile glucose (mmol/L) at 2 and 4 hours and end of NMP
12.8. Total bile volume (ml) for the duration of perfusion.
12.9. Graft histology, including degree of macrosteatosis (semi-quantitative score for macrosteatosis as mild, moderate and severe), following organ reperfusion.

Overall study start date
01/06/2020

Completion date
30/09/2026

Eligibility

Key inclusion criteria
The enrolled entity in this study is a liver offer, rather than a transplant recipient.

Inclusion criteria for liver offers:
1. Deceased donors aged 16 years or over
2. Offered through the national offering scheme
3. Donor Utilisation Index (DUI) greater than 0.27

Inclusion criteria for liver transplant recipients:
1. Recipients 18 years of age or above
2. Elective and super-urgent
3. Participant is willing and able to give informed consent for participation in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2465 retrospective and 1035 prospective livers

Total final enrolment
3500

Key exclusion criteria
Current exclusion criteria as of 06/06/2023:
Exclusion criteria for liver offers:
1. Donors falling outside national offering scheme
2. Donors from outside of the UK
3. Donor is HIV or hepatitis C positive
4. Donor Utilisation Index ≤0.27
5. Donor not donation after brain death (DBD) or donation after circulatory death (DCD)
6. Donors aged <16 years
7. Livers undergoing any other form of ex-situ machine preservation
8. Participating centre cannot offer NMP due to logistical reasons (e.g., lack of appropriate personnel or device availability)

Liver transplant recipients:
1. Have not agreed to use of NMP according to local consent policy

2. Receipt of a split liver or reduced liver transplant
3. Receipt of a multi-organ transplant
4. Transplanted outside of the 7 participating centres

Previous exclusion criteria:
Exclusion criteria for liver offers:
1. Donors falling outside national offering scheme
2. Donors where information about participation was not sent with the organ offer
3. Donors from outside of the UK
4. Donor is HIV or hepatitis C positive
5. Livers undergoing any other form of ex-vivo machine preservation
6. Participating centre cannot offer NMP due to device, logistical or staffing reasons

Liver transplant recipients:
1. Receipt of a liver that has not been recruited to the study
2. Have not agreed to use of NMP according to local consent policy
3. Receipt of a split liver transplant
4. Receipt of a multi-organ transplant
5. Transplanted outside of the 7 participating centres

Date of first enrolment
11/04/2022

Date of final enrolment
04/04/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Queen Elizabeth Hospital Birmingham
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way

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United Kingdom
B15 2TH

Study participating centre
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Study participating centre
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Study participating centre
Freeman Hospital
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NE7 7DN

Study participating centre
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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF)

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
30/09/2027

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 3.1	24/07/2023	22/11/2024	No	No