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Normothermic (normal body temperature) machine perfusion to remove fat from donor livers prior to transplantation

Submission date
22/09/2022

Recruitment status
No longer recruiting

Registration date
07/10/2022

Overall study status
Completed

Last Edited
28/01/2026

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Liver disease is the third leading cause of premature death in the UK. Liver transplantation is the only successful treatment for end-stage liver disease but is limited by a shortage of suitable donor organs.

A third of donated livers are declined for transplants due to the presence of fat within the liver cells (known as non-alcoholic fatty liver disease, NAFLD). Transplanting a fatty liver carries a greater risk to the patient compared to a normal liver as these livers do not tolerate conventional ice-box storage before transplantation.

Our preliminary experiments point to an innovative defatting strategy for treatment of fatty human livers that were declined for transplantation. These livers were preserved on a machine in very similar conditions to those in the body (termed normothermic machine perfusion; NMP). We added a combination of currently available drugs to release fat from liver cells, and we then removed the fat from the perfusion machine using a filter. This reduced the amount of fat in the liver and improved its function.

None of the livers treated in this experimental study were actually transplanted: if used for patients, we believe that this might increase the number of livers that could be transplanted safely.

Who can participate?
Liver donors and liver transplant recipients aged 18 years and older.

What does the study involve?
In the proposed trial, we will randomly assign 60 livers from donors with a high risk of fatty liver disease to either NMP alone or NMP with fat removal treatment. We will assess how many of these livers are safe to transplant and, in those that are transplanted, follow the outcomes after

the operation. The main objective is to show whether this treatment is safe; it will also help us to design a future, larger study which will test the extent to which fat removal actually leads to additional transplants.

What are the possible benefits and risks of participating?
The aim of the study is to demonstrate whether the fat removal process during normothermic machine perfusion is safe. Your new liver will be randomly allocated to receive either normothermic perfusion alone or normothermic perfusion with the additional process of fat removal treatment (defatting) in order to test whether liver function improves prior to transplantation. There are no anticipated side effects or risks related to the preservation and defatting process itself on the machine – all defatting agents are flushed from the liver before transplant.

As your liver will undergo normothermic machine perfusion alone or with fat removal treatment, it is possible that the additional information from the device may improve the confidence of your surgeons in deciding whether to transplant the liver, and/or improve the condition of the liver. Taking part in this study does not increase your chances of an organ offer – your place on the waiting list will not change.

However, the reason that we are undertaking this study is that the effect of defatting on post-transplant outcomes 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?
April 2021 to November 2025

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

Who is the main contact?
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Contact information

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
300545

Protocol serial number
CPMS 52503, NIHR131163, IRAS 300545

Study information

Scientific Title
Defatting of donor transplant livers during normothermic perfusion - a randomised clinical trial

Acronym
DeFat

Study objectives
The combination of normothermic machine perfusion (NMP) with defatting strategies may be effective in reducing the fat content of donor livers with evidence of moderate-severe steatosis and improving perfusion parameters to meet functional criteria for transplantation. In this first clinical study, we intend to test the safety and feasibility of the intervention, and to obtain initial data regarding efficacy and effect size.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/05/2022, London – Brighton & Sussex Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; +44 207 104 8241; brightonandsussex.rec@hra.nhs.uk), ref: 22/LO/0257

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Defatting of donor transplant livers

Interventions
In the proposed multi-centre pilot clinical trial, we will randomly assign 60 livers from donors with a high-risk of hepatic steatosis to either NMP alone or NMP with defatting interventions. We aim to test the safety and feasibility of the defatting intervention, and will explore efficacy by comparing ex-situ and post-reperfusion liver function between the groups.

The primary endpoint will be the proportion of livers that achieve predefined functional criteria during perfusion which indicate potential suitability for transplantation. These criteria reflect hepatic metabolism and injury and include: lactate clearance; perfusate pH; glucose metabolism; bile composition; vascular flows; transaminase levels.

Clinical secondary endpoints will include: proportion of livers transplanted in the 2 arms, graft function; cell-free DNA (cfDNA) at follow-up visits (cfDNA has been correlated with allograft injury, rejection and formation of de novo donor specific antibodies); patient and graft survival; hospital and ITU stay; evidence of ischemia-reperfusion injury (IRI); ischaemic cholangiopathy; recurrence of steatosis (determined on MRI at 6 months).

Mechanistic secondary endpoints will include histological quantification of steatosis sequentially during perfusion and following reperfusion (in recipients). We will measure markers of hepatic lipid metabolism, allograft injury (cfDNA) and cytokines implicated in ischaemia-reperfusion injury (IRI) during ex-situ perfusion and peri-operatively (prior to and following reperfusion in the recipient). RNA sequencing, proteomic and glycomic analysis will investigate the effect of defatting on the expression of genes and proteins associated with post-transplant outcome, testing proposed viability markers for use in future studies and/or clinical practice.

Intervention Type
Other

Primary outcome(s)
The primary endpoint is the proportion of livers that achieve all of the following functional criteria at 6 hours of perfusion, as defined by:
1. Clearance of lactate to a level <2.5mmol/L
2. Perfusate pH ≥7.20
3. Evidence of glucose metabolism (spontaneous fall in perfusate glucose)
4. Minimum bile pH ≥7.5 (if bile produced)
5. Bile glucose concentration ≤3 mmol/L or ≥10 mmol less than perfusate glucose
6. Hepatic arterial flow ≥100ml/min; portal venous flow ≥500ml/min
7. Perfusate alanine aminotransferase (ALT) <6000U/L at 6 hours

These objective criteria, reflecting hepatic metabolism and injury, have been derived by a process of consensus amongst current NMP users and are increasingly recognised as a way to discriminate livers with favourable post-transplant outcomes. These parameters are not intended as an instruction to the implanting surgeon, but rather as a consistent endpoint for the trial. The decision as to whether a liver is actually transplanted will remain with the implanting surgeon, who will base this on a number of criteria, including some that are recipient-related

rather than donor organ-related (e.g. the urgency with which the patient needs a transplant may determine the decision).

Key secondary outcome(s))
Clinical secondary endpoints:
1. Proportion of livers transplanted in the 2 arms, graft function;
2. Cell-free DNA (cfDNA) at follow-up visits (cfDNA has been correlated with allograft injury, rejection and formation of de novo donor specific antibodies);
3. Patient and graft survival;
4. Hospital and ITU stay;
5. Evidence of ischemia-reperfusion injury (IRI);
6. Ischaemic cholangiopathy;
7. Recurrence of steatosis (determined on MRI at 6 months).

Mechanistic secondary endpoints (analysed subsequent to the main clinical outcomes):
Histological quantification of steatosis sequentially during perfusion and following reperfusion (in recipients). We will measure markers of hepatic lipid metabolism, allograft injury (cfDNA) and cytokines implicated in ischaemia-reperfusion injury (IRI) during ex-situ perfusion and peri-operatively (prior to and following reperfusion in the recipient). RNA sequencing, proteomic and glycomic analysis will investigate the effect of defatting on the expression of genes and proteins associated with post-transplant outcome, testing proposed viability markers for use in future studies and/or clinical practice.

Completion date
30/11/2025

Eligibility

Key inclusion criteria
Donor Livers:
1. Donors aged 18 years or over
2. Offered through the national offering scheme and accepted by participating liver transplant centre
3. Moderate-severe steatosis: macroscopic characteristics based on colour, texture, rounded edges, size and weight at point of inspection at the transplant hospital to confirm suitability for randomisation. Where available, the results of clinical biopsies demonstrating moderate-severe steatosis (> 30%) will also be taken into account to assess suitability for randomisation.

Liver transplant recipients:
1. Recipients 18 years of age or above
2. Elective waiting list at a participating centre
3. Willing to consent for inclusion into the study and collection and use of their data

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
110 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 17/10/2023:

Donor Livers:
1. Donors from outside of the UK
2. Donor is HIV, hepatitis B or C positive
3. Cold ischaemia time (CIT) expected to exceed > 10 hours
4. Macroscopic evidence of fibrosis
5. Livers undergoing any other form of ex-situ 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 undergone randomisation
2. Receipt of super urgent transplant for acute liver failure
3. Receipt of a split liver transplant
4. Receipt of a multi-organ transplant
5. Transplanted outside of the participating centres
6. Contra-indication to MRI e.g. pacemaker

_____

Previous exclusion criteria:

Donor Livers:
1. Donors from outside of the UK
2. Donor is HIV, hepatitis B or C positive
3. Cold ischaemia time (CIT) expected to exceed > 10 hours
4. Macroscopic evidence of fibrosis
5. Livers undergoing normothermic regional perfusion (NRP)
6. Livers undergoing any other form of ex-situ machine preservation
7. Participating centre cannot offer NMP due to device, logistical or staffing reasons

Liver transplant recipients:
8. Receipt of a liver that has not undergone randomisation
9. Receipt of super urgent transplant for acute liver failure
10. Receipt of a split liver transplant

11. Receipt of a multi-organ transplant
12. Transplanted outside of the participating centres
13. Contra-indication to MRI e.g. pacemaker

Date of first enrolment
23/02/2023

Date of final enrolment
31/07/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Royal Free Hospital
Royal Free London NHS Foundation Trust
Pond Street
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England
NW3 2QG

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Edgbaston
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B15 2GW

Study participating centre

Kings College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
London
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SE5 9RS

Study participating centre
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request from DeFat@nhsbt.nhs.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/06/2024	25/06/2024	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes