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Reducing blood clots in donated livers before transplantation

Submission date
26/08/2025

Recruitment status
Recruiting

Registration date
10/12/2025

Overall study status
Ongoing

Last Edited
10/12/2025

Condition category
Surgery

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

Plain English summary of protocol

Background and study aims
Bile is something that is made by the liver to help digest fats in our diet. Bile ducts are the tubes that drain bile from the liver to the gut. Some livers develop bile duct damage after they are transplanted, resulting in scarring. These scarred areas are called “strictures”. They are narrowed sections of the bile duct which can block the flow of bile from the liver and cause infection (cholangitis) after the transplant. Occasionally, this complication can be severe enough that the transplanted liver may need to be replaced. Recent research suggests these strictures may be due to clots forming in the blood vessels supplying the bile ducts during the donation and organ preservation process. If the clots can be dissolved before liver transplantation, this may improve blood supply to the bile ducts and prevent bile duct damage, potentially reducing complications after the procedure.

Who can participate?
Liver transplant recipients aged 18 or over, who have the capacity to provide written informed consent.

What does the study involve?
The donor liver is randomly assigned to be placed on a perfusion machine and treated with a drug that dissolves clots (a “clot-buster”) before it is transplanted. Alternatively, it may be treated in the normal way – this is either in an ice box (this is called static cold storage) or it might be connected to the perfusion machine, but without the clot-buster medication.

The perfusion machine provides the liver with an artificial blood supply while it is being treated. This machine is used across the NHS; however, it is the addition of the clot-buster medication which is unique to our study.

If the liver has been allocated to receive the clot-buster treatment, it will be placed on the machine for at least 2 hours, during which time it is hoped that any clots will have been broken down. It is then removed and transplanted in the normal way.

The donor liver will have small samples (biopsies) taken from it before and after arrival at the transplant centre. Furthermore, if the donor liver is placed on the perfusion machine, we will

also take a biopsy after the liver has been on the perfusion machine. A final biopsy of the liver may also be taken once it is transplanted into the participant.

The blood supply which the liver gets from the perfusion machine is called the perfusate. If the donor liver is placed on the perfusion machine, samples of the perfusate are taken at specified time points.

Blood samples from the participant that are required as part of routine clinical care will be processed in the usual manner at the local hospital laboratories.

At 3 and 6 months after the participant's transplant, results from standard tests will be collected that have been undertaken during normal transplant clinic follow-up visits. If some of these results are not available, the UK Transplant Registry may be accessed to get the results.

At six months after the transplant, participants are invited to have an MRI scan of the bile ducts called magnetic resonance cholangiopancreatography, or MRCP. This scan may be something the participant requires as part of their normal care anyway, or it may be done purely for our research.

What are the possible benefits and risks of participating?
It is possible that participants will not immediately benefit from taking part in the study, but it is possible that, if the transplanted liver receives machine perfusion plus the "clot-buster" medication before transplant, participants may be less likely to develop bile duct problems after the transplant. However, until the study has finished, it is unknown if the treatment is effective.

If the donor liver receives machine perfusion plus the "clot-buster" medication before transplant, the treatment may turn out not to be as effective as we hope, and there is also a chance it is less effective than what is currently used. It is also possible that the use of machine perfusion plus the "clot-buster" medication on the donated liver may cause more bleeding during the transplant operation, but our experience so far suggests that this is not the case.

There may also be bleeding or leakage of bile from the biopsy sites on the liver. If there is bleeding, participants may need to receive an additional blood transfusion – blood transfusions are common during and after a liver transplant. On occasion, a further operation may be required to treat bleeding or a bile leak from a biopsy.

Where is the study run from?
Joint Sponsorship between: The University of Cambridge, UK, and Cambridge University Hospitals NHS FT, UK.

When is the study starting and how long is it expected to run for?
August 2023 to February 2029.

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

Who is the main contact?
NHSBT Clinical Trials Unit: CLOTBUSTL@nhsbt.nhs.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
332692

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 57913, NIHR161200

Study information

Scientific Title
CLOTBUST-L: An open-label, multicentre, randomised controlled trial to evaluate the efficacy of ex situ fibrinolysis during normothermic perfusion in liver transplantation from donation after circulatory death donors

Acronym
CLOTBUST-L

Study objectives
Primary objective:
To demonstrate that fibrinolysis using alteplase with fresh frozen plasma infused during normothermic machine perfusion of DCD donor livers is superior to the current standard of care in reducing the incidence of symptomatic cholangiopathy in DCD liver transplantation.

Secondary objectives:
1. To compare graft and patient survival between intervention and comparator groups.
2. To compare biochemical liver function between the intervention and comparator groups.
3. To compare biliary complications beyond the primary outcome between the intervention and comparator groups.
4. To compare the use of postoperative hospital resources between intervention and comparator groups.
5. To assess the safety of the intervention compared to the comparator group.
6. To assess the ability of NMP perfusion parameters and biomarkers in perfusion fluids and liver biopsy to predict clinical outcomes after transplantation and to develop organ viability markers.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 08/10/2025, North West - Greater Manchester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8014, 2071048065; gmsouth.rec@hra.nhs.uk), ref: 25/NW/0229

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Liver transplantation

Interventions
Once the centre accepts the liver for their recipient, and the potential recipient has consented to be part of the study, the donor livers will be randomised (50/50) between two arms: the comparator arm and the intervention arm.

There is no trial treatment given to the recipient in either arm of the study (the trial treatment is given directly to the liver before implantation into the recipient).

In the intervention arm, clot busting medication (Alteplase) and fresh frozen plasma (FFP) is given for an hour while the liver is being perfused outside of the body on a liver perfusion machine.

Once the recipient is prepared and their own liver removed, the transplant liver will be removed from the perfusion machine, flushed with a special preservation solution and then implanted. Our pilot study suggests that treating DCD donor livers in this way reduces the incidence of cholangiopathy to 5%.

Those participants not allocated to the Alteplase + FFP arm will receive livers from DCD donors treated with NHS standard care, which is either using normothermic perfusion on the same machine (without Alteplase + FFP), or simply cold flushing the liver at the donor centre and implanting it in the recipient without any special treatment.

Participants will have a liver biopsy taken once the liver has been implanted, before the abdomen is closed. Routine intra-operative and post-transplant data will be collected from participants' medical records and the UK Transplant Registry (UKTR). Follow-up visits have been designed to coincide with the patient's usual clinic visits.

An additional scan called a Magnetic Resonance Cholangiopancreaticography (MRCP) may be performed 6-months after the transplant, if one has not been performed for clinical reasons. It is this scan which is used to detect the incidence of symptomatic cholangiopathy (bile duct scarring), which is our primary endpoint.

To provide enough statistical confidence that the proposed intervention reduces the incidence of cholangiopathy to 5% in the intervention group, we will need to include 210 liver transplants.

Given that not all DCD donor livers are transplanted once they have been assessed by a surgeon, and some fail within the first 6 months, we will need to recruit 314 DCD donor livers to achieve 210 liver transplants. Given that not all DCD donor livers are transplanted once they have been assessed by a surgeon, and some fail within the first 6 months, we will need to recruit 314 DCD donor livers to achieve 210 liver transplants.

Intervention Type
Procedure/Surgery

Primary outcome(s)
The proportion of transplanted randomised livers where symptomatic non- anastomotic biliary strictures are confirmed by a cholangiogram with agreement between at least two radiographers by 6 months post-transplant (+/- 2 months)

Key secondary outcome(s))
1. Graft and patient survival between intervention and comparator groups will be measured using:
1.1. Proportion of transplanted livers with primary non-function: defined as graft failure resulting in death or retransplantation within 14 days after transplantation, excluding hepatic artery thrombosis, biliary complication, recurrent disease or acute rejection.
1.2. Graft survival proportion estimated at 3 and 6 months following transplantation (defined as a functioning transplant in the absence of retransplantation and censored for death).
1.3. Transplant survival proportion estimated at 3 and 6 months following transplantation (graft survival not censored for death – i.e. defined as a surviving recipient with a functioning transplant in the absence of retransplantation).
1.4. Patient survival proportion estimated at 3 and 6 months following transplantation.
2. Biochemical liver function between intervention and comparator groups will be measured using:
2.1. Mean biochemical liver function (ALP, ALT/AST, INR, Bilirubin) at days 1 to 7 and months 3 and 6 following transplantation.
2.2. Early allograft function measured via Olthoff criteria and MEAF score. Olthoff criteria uses the day 7 bilirubin and INR value and day 1-7 ALT or AST values. The MEAF score is calculated using the day 1-3 ALT and INR values and the day 3 bilirubin value.

3. Biliary complications beyond the primary outcome between groups will be measured using:
3.1. Proportion of transplanted livers with symptomatic (requiring intervention) anastomotic strictures by 6 months (+/2 months) post-transplant confirmed by MRCP (or ERCP/PTC if done for clinical reasons).
3.2. Proportion of transplanted livers with asymptomatic anastomotic or non-anastomotic strictures at 6 months (+/2 months) post-transplant confirmed by MRCP, excluding those related to hepatic artery thrombosis.
3.3. Proportion of transplanted livers with bile leaks requiring stenting or surgery during post-transplantation in-patient stay or in the first 30 days post-transplantation, whichever is earlier.
4. Post-operative hospital resource use between intervention and comparator groups will be measured by:
4.1. Median length of ICU stay as calendar days in level 3 care.
4.2. Median length of hospital stay as calendar days between transplant and discharge.
4.3. Proportion of recipients who needed any renal replacement therapy during post-transplantation in-patient stay or in the first 7 days post-transplantation, whichever is earlier.
5. The safety of the intervention compared to the comparator group will be assessed by measuring:
5.1. Liver utilisation measured as the proportion of randomised donor livers resulting in a transplant.
5.2. Proportion of recipients with at least one adverse event (Clavien-Dindo grade 3 or higher, i. e. Grade IIIa, Grade IIIb, Grade IVa, Grade IVb, or Grade V) within the 6-month trial period and the proportion of recipients with each of the five Clavien-Dindo grades listed above.
5.3. Proportion of recipients with at least one instance of biopsy-proven acute rejection during post-transplantation in-patient stay or in the first 30 days post transplantation.
5.4. Proportion of recipients who had to return to theatre for bleeding in the first 48 hours post-transplant.
5.5. Proportion of recipients who required peri-hepatic packing because of bleeding during transplant surgery.
5.6. Median total and post-reperfusion intra-operative units of blood components transfused (red blood cells, fresh frozen plasma, platelets and cryoprecipitate)
5.7. Proportion of recipients with at least one hepatic artery or portal vein complication (thrombosis or stenosis) requiring radiological or surgical intervention or leading to graft loss during post-transplantation in-patient stay or in the first 30 days post-transplantation, whichever is earlier.
5.8. Proportion of recipients with at least one hepatic artery complication (stenosis requiring intervention, thrombosis) within 6 months post-transplant.
5.9. Proportion of recipients with acute kidney injury (according to RIFLE criteria: an increase in peak serum creatinine ≥2 times the baseline creatinine in the first 7 days post-transplantation or a need for renal support (haemofiltration or dialysis) within the post-transplant inpatient stay or the first 7 days post-transplant, whichever is sooner.
5.10. Proportion of recipients with post reperfusion syndrome defined as a fall of 30% or greater in mean BP lasting at least a minute in the first 5 minutes post reperfusion or the need for adrenaline or doubling of noradrenaline to support the circulation.
5.11. Total number of investigational device deficiencies within the trial recruitment period.
5.12. Proportion of recipients with at least one infection, during post-transplantation in-patient stay or in the first 30 days post-transplantation, whichever is earlier.
5.13. Proportion of recipients with bleeding requiring transfusion and/or radiological/surgical intervention within the first 7 days post-transplant.
5.14. Proportion of perfusate samples with a positive microbiology culture within 7 days of perfusion.
6. The ability of NMP perfusion parameters and biomarkers in perfusion fluids and liver biopsy to predict clinical outcomes after transplantation and to develop organ viability markers will be

examined, including: mean perfusate ALT at 1 and 2 hours of NMP, mean perfusate lactate at 1, 2 and 4 hours and end of NMP and mean perfusate D-dimer concentration after 1 and 2 hours of NMP

Completion date
28/02/2029

Eligibility

Key inclusion criteria
Donor livers:
1. Whole livers
2. Donor family consent for research
3. Donor aged 18 years or over
4. Liver donated after circulatory death, including livers donated by Maastricht IV donors (donation after treatment withdrawal in a patient previously diagnosed dead by neurological criteria)

Liver transplant recipient:
1. Recipients 18 years of age and above
2. On the liver transplant waiting list at a participating centre, awaiting a liver transplant
3. Participant must have capacity to provide written informed consent to the trial. Where capacity is subsequently lost, the research team must seek the views of a consultee

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Donor livers:
1. Livers recovered using in situ normothermic regional perfusion
2. Livers preserved with ex situ hypothermic oxygenated perfusion
3. Livers donated after brain death, excluding Maastricht IV donors

4. Split or partial liver grafts
5. Donor is HIV positive
6. Liver transplanted outside one of the trial participating centres
7. Livers subject to traumatic injury at the time of death which has stopped bleeding but which may start with the infusion of alteplase
8. Participating centre (or alternative participating centre with capacity for NMP) cannot offer NMP due to device, logistical or staffing issues

Liver transplant recipients:
1. Recipient is a multiorgan recipient (excluding liver + kidney)
2. There are foreseeable contraindications for recipient to have an MRCP

Date of first enrolment
15/01/2026

Date of final enrolment
14/02/2029

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
England
SE5 9RS

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London

England
NW3 2QG

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

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
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NE7 7DN

Sponsor information

Organisation
University of Cambridge

ROR
https://ror.org/013meh722

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the NHSBT Clinical Trials Unit after de-identification, 9 months after publication and ending 5 years following article publication. Data will be shared with investigators whose use of the data has been assessed and approved by an NHSBT review committee as a methodologically sound proposal. An appropriate data sharing agreement will be required before the transfer of any data. Contact: clotbustl@nhsbt.nhs.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website			24/11/2025	No	No