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A clinical trial to test whether treating patients with liver cirrhosis with capsules containing healthy stool bacteria or a dummy capsule (placebo) will reduce the time it takes to develop an infection resulting in hospital admission

Submission date
14/03/2022

Registration date
25/03/2022

Last Edited
22/11/2024

Recruitment status
Recruiting

Overall study status
Ongoing

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Our body contains trillions of bacteria. Many of these live in our bowels which keeps us healthy and helps our immune system to fight against infections. However, an increased number of ‘unfriendly’ bacteria are found in the bowel of patients with liver cirrhosis (permanent liver damage), which makes them highly susceptible to infections. Antibiotics are becoming less effective as they are used so frequently, and the bowel can become infected with ‘super-bugs’. Replacing the unfriendly bowel bacteria in patients with cirrhosis with healthy bacteria donated from healthy volunteers (faecal microbiota transplantation) could be highly beneficial and reduce antibiotic usage. Findings from the initial FMT trial (the PROFIT trial) showed that FMT administered during endoscopy was safe with no serious side effects. However, patients said that they would prefer to take tablets rather than have an endoscopy. The researchers have therefore made an FMT capsule from freeze-dried stool and this study will test whether treating patients with these FMT capsules reduces their likelihood of getting an infection.

Who can participate?
Patients aged 18 years and above who have been diagnosed with alcohol-related cirrhosis or non-alcoholic fatty liver disease (sometimes referred to as metabolic-associated fatty liver disease) cirrhosis at any time point

What does the study involve?
Participants will be selected at random to take FMT capsules or 'dummy’ capsules that contain no FMT (placebo) and both the study team and the participants will not know which treatment they are taking. The participants will need to take five capsules every 3 months for a total of 21 months or until they develop their first infection leading to hospital admission, and will be

followed up for a maximum of 2 years. This study will also examine whether FMT reduces the side effects of cirrhosis and has beneficial effects on the liver and immune system. The researchers will look at whether FMT reduces hospital admissions, the incidence of 'super-bug' infections and death. Laboratory studies will look at whether FMT treatment will help the immune system fight infection.

What are the possible benefits and risks of participating?
Patients will be taking part in a new and innovative trial to assess the beneficial effects of FMT capsules in patients with cirrhosis. There are no curative treatments available to patients with cirrhosis, aside from liver transplantation. Unfortunately, due to the scarcity of donor organs, even those listed for transplant can wait months or even years for a new liver. Others are too unwell or frail or deemed ineligible to be listed for a liver transplant.
The researchers will also gather information during the trial on how the FMT works in patients with cirrhosis including the impact on the make-up and function of the gut microbiome. They will examine whether FMT can reduce the likelihood of developing an infection and being admitted to the hospital.
There are no risks involved in taking part with regard to the samples being obtained, and the amount of blood taken will not be harmful to the patient. The placebo treatment is not harmful but is not expected to have any benefit as it contains no active drug or treatment. All patients, regardless of whether they receive placebo or FMT have the same rigorous follow-up and support from the trials team. They will be closely monitored after the treatment is given and will be seen at regular intervals afterwards to see if they have experienced any side effects. The researchers do not anticipate any serious problems to occur after the FMT or placebo treatment, but the participants will be given contact numbers should they run into any problems outside of the trial visits.

Where is the study run from?
King's College Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
November 2021 to June 2028

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

Who is the main contact?
1. Prof. Debbie Shawcross (Chief Investigator), debbie.shawcross@kcl.ac.uk
2. Ms Sue Cheung, promise@kcl.ac.uk

Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000300-35

Integrated Research Application System (IRAS)
1004822

ClinicalTrials.gov (NCT)
NCT06461208

Protocol serial number
Nil known

Study information

Scientific Title
A PROspective randomised double-blind parallel-group placebo-controlled multicentre trial of faecal MIcrobiota tranSplantation to improve the primary outcomE (first hospitalisation due to infection) in patients with cirrhosis over 24 months (PROMISE)

Acronym
PROMISE

Study objectives

The researchers will perform a clinical trial to test whether treating patients with alcohol-related and metabolic-associated fatty liver cirrhosis with faecal microbiota transplantation (FMT) capsules vs placebo capsules will reduce the likelihood of them getting an infection by measuring the time it takes to develop an infection resulting in hospital admission.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/03/2023, East of England – Cambridge South Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8084; cambridgesouth.rec@hra.nhs.uk), ref: 22/EE/0247

Study design
Multicentre randomized double-blind parallel-group placebo-controlled multi-centre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Infection in patients with cirrhosis

Interventions
Randomisation:
Patients will be randomised on a 1:1 basis to either FMT or placebo using the King's Clinical Trial Unit (KCTU) web-based randomisation system. Randomisation will be at the level of the individual using the method of block randomisation with varying block sizes, stratified by site.

Intervention:
Patients will be randomly allocated to two treatment arms:
1. Active treatment - patients assigned to this group will receive the active drug (FMT capsules)
2. The comparison or ‘control group’: Participants in this group will receive a ‘placebo’ treatment. The placebo will be a dummy capsule and will NOT contain any stool

The FMT product contains 0.9% sodium chloride and 5% trehalose (cryoprotectant) as excipients. A minimum of 80 g of faeces from a single donor will be used to manufacture one batch of five capsules. Following lyophilisation, the material will be encapsulated in five size 0 delayed-release methylcellulose capsules (DRcaps™, Capsugel®, Livingston, UK). Placebo capsules will contain microcrystalline cellulose. The capsules for the FMT and placebo will be identical in appearance. The capsules are coloured Swedish orange, resulting in an opaque appearance through which the contents cannot be seen. FMT material will be fully traceable from donor to recipient. Aliquots of donor stool will be kept for 30 years to allow for future testing if required.

The patients will need to take five capsules every 3 months. Patients will continue treatment for a total of 21 months or until they develop their first infection leading to hospital admission and will be followed up for a maximum of 2 years at different timepoints - baseline, 30 days

(telephone call), 3, 6, 9, 12, 15, 18, 21 and 24 months. At each clinic visit, patients will receive five capsules of the medicine (either the FMT or the placebo) to be taken by mouth and swallowed with water or cordial.

Intervention Type
Biological/Vaccine

Phase
Phase III

Drug/device/biological/vaccine name(s)
Faecal microbiota transplantation (FMT)

Primary outcome(s)
Time to the first infection resulting in hospital admission i.e., the date the patient is admitted to the hospital due to infection, collected using the King's Clinical Trials Unit Index Hospitalisation (Primary Endpoint) form administered by the research nurse at each clinic visit i.e, 3, 6, 9, 12, 15, 18, 21 and 24 months. When the patients meet the primary endpoint, they do not receive further IMP or attend trial visits, but they will continue to be enrolled in the trial for the purposes of monitoring of other clinical endpoints, e.g. all-cause mortality and liver-related mortality.

Key secondary outcome(s))
1. Incidence of decompensating events including hepatic encephalopathy, new-onset ascites, variceal bleeding and spontaneous bacterial peritonitis, measured using study-specific laboratory analyses on blood, stool and urine samples at baseline, 3, 6 and 12 months
2. Progression to acute-on-chronic liver failure (ACLF) (the development of one or more organ failures) measured using study-specific laboratory analyses on blood, stool and urine samples at baseline, 3, 6 and 12 months
3. Infection rates and antibiotic usage collected using the concomitant medications log following randomisation
4. Incidence of AMR including skin and nose colonisation with methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), extended-spectrum beta-lactamase-producing bacteria (ESBL), fluoroquinolone-resistant Gram-negative and carbapenem-resistant Enterobacteriales, measured using study-specific laboratory analyses on blood, stool and urine samples at baseline, 3, 6 and 12 months
5. Hospitalisation rates (liver-related and all-cause), including the length of stay and admission to high dependency/intensive care, collected using the King's Clinical Trials Unit Hospitalisation Log and patient medical notes at 3, 6, 9, 12, 15, 18, 21 and 24 months
6. Liver disease severity measured using the Child-Pugh, Model For End-Stage Liver Disease (MELD) and United Kingdom Model for End-Stage Liver Disease (UKELD) scores at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
7. Quality of life measured using the EQ-5D-5L questionnaire at baseline, 3, 6, 12 and 24 months
8. All-cause mortality and liver-related mortality collected from patient medical notes and adverse events log at day 30 over the telephone and thereafter at each clinic visit i.e., 3, 6, 9, 12, 15, 18, 21 and 24 months
9. Depression and anxiety measured using the Hospital Anxiety and Depression Scale (HADS) at baseline, 3, 6, 12 and 24 months
10. Alcohol use disorder-related events in patients enrolled with alcohol-related cirrhosis, measured using the alcohol-use disorders identification test (AUDIT questionnaire) at baseline, 3, 6, 12 and 24 months and urinary ethyl glucuronide/ethyl sulphate levels if tested as part of the standard of care

11. Faecal microbiome composition analysed by sequencing and metabolome analysis at baseline, 3, 6 and 12 months
12. Dietary habits measured using a study-specific dietary questionnaire developed by the team at baseline

Completion date
30/06/2028

Eligibility

Key inclusion criteria
1. Age 18 years or over
2. Confirmed alcohol-related cirrhosis or metabolic-associated fatty liver (MAFLD) cirrhosis based on clinical, radiological and/or histological criteria
3. Model For End-Stage Liver Disease (MELD) score 8-16
4. Patients with alcohol-related cirrhosis must have been abstinent for a minimum of 4 weeks prior to randomisation
5. Patients must be deemed to have the capacity to consent (if patients lose capacity during the trial a legal representative will be appointed on their behalf)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Severe or life-threatening food allergy (e.g., peanut allergy)
2. Pregnancy or planned pregnancy. Urine testing will be performed at randomisation to rule out pregnancy in females
3. Breastfeeding
4. Patients treated for acute variceal bleeding, infection, overt hepatic encephalopathy, bacterial peritonitis or ACLF within 14 days prior to randomisation
5. Active alcohol consumption of >20 g/day (1 unit of alcohol contains 10 ml or 8 g of alcohol)
6. Had a previous liver transplant
7. Patients with inflammatory bowel disease
8. Patients with coeliac disease.
9. Patients with a history of prior gastrointestinal resection such as gastric bypass
10. Active malignancy including hepatocellular carcinoma
11. Patients with an expected life expectancy <6 months or listed for liver transplantation
12. Infected with HIV, hepatitis B or C (patients who have undetectable hepatitis B or C DNA

/RNA can be recruited)
13. Patients who have received antibiotics or probiotics (excluding foodstuffs containing ‘live bacteria’ such as live yoghurts, kefir, fermented vegetables such as sauerkraut/kombucha or cheese) within 7 days prior to randomisation
14. Swallowing disorder, oral-motor dyscoordination or likely inability/unwillingness to ingest study medication
15. Patients who have received another investigational drug or device within 4 months prior to randomisation

Date of first enrolment
21/06/2023

Date of final enrolment
30/01/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
King's College Hospital
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Denmark Hill
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Study participating centre
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Sponsor information

Organisation
King's College Hospital NHS Foundation Trust

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

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 and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
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