The trial design of PROMISE – A PROspective double-blind placebo-controlled multicentre trial of faecal MIcrobiota tranSplantation to improve outcomEs in patients with cirrhosis

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ABSTRACT

INTRODUCTION

Patients with cirrhosis exhibit gut dysbiosis, resulting in increased bacterial translocation and systemic inflammation – a central feature of cirrhosis-associated immune dysfunction (CAID). CAID predisposes cirrhotic patients to infection. Faecal microbiota transplantation (FMT) may restore gut eubiosis and decrease systemic inflammation in cirrhosis. This study aims to evaluate the efficacy and mechanisms of action of encapsulated FMT, versus placebo, to reduce infection and mortality in patients with alcohol-related (ALD) metabolic-related (non-alcoholic fatty liver disease (NAFLD)) cirrhosis.

METHODS AND ANALYSIS

This is a **phase 2b multicentre, randomised, double-blinded, placebo-controlled trial** evaluating encapsulated FMT versus matched placebo for 2 years in 300 patients (recruited from 10-12 UK centres) with ALD or NAFLD related cirrhosis (MELD score 8-16). Patients will be randomised to encapsulated FMT or placebo in a 1:1 ratio. Patients will receive the investigational medicinal product (IMP)/placebo every 91 days +/- 14 days for 21 months and will be evaluated at baseline,30-days, 3-months, 6-months, 1 and 2 years. Blood, stool and urine will be collected at baseline, 3-months, 6-months and 1 year. Primary endpoint will be time to first infection resulting in hospital admission. The trial will open on 01.03.22.

BACKGROUND

- Increased incidence of **infection** in cirrhosis, occurs in 40% admissions. [1]
- Infection can worsen liver function and precipitate decompensation and multi-organ failure leading to **high mortality.** [2]
- **Gut dysbiosis** occurs in cirrhosis**,** causing increased intestinal permeability, leading to increased bacterial translocation and resultant system inflammation. [3]
- Striking differences in gut microbial composition have been shown between cirrhotic patients and healthy controls. [4-6]

- Our recently completed NIHR-RfPB funded feasibility PROFIT trial (**PRO**spective, randomised placebo-controlled feasibility trial of **F**aecal m**I**crobiota **T**ransplantation in cirrhosis NCT02862249) revealed that **FMT**, delivered by upper gastrointestinal endoscopy, **was well tolerated and safe in cirrhosis.** [7]

- Mechanistic data revealed that cirrhotic patients have excessive non-specific inflammation and blunted anti-bacterial responses at baseline.
- Following FMT, significantly increased production of IL-1β followed HKEB exposure was observed suggesting that **FMT may improve immune responsiveness to bacterial exposure.**
- Mean venous ammonia reduced at D30 in the FMT cohort, but increased in the placebo group.
- The decrease in ammonia was associated with a significant reduction by D90 in stool *Enterococcus faecalis* and enteropathogenic *Escherichia coli* in the FMT group, but not placebo.

- The beneficial effect of FMT **waned by day-90** suggesting its efficacy was short to medium term, and **regular dosing is required.**
- During the trial, it became clear that patients were not keen on undergoing repeat invasive endoscopy to receive FMT, and expressed **a pill would be preferable.**

AIMS AND OBJECTIVE

Primary aim:
- To evaluate the efficacy and mechanisms of action of encapsulated FMT (versus placebo) to reduce infection and mortality in patients with alcohol-related (ALD) and metabolic-related (non-alcoholic fatty liver disease – NAFLD) cirrhosis.

Mechanistic aims:
- To determine the mechanisms of action on the basis of the hypothesis that the characteristics of the gut microbiome in cirrhosis drive the development of CAID.
- To determine if FMT will favourably modify key contributors by improving gut microbiome diversity and reducing bacterial translocation into the systemic circulation.

Primary endpoint:
- Time to first infection resulting in hospital admission.

Secondary endpoints:
- Incidence of decompensating events, progression to ACLF, infection rates and antibiotic usage, incidence of AMR, change in liver disease severity scores, change in quality of life (EQ-5D-3L score), change in mental health outcomes (HADS), all-cause mortality, and liver-related mortality, change in alcohol use disorder-related events (AUDIT) in ALD cirrhosis.

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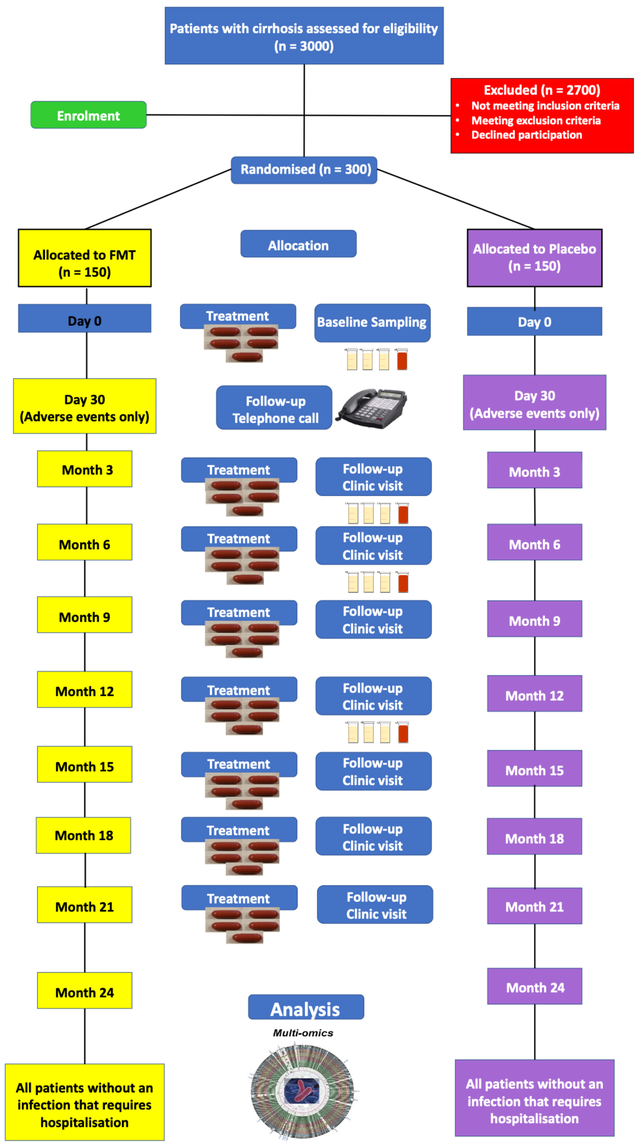
METHODS



Inclusion Criteria	Exclusion Criteria
Age 18 or >	Severe/life-threatening food allergy
ALD or NAFLD cirrhosis*	Pregnancy/planned pregnancy
MELD score 8-16	Breastfeeding
If ALD – abstinent for minimum of 4 weeks	Treated for variceal bleed, infection overt HE, SBP, ACLF in within 14 days
Capacity to consent	Active alcohol consumption (>20 grams/day)
	Liver transplant recipient
	Active malignancy including HCC
	Expected life expectancy <6 months
	Listed for liver transplant
	HIV, hepatitis B or C (unless undetectable HBV DNA, HCV RNA)
	Antibiotics or probiotics within 7 days
	Swallowing disorder or oral-motor dyscoordination
	Received another IMP within 4 months

** Based on clinical, radiological and/or histological criteria*

IMP:
- Lyophilised encapsulated FMT.
- Minimum of 80 gram faeces from **single carefully screened healthy donor** to manufacture 1 batch of 5 capsules, testing for range of infectious agents performed.
- Patients will receive **5 capsules** of IMP to be taken by mouth.
- Taken at hospital visit - adherence **directly observed.**

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