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FAecal micRobiota transplantation in primary sclerosinG chOlangitis (FARGO): study protocol for a randomised, multicentre, phase IIa, placebo-controlled trial

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To cite: Al-Shakhshir S, Quraishi MN, Mullish B, *et al*. FAecal micRobiota transplantation in primary sclerosinG chOlangitis (FARGO): study protocol for a randomised, multicentre, phase IIa, placebo-controlled trial. *BMJ Open* 2025;**15**:e095392. doi:10.1136/bmjopen-2024-095392

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-095392).

Received 21 October 2024
Accepted 10 December 2024

Check for updates

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ABSTRACT

Introduction Primary sclerosing cholangitis (PSC) is the classical hepatobiliary manifestation of inflammatory bowel disease (IBD). The strong association between gut and liver inflammation has driven several pathogenic hypotheses to which the intestinal microbiome is proposed to contribute. Pilot studies of faecal microbiota transplantation (FMT) in PSC and IBD are demonstrated to be safe and associated with increased gut bacterial diversity. However, the longevity of such changes and the impact on markers of disease activity and disease progression have not been studied. The aim of this clinical trial is to determine the effects of repeated FMT as a treatment for PSC-IBD.

Methods and analysis FAecal micRobiota transplantation in primary sclerosinG chOlangitis (FARGO) is a phase IIa randomised placebo-controlled trial to assess the efficacy and safety of repeated colonic administration of FMT in patients with non-cirrhotic PSC-IBD. Fifty-eight patients will be recruited from six sites across England and randomised in a 1:1 ratio between active FMT or FMT placebo arms. FMT will be manufactured by the University of Birmingham Microbiome Treatment Centre, using stool collected from rigorously screened healthy donors. A total of 8 weekly treatments will be delivered; the first through colonoscopic administration (week 1) and the remaining seven via once-weekly enema (up to week 8). Participants will then be followed on a 12-weekly basis until week 48 from the first treatment visit. The primary efficacy outcome will be to determine the effect of FMT on serum alkaline phosphatase values over time (end of study at 48 weeks). Key secondary outcomes will be to evaluate the impact of FMT on other liver biochemical parameters, PSC risk scores, circulating and imaging markers of liver fibrosis, health-related quality of life measures, IBD activity and the incidence of PSC-related clinical events. Key translational objectives will be to identify mucosal metagenomic, metatranscriptomic, metabolomic and immunological pathways associated with the administration of FMT.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Use of a randomised placebo-controlled trial design to assess the efficacy and safety of multidose faecal microbiota transplantation in primary sclerosing cholangitis (PSC).
⇒ The integration of clinical, biochemical, imaging and patient-reported outcome data will allow a holistic evaluation of therapeutic effect and longevity.
⇒ Multiple colonic sampling time points, enabling microbiome profiling at the mucosal level and within the stool, mapping its evolution throughout the trial period.
⇒ The use of multiple doses requiring weekly hospital attendance may impact recruitment and attrition rates.
⇒ Generalisability is limited to early-to-moderate stage PSC with concomitant colonic inflammatory bowel disease and those who have undergone subtotal colectomy with an ileal pouch anal anastomosis.

Ethics and dissemination The protocol was approved by the South Central—Hampshire B Research Ethics Committee (REC 23/SC/0147). Participants will be required to provide written informed consent. The results of this trial will be disseminated through national and international presentations and peer-reviewed publications.

Trial registration number The trial was registered at ClinicalTrials.gov on 23 February 2024 (NCT06286709). Weblink: Study Details | FAecal Microbiota Transplantation in primaRy sclerosinG chOlangitis | ClinicalTrials.gov.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is an immune-mediated stricturing disease that affects the biliary tree.[1] The disease is rare with contemporary estimates indicating an

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incidence and prevalence of 0.6 and 7.6 per 100 000 population, respectively.[2–5] At present, there are no medical therapies proven to slow disease progression, with median liver transplant-free survival ranging 14–21 years from first presentation.[6 7] The clinical course is invariably progressive; and whilst many are asymptomatic at presentation patients can develop abdominal pain and pruritus, recurrent ascending cholangitis and eventually complications of cirrhosis. Additionally, 10–15% of patients develop biliary tract cancer (cholangiocarcinoma) which is often fatal except when diagnosed in the very early stages.[2 8] The vast majority of patients (70–80%) also develop inflammatory bowel disease (IBD), typically pancolitis.[9 10] Importantly, PSC-colitis is associated with a heightened lifetime risk of colorectal cancer when compared with IBD alone, necessitating annual colonoscopic surveillance.[11–14] Given the absence of disease-modifying treatment, current management is limited to 12-monthly hepatobiliary imaging, targeting complete mucosal healing for IBD, symptom-directed care, and timely liver transplant assessment.

The interplay between gut inflammation and PSC has been at the centre of pathophysiological hypotheses, with a particular focus on studying dysregulated mucosal immune responses.[15 16] Comparative data from stool and mucosa-adherent sampling show that the gut microbial profile in PSC is distinct from that seen in IBD alone, healthy volunteers and other chronic liver diseases. A repeated finding is the abundance of *Veillonella* (a group of gram-negative anaerobic cocci) and to a lesser extent enrichment of *Enterococcus* and *Escherichia*. This is alongside reduced levels of *Lachnospiraceae, Faecalibacterium, Roseburia* and *Akermansia*. Collectively, these changes give way to an abundance of species involved in the dehydroxylation of primary bile acids and an enrichment of organisms capable of synthesising primary amine oxidase substrates (which subsequently drive liver inflammation and fibrosis). Reciprocally, lower levels of butyrate production, reduced branched-chain amino acids and less vitamin B6 synthesis are observed—the latter being associated with poorer transplant-free survival.[15–20] The gut microbiome in PSC has also been shown to exacerbate proinflammatory immune responses; where microbiota-induced regulatory T-cells that express the nuclear hormone receptor RORγt actively differentiate into proinflammatory T_h17 cells.[21] Notably, PSC liver and bowel disease are characterised by heightened T_h17 responses to gut pathogens; and preclinical data highlight the immunopathogenic impact of differential gut bacterial populations. Faecal transplants derived from patients with PSC can also induce sclerosing cholangitis in gnotobiotic mice, providing further evidence for a possible mechanism of action related to specific bacterial species.[22] Notably, inoculation with PSC patient-derived stool has been shown to compromise intestinal permeability, drive the recruitment of proinflammatory T_h17 cells to the gut and liver and lead to hepatobiliary inflammation.[22] In other animal models, liver disease is exacerbated when mice are reared in germ-free conditions.[23] Reciprocally, faecal microbiota transplantation (FMT) from specific pathogen-free mice has been shown to attenuate hepatobiliary inflammation and fibrosis in animal models of PSC.[24] Collectively, this suggests that there may be a protective role conferred by certain gut microbial communities.

The gut microbiome has evolved into a therapeutic target, on the premise that manipulation may slow disease progression. Indeed, studies of the gut-specific antibiotic vancomycin have been shown to improve liver biochemistry and colitis activity for the duration of treatment, although derangement resurfaces within weeks of completing treatment.[25–28 29] This strategy is limited further by concerns regarding long-term or continuous antibiotic use, especially in the context of multidrug resistant infections.[30] Controlled clinical trial data using probiotics have also been presented but show no impact on symptoms or liver biochemistry.[31]

A recent pilot study demonstrated that gut microbiome composition in PSC can be modulated using FMT, a process by which minimally manipulated stool from healthy screened donors is processed in an approved facility and administered to patients.[32] Presently, FMT is an established and licensed therapeutic option for the treatment of refractory and recurrent *Clostridioides difficile* infection[33] and its application has been explored in other clinical settings including idiopathic IBD,[33–35] hepatic encephalopathy[36] and in modulating the efficacy of immune checkpoint inhibitors in cancer treatment.[37 38] A systematic review in mild-to-moderate ulcerative colitis found that treatment with FMT achieved symptomatic improvement or resolution in 76% of patients, with the effect being sustained for at least 12 weeks.[34] Further data from an open-label pilot study in PSC demonstrated that a single colonic administration of FMT improved liver biochemistry in 7/9 participants and increased bacterial diversity.[32] However, the longevity of treatment effect was not assessed beyond 24 weeks and the results limited by small sample size. The effect of recurrent FMT administrations was explored in the STOP-Colitis trial whereby colonic and nasogastric (NG) delivery were also compared.[39] The colonic route was found to be safer and better tolerated by participants compared with oral or enteral routes of administration, with clinical remission achieved in 50% compared with 25% in the NG arm.[35] This study also reinforced the notion that multiple administrations of FMT are required to achieve remission in IBD activity.

Hypothesis

We hypothesise that colonic-administered FMT is able to attenuate PSC disease activity, early in the clinical course of the disease, by inducing a sustained and favourable change in composition and function of the gut microbial community.

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OBJECTIVES

Primary objective

The primary objective is to assess the efficacy of once weekly, colonic FMT administration on changes in serum alkaline phosphatase (ALP) values over time in patients with PSC-IBD.

Secondary objectives

Secondary objectives are to validate the safety of FMT; and to assess its effects on other liver biochemical parameters, radiological indices of PSC disease stage, colonic IBD activity (assessed endoscopically and through stool biomarkers), patient-reported outcome measures (PROMs) relating to liver and bowel disease and the incidence of PSC-specific and IBD-specific clinical events.

Translational research objectives

Translational research objectives have been set to explore the mechanisms by which FMT may alter host and microbial pathways implicated in the pathogenesis of PSC-IBD which will help identify new druggable host molecular and microbial targets associated with clinical response through multiomic integration analysis.

METHODS AND ANALYSIS

Overview of trial design

The FAecal micRobiota transplantation in primary sclerosinG chOlangitis (FARGO) trial is a phase IIa, parallel-group, two-arm, partial-blind randomised controlled trial, conducted across participating centres across the UK. Arm 1 is composed of those receiving active FMT and arm 2 is composed of FMT placebo. Potential participants will be identified and invited for screening. Those who meet prespecified eligibility criteria and pass screening will be randomised 1:1 to receive either active FMT or FMT placebo; the first dose of which will be administered via colonoscopy. Thereafter, participants will attend once weekly for administration of active FMT or FMT placebo, administered via enema, for a total treatment duration of 8 weeks. Participants will then be invited to undergo a flexible sigmoidoscopy at week 12 (to facilitate mechanistic sample collection). Further trial visits and clinical assessments will take place 12-weekly thereafter. The last trial visit will be at week 48, at which point participants will undergo a further colonoscopy, clinical assessment and analysis of blood and stool to facilitate assessment of primary, secondary and translational research objectives (figure 1, table 1). The trial is managed and conducted by the Birmingham Cancer Research UK Clinical Trials Unit (CRCTU) under the auspices of the sponsor, the University of Birmingham, UK.

Study setting

This study aims to recruit 58 patients with PSC and concomitant IBD from six participating centres, alongside three participant identification centre sites across England.

Eligibility criteria

Inclusion criteria

To be considered for inclusion in the trial, participants must fulfil all the following criteria at screening:

1. Age 18 years or older.
2. Have an established diagnosis of large duct PSC, diagnosed on magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography.
3. Have an established diagnosis of colonic IBD with a willingness to participate in an annual colonoscopic surveillance programme as per routine standard of care.
4. A colonoscopy showing no evidence of dysplasia/neoplasia within 24 months prior to screening.
5. No evidence of moderate-to-severe active colitis, as evidenced by having a Partial Mayo Score of≤4, with a score of<2 on the rectal bleeding domain at screening.
6. Be able to provide written informed consent and be willing to undertake trial procedures.
7. Have a persistently elevated ALP value above the upper limit of normal (ULN), on at least two readings greater than 6 months before screening. Note: ALP elevations must be deemed related to hepatobiliary disease (ie, not related to another source such as metabolic bone disease) as per investigator discretion.
8. PSC with overlapping features of autoimmune hepatitis may be permitted entry, if they have concomitant IBD and have remained on stable doses of immunosuppressive treatment for the preceding 12 weeks with the expectation that they remain on the same medication and dose for the duration of the trial.
9. If established on immunosuppressive treatment, participants must be on a stable dose for at least 12 weeks prior to screening with no anticipated change to medication or dose for the duration of the trial.

Exclusion criteria

Participants with any of the following will not be eligible for entry into the trial:

1. Have a diagnosis of secondary sclerosing cholangitis or an alternative cause of liver disease (online supplemental file 1). Patients with a concomitant diagnosis of autoimmune hepatitis/overlap syndrome may be permitted entry as per inclusion criteria #8, above.
2. Presence of a clinically significant high-grade stricture, except for where this has been stable for 6 months and there is no planned intervention.
3. Presence of a percutaneous drain or bile duct stent.
4. Evidence of hepatic decompensation within 12 weeks prior to screening, or risk of hepatic decompensation during the trial period, at the discretion of the principal investigator (online supplemental file 2).
5. Biochemical evidence of advanced hepatic dysfunction (online supplemental file 3).
6. Ascending cholangitis, in the 12 weeks prior to screening, according to investigator discretion.

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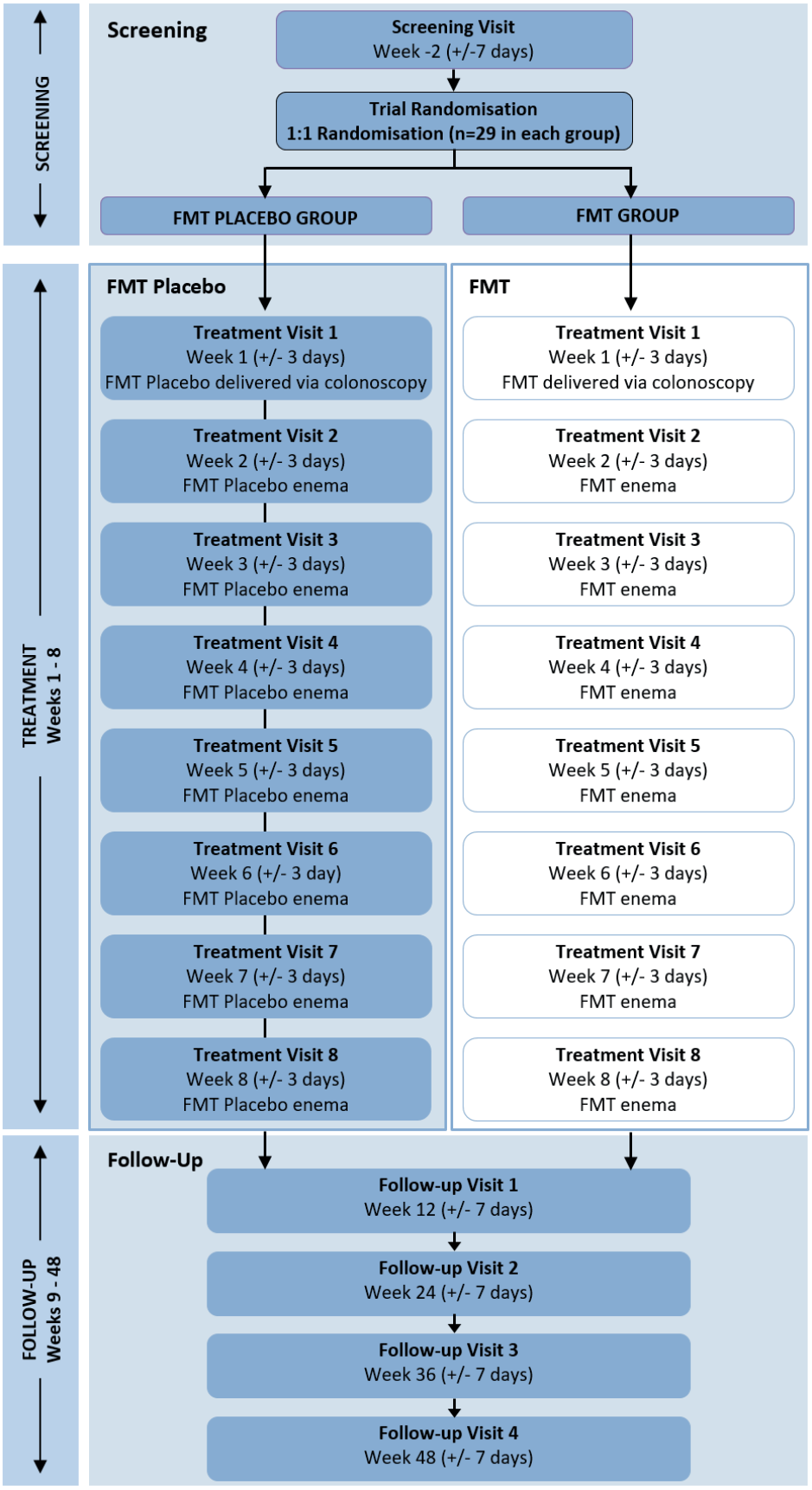


Figure 1 FARGO trial schema. FARGO, FAecal micRobiota transplantation in primary sclerosinG chOlangitis; FMT, faecal microbiota transplantation.

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Table 1 Sample analysis plan

Sample type	Intended analysis
Peripheral blood	Exploratory biomarkers; serum and plasma save
	Metabolomics
	Enhanced liver fibrosis test
	Mass cytometry (UHB participants only)
Urine	Metabolomics
Colonic biopsies	Mass cytometry (UHB participants only)
	Extraction and sequencing (16S and metagenomics); biopsy save
Stool	Extraction and sequencing (16S and metagenomics); stool save
	Metabolomics
	Postsequencing analysis; Stool culture

UHB, University Hospitals Birmingham.

7. Use of systemic antibiotics (oral or intravenous) in the 12 weeks prior to screening.
8. On a liver transplant waiting list or have a likelihood of needing transplant assessment/being listed for a liver transplant during the trial period according to the investigator.
9. Small duct PSC (ie, normal bile duct appearances on a cholangiogram, with histological features evident on liver biopsy alone).
10. Advanced-stage liver fibrosis (for instance, a vibration-controlled transient elastography (VCTE) score>14.4 kPa, or a liver biopsy showing Ishak fibrosis stage>III, or equivalent).
11. Evidence of active colitis as evidenced by a Partial Mayo Colitis Score of>4, with a score of>2 on the rectal bleeding domain at screening.
12. Colonic dysplasia or neoplasia within 24 months prior to screening.
13. Significant renal dysfunction (estimated glomerular filtration rate <60 mL/min) or dialysis dependent.
14. HIV infection.
15. A symptomatic positive test result for Serious Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection within 4 weeks of screening. Note: SARS CoV-2 testing is not required prior to screening but should be conducted in the event a patient has symptoms or at investigator discretion.
16. A history of malignancy within the past 3 years (or ongoing malignancy), excluding non-melanomatous skin cancer or treated cervical carcinoma in situ.
17. A history of any prior small bowel or colonic resection or a likelihood of needing a small bowel or colonic resection during the trial period. Note: Individuals with a subtotal colectomy and ileal pouch anal anastomosis (IPAA) are eligible to participate.
18. Pregnancy or breastfeeding.
19. Women of childbearing potential who confirm they are not willing to practice effective contraception for the duration of the trial and for 4 weeks after the last dose of the trial drug. Those on hormonal contraception must be on a stable dose and formulation for at least 6 weeks prior to treatment.
20. Alcohol consumption>21 units per week for men and>14 units per week for women.
21. Positive urine drug screen at screening.
22. Positive stool culture or microscopy for enteric infection within 12 weeks of screening.
23. Participation in an interventional trial or use of a non-licensed investigational agent within 12 weeks of screening or five half-lives of the investigational drug (whichever is longer).
24. New introduction or change in dosage of any of the following medications within 12 weeks prior to screening:
    a. Fibric acid derivatives/fibrates.
    b. Farnesoid X-receptor agonists.
    c. Antigastrointestinal motility agents, for example, loperamide or opioids (with the exception of loperamide administered at time of FMT / FMT placebo administration).
    d. Bile acid sequestrants for example, colestyramine.
    e. Ursodeoxycholic acid.
25. Use of any of the following medications 12 weeks prior to screening:
    a. Oral or intravenous antibiotics, including, but not limited to, vancomycin, rifaximin, rifampicin and metronidazole.
    b. Probiotics or prebiotic preparations, including (but not limited to) VSL#3 and Symprove.

Randomisation and blinding

Participants who enter the trial will be randomised prior to receiving first dose of the investigational medicinal product. Randomisation will be conducted on a 1:1 basis via a bespoke online Electronic Remote Data Capture system (eRDC). A minimisation procedure will be applied with the following stratification variables: (1) baseline serum ALP values (≤2× ULN vs>2× ULN), (2) baseline serum bilirubin values (≤2× ULN vs>2 ULN) and (3) transient elastography values (≤8.0 kPa vs>8.0 kPa). Allocation will be to arm 1 (active FMT) or arm 2 (FMT placebo).

A partial-blinded approach will be used. Patients, trial management staff and site principal and subinvestigators performing study assessments will be blinded to treatment allocation. Reciprocally, trial statisticians, the clinician conducting the first colonoscopy (and administering the active FMT or FMT placebo), the trial nurses administering active FMT or FMT placebo via enema and members of the Data and Safety Monitoring Committee are unblinded to treatment group allocation. Analysis of randomisation will include the number of patients randomised by treatment group including stratification variables and the number of patients who have been unblinded by treatment group and the reasons provided for unblinding.

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Table 2 Roles of blinding and unblinding staff at investigator sites

	Unblinded		Blinded	
Staff role	Clinical investigator #1	Trial nurse #1	Clinical investigator #2	Trial nurse #2
Colonoscopy (week 1)	x			
Treatment by colonoscopy (week 1)	x			
Full Mayo Score (week 1)	x			
Weekly Partial Mayo Scores	x		x	x
Treatments by enema (weeks 2–8)	x	x		
Flexible sigmoidoscopy (week 12)			x	
Colonoscopy (week 48)			x	
Full Mayo Score (weeks 12 and 48)			x	
Participant deterioration			x	

To maintain blinding, the active FMT and FMT placebo will be concealed in opaque packaging prior to and during administration to patients. A summary of unblinding points is provided in table 2.

Recruitment and trial schedule

Screening

Potential trial participants will be identified in specialist gastroenterology and hepatology clinics and site-specific databases, by a medical doctor or nurse who is part of their clinical care team. Additionally, registrants of the national UK-PSC registry who fulfil eligibility criteria will be contacted by the study team and invited to participate at one of the six trial sites.

Study eligibility will be confirmed by the research team (online supplemental file 4). Patients who wish to participate in the trial will undertake further screening tests to confirm eligibility. These will include stool microbiology if indicated, urine drug screen, urine pregnancy test, VCTE, Child-Turcotte-Pugh score, Model for End-Stage Liver Disease score and Partial Mayo score. Screening procedures are further detailed in the Schedule of Events (online supplemental table 5). Following confirmation of eligibility, participants will be consented (online supplemental file 6) by a medical doctor who is part of the research team. Baseline clinical data will be collected and participants allocated a trial identification (ID) number. Randomisation will be completed once all results from screening investigations are available.

Participants are asked to provide a stool sample at every trial visit as per the Participant Instructions for Stool Collection instructions (online supplemental file 7). For week 1 and week 48 visits, stool samples are collected prior to commencing bowel preparation and kept at 4°C. For all other trial visits, samples are collected on the morning of the trial visit (ideally within 6 hours of the appointment). An OM-AC1 toilet accessory kit is provided to facilitate sample collection into a DNA/RNA Shield Faecal Collection Tube and a 30 mL Universal Tube.

Study visits

Week 1: treatment visit

Consent will be confirmed at this visit and baseline samples collected (online supplemental table 5). Participants will then undergo their annual standard of care surveillance colonoscopy, in which mucosal biopsy samples will be taken throughout the colon, in keeping with routine clinical care. Additionally, colon samples will be obtained systematically throughout the colon (two from each site: caecum, ascending colon, transverse colon, descending colon, sigmoid and rectum) to facilitate delivery of our translational research objectives. Thereafter, the first treatment will be administered (active FMT or FMT placebo), via a colonoscopy dye-spray catheter.

Weeks 2–8: treatment visits

Participants will attend once weekly for 7 weeks to undergo further treatment administration via enema, alongside further clinical data and sample collection (online supplemental table 5).

Week 12: follow-up visit

At week 12, participants will attend their study site and undergo a flexible sigmoidoscopy; the biopsies of which will be needed to facilitate mechanistic sample collection. Principally, the purpose of this visit will be to study the engraftment of microbial communities from donor to recipient. Alongside, clinical, stool and laboratory data will be collected to facilitate the analysis of secondary outcome measures at the end of the study.

Weeks 24 and 36: follow-up visits

Further follow-up visits will occur on weeks 24 and 36, where further clinical, stool and laboratory data will be collected, alongside PROMs (online supplemental table 5).

Week 48: end-of-trial visit

At week 48, participants will attend the study site, where further clinical, stool and laboratory data will be collected, alongside PROMs (online supplemental table 5). Moreover, participants will undergo a repeat colonoscopy, in

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keeping with annual surveillance for PSC-IBD. In addition to mucosal biopsies taken for routine clinical care purposes, samples will be taken systematically throughout the colon (two from each site: caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum) to facilitate delivery of our translational research objectives. Note: Stool samples and PROMs will be completed by participants, up until the point they take colonic/bowel preparation needed for the colonoscopy procedure. Week 48 signifies the end of the trial where participants will exit the study (figure 1).

Trial intervention

Justification for trial intervention

In designing this study, colonic FMT was selected as the primary intervention in comparison to the alternative modalities available, including capsule and NG FMT. This selection was made based on the well-elucidated pharmacokinetic properties of colonic FMT, the local expertise in the manufacturing of FMT and feedback from our patient and public involvement and engagement (PPIE) group on the acceptability of the intervention. The feedback favouring colonic administration was large because patients with PSC (1) undergo annual surveillance colonoscopy as per routine care, (2) felt more confident in FMT being delivered directly to the site of their colonic IBD (rather than capsules which may release content higher up in the gastrointestinal tract), (3) were concerned about capsule rupture/mistakenly biting or chewing on capsules erroneously, and (4) were concerned about loss of microbiome viability associated with the lyophilisation process.[40] Additionally, previous work has demonstrated higher attrition rates following NG administration (n=5/9) compared with colonic delivery (n=1/8).[35]

Donor selection and screening

Healthy donors, who will provide a stool for making the active FMT product, will be recruited through the University of Birmingham Microbiome Treatment Centre (UoBMTC) in line with previously written protocols (online supplemental figure 8).[39 41] Briefly, potential donors will be asked to complete a Donor Health Questionnaire (online supplemental file 9) at first donation. Those who pass screening will be asked to donate their first-morning stool sample for 10 consecutive days (delivered within 6 hours of defaecation) for processing. All stool samples will be screened to exclude transmissible pathogens, in accordance with UK and international guidelines.[33 41–44] Healthcare workers will be excluded from stool donation. Importantly, FMT from a single donor will be used throughout each trial participant's treatment course. More specifically, a trial participant recruited to the active FMT arm can only receive stool from a single donor for the duration of the trial; however, one donor may provide FMT to multiple trial participants. A log of which participants received treatment from which donor will be maintained throughout the trial period. This will facilitate additional analyses to explore the hypotheses that different FMT donors may elicit different responses based on the donor microbiome. Where appropriate data is available for patients in the FMT arm, supplementary analyses will be performed by cross-tabulating donors with responses to ascertain if this response is contingent on the donor. This will be appraised after the first 10 patients allocated active treatment have completed treatment and at the end of the trial.

Active FMT and FMT placebo preparation

Donated stool samples will be processed at the UoBMTC. At least 30 g of stool is mixed with preservative-free sterile 0.9% saline and 10% glycerol for cryoprotection in a ratio of 9-part saline:1-part glycerol. The stool is then homogenised and filtered according to Good Manufacturing Procedure standards. The liquid filtrate is then removed and classified as FMT. Stool filtrates are stored in 50 mL aliquots ready for use at −80°C for up to 52 weeks. Each FMT treatment set prepared will be allocated a unique batch and lot number and cross-referenced to FMT preparation records and donor screening records to ensure full traceability of FMT material.

Normal saline will be used for the preparation of FMT placebo material, as this is biologically inert and will not stimulate gut motility or induce any inflammatory response. FMT placebo will contain 0.9% saline and 10% glycerol in a ratio of 9-part saline:1-part glycerol. This will be stored in 50 mL aliquots ready for use at −80°C for up to 52 weeks.

Dosage and administration

FMT will be delivered via colonoscopy at a dose of 150 g of stool made up of 250 mL, whereas treatments delivered via enema will be at a dose of 30 g of stool in 100 mL. FMT prepared for administration via flexible sigmoidoscopy in participants with an IPAA, will be made up of 30 g stool in 50 mL. Participants who complete the FMT treatment course will receive 600 mL FMT (360 g donor stool) in total or 400 mL FMT (240 g donor stool) in the case of those with an IPAA.

Participants will undergo standard of care bowel preparation in advance of surveillance colonoscopy. Additionally, 2 mg of oral loperamide will be administered 10–15 min prior to the procedure to reduce bowel motility and allow the FMT to be retained within the bowel. Colonoscopy will be performed as per standard clinical practice, with the caveat that inspection will be performed and pancolonic biopsies taken on insertion (rather than withdrawal) to facilitate FMT administration on scope withdrawal. 250 mL of thawed active FMT product (or FMT placebo) will be administered into the large bowel, with 125 mL sprayed into the caecum and the remaining 125 mL evenly throughout the rest of the colon. Those with IPAA will have 150 mL of FMT or FMT placebo sprayed onto the pouch mucosa via pouchoscopy.

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Subsequent doses of active FMT or FMT placebo will be delivered at week 2–8 treatment visits via enema. Patients will be given a single 2 mg dose of oral loperamide 10–15 min prior to administration of treatment. A 100 mL volume enema will be administered by a trained research nurse.

Unblinding

Emergency unblinding can be performed in the event of exceptional clinical circumstances where knowledge of the treatment will guide further care. This can be done via the eRDC.

Treatment discontinuation

Treatment may be discontinued in the event of a serious adverse event (SAE), change in the participant's clinical state barring eligibility or at the participant's request. In addition, treatment may be paused if a participant is commenced on antibiotic treatment or prebiotic/probiotic preparations and recommenced once the treatment course is completed. Should the treatment be discontinued, this alongside its reasons will be recorded and follow-up will continue.

Data management

Clinical data will be collected via an eRDC developed by the CRCTU Programming Team. Data will be pseudoanonymised through the synthesis of individual patient trial IDs and inputted at the sites. Paper case report forms will also be kept as backup. Access to the eRDC will be restricted to site staff on the delegation log for data management. Data collected will vary by visit. A summary of the data collected at each visit is given in the Schedule of Events (online supplemental table 5). Adverse events (AEs) will be recorded at each visit and managed according to the trial protocol as detailed later. Participants may withdraw from the trial at any time. Withdrawal may be graded with either withdrawal from treatment only, withdrawal from treatment and trial-specific follow-up (with data collected at standard clinic visits) or full withdrawal of consent to participate in the trial in which case no further data is collected and only data collected prior to withdrawal of consent will be analysed. Trial data will be stored for a period of 15 years after completion of the trial.

AEs management

AEs will be collected for the duration of the trial. AEs and SAE data, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) (44), for each treatment group will be collected and reported from the date of informed consent until the last follow-up visit at 48 weeks. A causality assessment will be performed to assess the relationship between the trial intervention and any AEs or SAEs. This will be performed by the appropriately delegated individuals within the trial team. AEs of special interest will also be reported on an SAE form and will include acute colitis flare, acute cholangitis flare, hepatic decompensation, sepsis and suspected transmission of an infectious agent via a trial product. Any SAEs designated as unexpected or related to the intervention will be reported to the Medicines and Healthcare products Regulatory Agency, research ethics committee and study sponsor.

STATISTICAL ANALYSIS

Primary outcome measure

The primary efficacy outcome measure is the reduction in serum ALP values from baseline, measured at 48 weeks following the first dose of active FMT or FMT Placebo. ALP will be modelled from baseline (pretreatment) to week 48 (end of follow-up) using Bayesian hierarchical repeated measures modelling that accounts for the nesting and serial correlation of the repeated measures data within the patient. The model formulation will incorporate a time-treatment interaction term (with the reference treatment category being placebo) and adjust for stratification variables as population-level effects. The inference will be made using posterior probabilities for the time and time-treatment terms within the model. Priors used will be chosen that is informative on the scale (ie, that rule out implausibly large effects) but non-informative on location (ie, do not pre-empt any positive or negative treatment effect). These priors will allow an informative analysis despite the modest sample size. Where possible, these will be informed by existing evidence. Moreover, where priors are informed by existing evidence, sensitivity analyses to prior (using minimally informative priors) will be performed. Full specification of the priors to be used will be given alongside results.

Plots and inferences will be presented to summarise the posterior beliefs. Reporting will include (but not be limited to) the probability that the treatment provides any beneficial treatment. The inference will be based on posterior probability statements for the treatment:time interaction within the model formulation, ascertaining whether treatment provides any benefit.

Sample size determinations

The recruitment target is a total of 58 participants who will be randomised 1:1 to receive either active FMT or FMT Placebo treatment. Power calculations have been derived from post hoc analysis of the phase II clinical trial of simtuzumab in PSC,[4] in which variation in serum ALP over time was calculated as part of the clinical course of PSC. As such, a sample size of 26 participants per treatment group would provide 90% power with a type I error rate of 0.05, to detect a mean difference of 30 units between active treatment and control groups, with regards per cent reduction in baseline of ALP, using a two-sample independent t-test. A pooled SD of 36.3 was used in this calculation (obtained from the simtuzumab data set).

Prior clinical trials in PSC observe an approximately 10–15% attrition rate; therefore, the current trial would require a total of 58 subjects (29 per treatment arm). Serum ALP will be collected at baseline and at multiple

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time points post-treatment. The proposed primary analysis would be to model post-treatment ALP using a Bayesian multilevel model that allows for nesting of the repeated measures data within the patient. The above sample size calculation is to provide insight into the magnitude of effect size that could be identified with reasonable error rates. However, the trial will aim to make more efficient use of the primary outcome data through the use of modelling and the trial will consider the totality of all data points with regard to the primary/secondary outcome evidence in making inferences.

Secondary outcome measures

Secondary outcomes measures analyse the effects of FMT on other markers of disease activity and severity throughout the course of the trial; specifically:

- Routine liver biochemical parameters beyond ALP: serum alanine aminotransferase, aspartate aminotransferase, bilirubin and albumin values.
- PSC-specific prognostic disease scores: the UK-PSC[45] and Amsterdam-Oxford PSC score.[46]
- Surrogate biomarkers of liver fibrosis: VCTE and the enhanced liver fibrosis score.
- PROMs: the PSC-PRO,[47] the short-form (SF)-36,[48] the 5-D itch tool[49] and the short IBD questionnaire SIBDQ.[50]
- Quantitative assessment of IBD activity: the Mayo colitis score (for patients with ulcerative colitis[51]) or the Simple Endoscopic Score for Crohn's Disease (for patients with Crohn's disease[52]) and faecal calprotectin.
- The incidence of clinical non-trial endpoint events: acute cholangitis flares (including those that are resistant to single-course antibiotic treatment), acute colitis flares and episodes/time to hepatic decompensation.
- The incidence of trial endpoint events: cholangiocarcinoma/hepatopancreatobiliary malignancy, referral for liver transplantation, colonic resection or colorectal cancer and/or mortality.
- The occurrence of AEs as measured by CTCAE V.5.0.[53]

Secondary outcome measures will be transformed as per their user manuals (where appropriate), summarised using descriptive statistics for each time point and plots over time. These will then be modelled using Bayesian hierarchical modelling using methods akin to those proposed for the primary outcome allowing for nesting of the measures within the patient; the only material difference will be the model type to ensure suitability for the dependant variable. Where there is a baseline and at least one postbaseline measurement of the dependant variable, repeated measures regression models will be used. Where the dependant variable is binary in nature, logistic regression models respectively will be used. Where the dependant variable is categorical in nature, ordinal logistic regression models respectively will be used.

Trial organisation structure

The trial sponsor is the University of Birmingham, UK and is being conducted under the auspices of the CRCTU, University of Birmingham. All clinicians involved in consent and sample collection will be on the trial delegation log and undertake trial-specific training. These will all have up-to-date Good Clinical Practice (GCP) training. Trial activity will be overseen by the trial management group (TMG). This will be composed of the chief investigator, co-investigators, trial management team leader, senior trial coordinator, trial coordinator, clinical research fellow and senior biostatistician. A separate data monitoring committee (DMC), comprised of experts, will be established to independently review trial outcomes and safety data. The DMC will report directly to the TMG.

Patient and public Involvement and engagement

The PSC patient community has been closely involved in the design of this trial, through PSC Support and the Birmingham gastroenterology and liver PPIE group. This was achieved through regular focus groups which shaped the research question and study design. The route of FMT delivery was guided by the outcomes of a survey of 60 individuals with PSC in which 93% were willing to receive FMT at the time of their annual surveillance colonoscopy and 79% via a rectal enema. This compares to 27% who were willing to receive FMT via an NG route or a capsule. PSC Support has been involved in designing the study protocol, participant invitation letter and trial information sheet and will represent patient interests as part of the TMG.

ETHICS AND DISSEMINATION

A standardised ethical approach will be taken as per previous work.[39] The trial will follow the principles of the Helsinki Declaration and will be conducted in accordance with the Research Governance Framework for Health and Social Care, Medicines for Human Use Clinical Trials 2004, General Data Protection Regulation, Data Protection Act 2018, Human Tissue Act 2008 and GCP. This study will be carried out under a Clinical Trial Authorisation in line with the Medicines for Human Use Clinical Trials regulations. Ethics approval has been granted by the South Central—Hampshire B Research Ethics Committee (REC 23/SC/0147). Trial reporting will be conducted in accordance with the Consolidated Standards of Reporting Trials Guidelines.[54] The trial findings will be published in a peer-reviewed journal and presented at relevant national and international gastroenterology and hepatology meetings. Authorship will be determined in line with International Committee of Medical Journal Editors guidance.[55] PSC Support and our PPIE group will guide patient-facing outputs to maximise impact and reach.

TRIAL STATUS

The trial opened for recruitment on 27 March 2024, is actively recruiting, with 11 participants at time of

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protocol paper submission. The trial is expected to continue recruitment for 18 months.

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Acknowledgements This study has been delivered through the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of LifeArc, PSC Support, the NIHR or the Department of Health and Social Care.

Contributors PJT is the chief investigator and guarantor. He conceived the trial, designed the protocol and acquired grant funding. TI, MNQ, RC, LA, CQ, ADB and BM are co-investigators and have contributed to study conception, design and protocol development. CW, SA-S, AP, EE, WvS and MH contributed to protocol development for translational outcomes. AV is the senior trial coordinator. AR is the trial team leader. AV and AR contributed to protocol development and coordinated the IRAS, research ethics committee, Medicines and Healthcare products Regulatory Agency, HRA and local R&D applications. DG is a trial coordinator and has been involved in protocol development and the coordination of local R&D applications. VH is the senior trial biostatistician and NJ is the trial biostatistician. Both have contributed to the study design, protocol development and statistical plan development. SS is the clinical services manager at University of Birmingham Microbiome Treatment Centre (UoBMTC). SM is the faecal microbiota transplantation production manager at UoBMTC. SS and SM are responsible for investigational medicinal product manufacturing and management. PR is a subinvestigator. SA-S is the lead author and drafted the initial version of the manuscript. All authors read and approved the final manuscript. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing this report.

Funding This project is co-funded by LifeArc (P2022-0001) and PSC Support (FARGO)

Disclaimer The views expressed are those of the author(s) and not necessarily those of LifeArc, PSC Support, the National Institute for Health and Care Research or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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