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Protocol for faecal microbiota transplantation in ulcerative colitis (FMTUC): a randomised feasibility study

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ABSTRACT

Background The interaction of the gut microbiota with the human host is implicated in the pathogenesis of inflammatory and immunological diseases including ulcerative colitis (UC). Faecal microbiota transplantation (FMT) as a method of restoring gut microbial diversity is of increasing interest as a therapeutic approach in the management of UC. The current literature lacks consensus about the dose of FMT, route of administration and duration of response.

Methods and analysis This single-blinded randomised trial will explore the feasibility of FMT in 30 treatment-naïve patients with histologically confirmed distal UC limited to the recto-sigmoid region (up to 40 cm from the anal verge). This study aims to estimate the magnitude of treatment response to FMT under controlled conditions. The intervention (FMT) will be administered by rectal retention enema. It will test the feasibility of randomising patients to: (i) single FMT dose, (ii) five daily FMT doses or (iii) control (no FMT dose). All groups will receive standard antibiotic gut decontamination and bowel preparation before FMT. Recruitment will take place over a 24-month period with a 12-week patient follow-up. Trial objectives include evaluation of the magnitude of treatment response to FMT, investigation of the clinical value of metabolic phenotyping for predicting the clinical response to FMT and testing the recruitment rate of donors and patients for a study in FMT. This feasibility trial will enable an estimate of number of patients needed, help determine optimal study conditions and inform the choice of endpoints for a future definitive phase III study.

Ethics and dissemination The trial is approved by the regional ethics committee and is sponsored by Abertawe Bro Morgannwg University's Health Board. Written informed consent from all patients will be obtained. Serious adverse events will be reported to the sponsor. Trial results will be disseminated via peer review publication and shared with trial participants.

Trial registration number ISRCTN 58082603; Pre-results.

Strengths and limitations of this study

- This is one of the first trials to have a homogeneous study group of newly diagnosed and treatment naïve patients with ulcerative colitis (UC).
- The trial will not only show the efficacy of faecal microbiota transplantation (FMT) treatment by rectal administration, but also help to define the optimal number of doses of FMT for treatment of UC.
- Metabolomic analysis will demonstrate mechanism of action of FMT in treatment responders.
- Patient's reported quality of life measures will be reported.
- This study is limited by a short (12 weeks) follow-up period.

INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing-remitting mucosal inflammatory bowel disease (IBD). Clinical features include rectal bleeding, diarrhoea, faecal urgency, fatigue and weight loss. The aetiology of UC is believed to be multifactorial involving immune dysregulation, mucosal disruption and genetic predisposition, though the precise cause is poorly understood.[1]

There is no curative treatment at present; thus the aim of current management is induction and maintenance of remission with immunosuppressive agents. Failure of medical therapy or refractory disease may require major resectional surgery with temporary or permanent ostomy formation. UC is also a recognised risk factor for colorectal cancer requiring lifelong surveillance.[2] However, it is uncertain how to predict which group of patients will respond to medical therapy.

The human gut microbiota consists of a diverse biological environment comprising bacteria, viruses and fungi within the gut

lumen and lining mucosa. The biodiversity of the gut microbiota is a dynamic process and is known to be affected by age, diet and lifestyle.[3 4] It has been referred as a hidden metabolic organ through its major role is as a driver of metabolic and immunological communications and the regulation of the immunological processes within the intestinal mucosa.[5–7] Disruption of the gut microbiota, also called dysbiosis, has been suggested to be responsible for not only intestinal pathology such as *Clostridium difficile* infection, but also for systemic conditions such as obesity, diabetes mellitus and IBD including UC.[3 8] The role of gut microbiota with host–microbiome interactions are likely to be a key driver in the pathogenesis of UC.[9 10] Antibiotics, which alter the human gut microbiome, have been shown to contribute to UC activity,[11] whereas probiotics have been implicated in UC remission.[12] The gut microbiota of patients with UC lacks diversity[13 14] and *Bacteroidetes* and *Firmicutes* are found in significantly less amounts in the microbiota of patients with UC.[13 15] Furthermore, reduced amounts of bacterial producers of short-chain fatty acids (SCFA) (butyrate, propionate and acetate) are found in the microbiota of patients with UC.[16 17] These SCFAs are products of starch fermentation from gut bacteria and are believed to have anti-inflammatory properties. Moreover, recent studies have shown that butyrate produced from *Faecalibacterium prausnitzii* not only has anti-inflammatory properties, but also provides the major nutrient for colonocytes,[18] and prevents intestinal mucosa atrophy and colonocyte autophagy.[19] A number of studies demonstrate that the butyrate producer *F. prausnitzii* was less abundant in patients with UC.[20–22] Moreover, recent studies have suggested that not only living bacteria may be responsible inflammatory process of UC, but also bacterial specific components and structures, antimicrobial compounds and metabolites produced by bacteria may contribute to the gut microenvironment and thus its inflammatory process.[23] Understanding of a critical role of secondary metabolites has also been highlighted recently by Buffie *et al* recently as they have indicated that certain species may inhibit *C. difficile* with their secondary metabolites, including secondary bile acids by *Clostridium scindens*.[24 25] Although the role of fungi in the human microbiome has not yet been fully understood, recent studies suggest microfragments of chitin, which is a substance produced by fungi and insects, display a significant immunomodulatory impact in the inflammatory process.[26 27] This suggests that not only viable common gut anaerobic micro-organisms, but also products and particles from other micro-organisms may be responsible for dysregulation of the immune response. Despite extensive studies, no single pathogen has been identified as responsible for the pathogenesis of UC. The current consensus is that the loss of certain bacterial strains with immunomodulatory as well as mucosal regulatory functions leads to gut dysbiosis, resulting in the pathogenesis of UC. Faecal microbiota transplantation (FMT) is an infusion of a faecal suspension from a healthy individual (donor) to restore the dysbiosis of affected individuals (recipient). Since the approval of FMT in the management of recurrent *C. difficile* infections in 2014 by the National Institute for Health and Care Excellence (NICE), FMT has been of increasing interest as a therapeutic approach in the management of UC. If we can successfully and durably alter the colonic microbiota,[28] it may be possible to achieve complete remission of this chronic debilitating disease without the use of lifelong immunosuppression or the need for major gastrointestinal surgery. The ability to induce remission and establish the microbiological basis for this would change the treatment paradigm for UC. Recent years have seen several randomised clinical studies emerging to investigate FMT in the management of UC with encouraging results.[14 29–31] Despite these studies, many unknown aspects remain in the clinical application of FMT in UC, such as the optimum dose, route of administration and frequency of treatments. Equally it is not known whether FMT is effective as a first line treatment in drug-naïve patients. To study the optimum parameters for delivering FMT in UC and estimating the clinical response, this randomised feasibility trial was designed.

The objectives of this feasibility study include evaluation of the magnitude of treatment response to FMT, investigation of the functional metabolic changes associated with FMT using a metabolic phenotyping methodology and testing the recruitment rate of donors and patients. Furthermore, we aim to measure the duration of clinical response with microbiome identification through 16S rRNA sequencing and metabolomic analysis. This will facilitate the design of a definitive multicentred study to confirm the efficacy of FMT as a first-line treatment option in UC.

Primary objectives

The primary objective of this phase II study is to estimate the magnitude of the treatment response to FMT in treatment naïve patients with UC.

Secondary objectives

- Determine the recruitment rate of donors and participants for a study of FMT.
- Determine the optimal study conditions and choice of endpoints for phase III study to include dosage and frequency of FMT treatments.
- Establish how many participants would be required for phase III to demonstrate the efficacy of FMT in the treatment of UC.

METHODS

This is a single-blinded interventional randomised feasibility study to estimate the magnitude of the treatment response to FMT in newly diagnosed patients with distal UC who are treatment naïve. Recruitment is proposed over a 2-year period with a 12-week post-treatment follow-up period. This feasibility trial will help determine the recruitment rate of donors and participants, define the optimal study conditions and choice of endpoints for

Table 1 Intervention arms (groups 1 and 2) and control arm (group 3)

	Group 1	Group 2	Group 3
Bowel decontamination and preparation	Yes	Yes	Yes
FMT treatment dose	1	Five consecutive days (single treatment per day)	None
Number of participants	12	12	6

FMT, faecal microbiota transplantation.

a phase III definitive study. It will also allow us to establish how many participants would be required at phase III to demonstrate the efficacy of FMT in the treatment of UC.

Trial design

We aim to recruit 30 subjects with histologically confirmed UC, whose disease is confined to the recto-sigmoid area (defined here as within 40 cm from the anal verge) and who are treatment naïve. Participants will be randomly assigned to study groups through a web-based application hosted by University of Aberdeen.

Eligible patients will be randomised into one of three groups with an allocation ratio of 2:2:1 as shown in table 1. Groups 1 and 2 are the intervention arms and 12 subjects will be assigned to each group respectively. Group 3 is the control arm and six subjects will be randomised into this group.

Intervention arms: groups 1 and 2

Participants randomly allocated to group 1 will receive one single FMT treatment administered as a rectal retention enema. Participants in group 2 will receive a single FMT treatment on five consecutive days (total of five treatments) also administered by rectal retention enema.

Control arm: group 3

Participants randomly allocated to group 3 will receive the pre-FMT preparation with antibiotics and bowel preparation but will not receive active FMT treatment.

Endpoints

Paired primary endpoints

- Remission of UC (mucosal healing) at 12 weeks as assessed by blinded sigmoidoscopy. Assessment defined as Mayo score ≤2 with an endoscopic Mayo score of 0
- Proportion of successful engraftment of donor faecal microbiota at 12 weeks in each group as analysed by 16S sequencing and longitudinal diversity index

Secondary endpoints

- Rate of recruitment of patients
- Disease specific scores after treatment using IBDex severity scoring index,[32] Crohns and Ulcerative Colitis Questionnaire (CUCQ)-32 severity scoring index[33] and Mayo scoring system[34]
- Histological grading of colitis severity after treatment
- Mucosal immunological response to treatment (tissue IL-10 and IL-21 by ELISA)
- Rate of development of adverse effects to FMT

Participant selection

Potential participants will be identified by their usual clinicians in clinics and endoscopy units within the Health Board. Each potential participant will be screened for eligibility once he or she is referred to the research team. All subjects must have a definitive histological diagnosis of UC before enrolment as made by a gastrointestinal pathologist with a special interest in colitis. The minimum required microscopic features include cryptitis, crypt abcesses, crypt distortion and mucin depletion in the absence of granulomata. Participants with any features not consistent with UC will be excluded. A minimum time period of 1 month from identification to screening will exclude participants with acute self-limiting colitis.

A written patient information sheet will be provided and participants will be offered a minimum of 24 hours to consider enrolment before providing written informed consent.

During the screening visit, the study will be fully explained, and consent will be obtained if the subject satisfies all inclusion and exclusion criteria (box 1).

Interventions and investigational products

All three study groups will complete a 10-day course of oral antibiotics (Metronidazole 400 mg, vancomycin 500 mg, rifampicin 150 mg twice daily), which should be completed at least 48 hours before the first FMT treatment. This will allow the poorly absorbed vancomycin to wash out of the gastrointestinal tract. Patients should therefore start the 10-day course of antibiotics 12 days before the first FMT is given. These antibiotics were chosen following the recently published guidelines on FMT in clinical practice[35] towards whole gut decontamination. Additionally, all participants will receive bowel preparation (polyethylene glycol, 2 L) on the day before transplantation to prepare the lumen for engraftment of the FMT treatment and to minimise interference from the existing gut microbiota.

Investigational product

The investigational product is donated faecal material from healthy volunteers who are unrelated and non-cohabiting to the study participants. The FMT products are obtained either from Wessex stool bank or material that has been locally processed using the identical FMT preparation technique by a physician for the purposes of the research trial. The pellet is resuspended and frozen in 20% glycerol and stored for up to 8 weeks at −80°C until the day of treatment. Donors are screened for infections in accordance with current best practice[35] (table 2). In the case of multiple treatments (group 2) all doses

Box 1 Participant selection criteria

Inclusion criteria

- Newly diagnosed histologically confirmed ulcerative colitis (UC) with inflammation limited to the rectum or recto-sigmoid (within 40 cm of anal verge as measured by flexible sigmoidoscopy).
- Age 18 years and older.
- Able to give full informed written consent.
- Willing to return for sequential faecal microbiota transplantation dosing and endoscopic assessment.
- Not in receipt of conventional medical treatment for colitis such as steroids or 5-aminosalicylic acid, that is, treatment naïve.

Exclusion criteria

- Patients without a definitive diagnosis of UC (for example, diagnosis of Crohn's disease or infectious colitis).
- Colitis extending beyond 40 cm from the anal verge.
- Diagnosis of acute severe colitis (defined as greater than six blood-stained stools per 24 hours with one of the following: pulse rate>90/ temperature>37.8° /haemoglobin < 105 g/L / erythrocyte sedimentation rate>30).
- Abdominal tenderness on examination.
- Already commenced standard medical therapy for UC.
- Contraindication to oral bowel preparation.
- Allergy to study antibiotics.
- Age less than 18.
- Patient is within a vulnerable group, defined as people who are unable to take care of him or herself, or unable to protect him or herself against significant harm or exploitation.
- Pregnant.
- Immunosuppressed for example, transplant patient.
- Known communicable disease or at least 2 weeks full recovery from infectious disease for example, chickenpox.
- Systemic autoimmunity, or atopic diseases.
- Previous prosthetic implant (for example, metallic heart valve, joint replacement, ventricular-peritoneal shunt, cardiac stent),
- Chronic pain syndromes (for example, fibromyalgia, chronic fatigue).
- Neurologic, neurodevelopmental or neurodegenerative disorders.
- Depression (requiring therapy).
- Obesity (body mass index>35).
- Malignancy.
- Use of antibiotics for any indication within the past 3 months.
- Foreign travel to areas of enteric disease prevalence within 3 months.
- High-risk sexual behaviour (examples: sexual contact with anyone with HIV/human T-lymphocyte virus/AIDS or hepatitis B/C carrier, men who have sex with men).
- Known exposure to HIV or hepatitis B/C.
- Current/previous use of injected drugs or intranasal cocaine.
- Tattooing, piercing, cosmetic botulinum toxin or permanent makeup within 120 days (as per Welsh blood transfusion guidelines).
- Recent blood transfusion, tissue/organ transplant or skin graft.
- Risk factors for variant Creutzfeldt-Jakob disease, for example, blood transfusion or transplant after 1 January 1980.

are obtained from the same donor to minimise variation. Faecal microbiota of the donated faecal samples is studied using 16S rRNA analysis. This will be used as a reference for the effect of FMT treatments, evaluation of magnitude of treatment response to FMT and durability of engraftment after FMT.

Table 2 Infectious disease screening

Blood tests	► Cytomegalovirus. ► Epstein-Barr virus. ► Hepatitis A virus. ► Hepatitis B virus. ► Hepatitis C virus. ► Hepatitis E virus. ► Syphilis. ► HIV-1 and HIV-2. ► *Entamoeba histolytica.* ► Human T-lymphotropic virus types I and II antibodies. ► *Strongyloides stercoralis.*
Faecal tests	► Detection of *C. difficile.* ► Detection of enteric pathogens, including *Salmonella, Shigella.* ► *Campylobacter, Escherichia coli O157 H7, Yersinia*, Vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, Gram-negative mutidrug-resistant bacteria. ► Norovirus. ► Antigens and/or acid fast staining for *Giardia sp* and *Cryptosporidium sp.* ► Protozoa (including *Blastocystis hominis*) and helminths.

Administration of investigational product

All three study groups will complete a 10-day course of oral antibiotics (vancomycin 500 mg; metronidazole 400 mg, rifampicin 150 mg—all taken twice daily) and bowel preparation (polyethylene glycol 2 L on the day before transplantation). The first FMT treatment dose will be commenced 48 hours after the final dose of antibiotics to preserve the activity of the FMT. Frozen FMT will be thawed over 4 hours at room temperature prior to infusion, which will subsequently be diluted to 250 mL with non-bacteriostatic normal saline prior to infusion. The subjects of groups 1 and 2, who receive FMT treatment, will also be given loperamide 4 mg orally 30 min prior to administration to maximise the chance of enema retention. Each participant receives 50 mL of enema every 15 min over 60 min. The subjects will be encouraged to retain the treatment samples as long as possible (ideally more than 1 hour).

Study setting

Recruitment will take place from clinics and endoscopy units within the Abertawe Bro Morgannwg University Health Board, Swansea. FMT will be administered at the Joint Clinical Research Facility within Swansea University.

Randomisation

Study participants will be randomised 2:2:1 by a web-based method hosted by the University of Aberdeen's Health Services Research Unit. The simple randomisation process employed in this allocation was not stratified by any factors (eg, age, gender). We aim to update the

randomisation process based on the results of this feasibility study for potential stratifying factors in phase III.

Blinding

The trial statistician, the assessing independent endoscopist and the pathologist undertaking macroscopic and microscopic disease assessments will be blinded to the treatment allocation.

Participant timeline and schedule of assessment

Figure 1 and table 3 show the follow-up schedule and assessment for the trial. At baseline the study participants will undergo assessment for disease activity with validated tools (CUCQ-32, IBDex and Mayo Score) alongside a full history and physical examination. Baseline biopsies of the rectum for 16S rRNA analysis and immunological

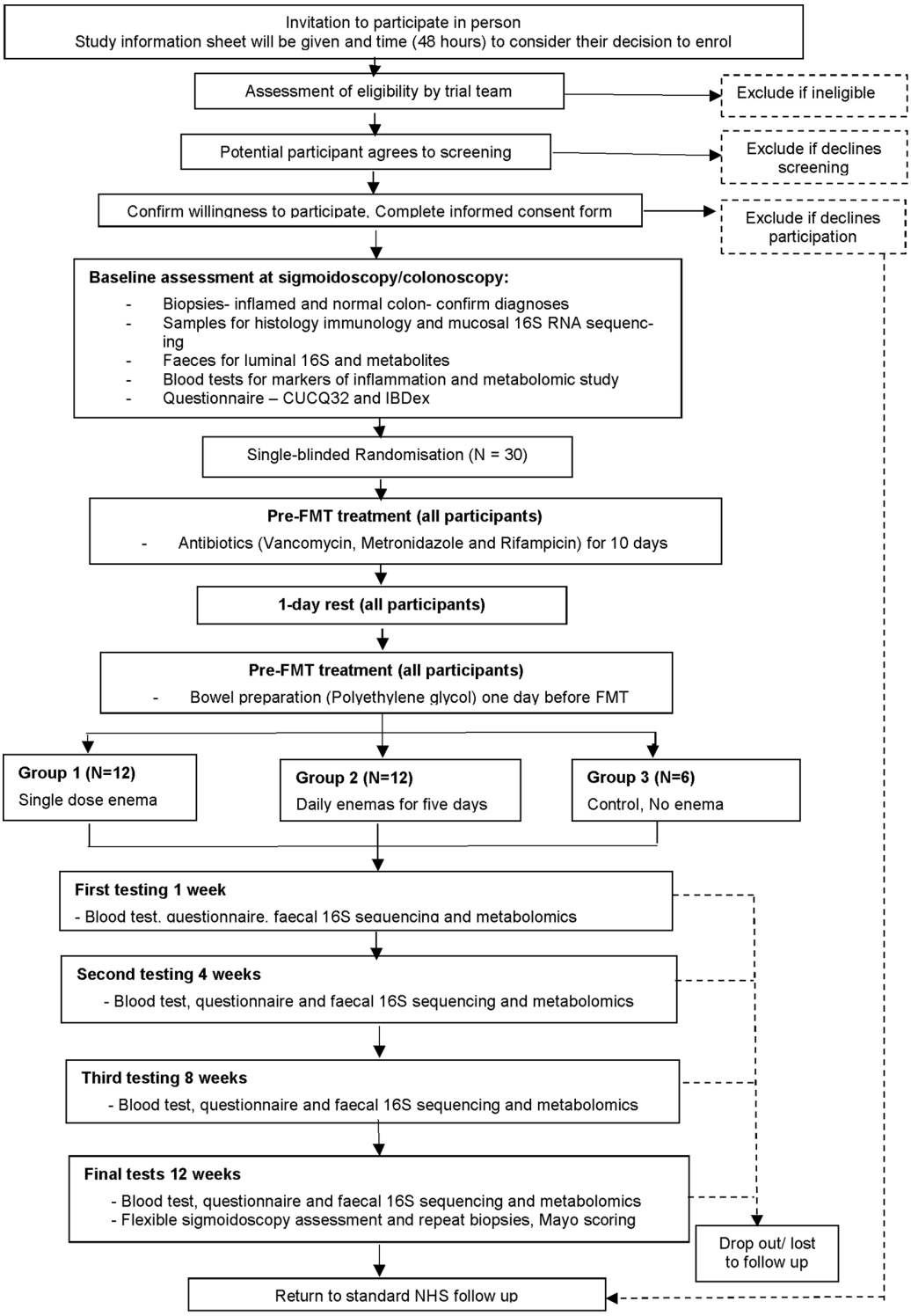

Figure 1 Study scheme flowchart.

Table 3 Follow-up schedule and assessments

	Baseline	Week 1	Week 4	Week 8	Week 12
Questionnaires					
CUCQ-32	•	•	•	•	•
IBDex	•	•	•	•	•
Mayo score	•				•
Endoscopy assessment					
Sigmoidoscopy	•				•
Rectal biopsy	•				•
Histology assessment					
Histological grading	•				•
Mucosal 16S sequencing	•				•
Mucosal IL-10	•				•
Mucosal IL-21	•				•
Blood tests					
Renal profile	•	•	•	•	•
Liver profile	•	•	•	•	•
Full blood count	•	•	•	•	•
C-reactive protein	•	•	•	•	•
Metabolomic profile	•	•	•	•	•
Faecal sample assessment					
16S sequencing	•	•	•	•	•
Metabolomic profile	•	•	•	•	•

studies (IL-10 and IL-21), faecal samples for 16S rRNA analysis and metabolomic profile, blood tests (renal function, liver function, full blood count, C-reactive protein, metabolomic profile) will be obtained. Furthermore, 16S rRNA analysis for the donors' faecal samples is performed. Subsequently, this will be studied together with 16S rRNA analysis of the participant's faecal samples for the study of durability of engraftment after FMT treatments during a 12-week follow-up period.

Follow-up visits will take place at week 1, 4, 8 and 12 for all the three study groups. Participants will undergo clinical examination, blood and faecal testing to include faecal microbiota profiling using the 16S rRNA analysis and metabolomic profile and complete disease activity scoring questionnaires (CUCQ-32 and IBDex) at baseline and thereafter at 1 week. At the final assessment (week 12), all subjects will also undertake a repeat flexible sigmoidoscopy for macroscopic assessment and biopsies for degree of inflammation or confirmation of remission. Participants who relapse or fail to improve after FMT will be offered conventional medical therapy.

Study participants will be instructed to inform the treating physician of any infectious symptom or new medical condition that develops after receiving FMT and a patient registry will be maintained.

Withdrawal

Participants may be withdrawn from the study if

- They wish to terminate treatment and/or follow-up assessments.
- Clinical features worsen during FMT or the 12 week follow-up period.
- The participant is non-compliant with the study in a manner that is either harmful to their health or interferes with the validity of the study results.
- Participants who withdraw their consent may not wish for their data to be used—if this is the case then it will be deleted.

Data collection and management

Data collection will be performed at baseline, week 1, 4, 8 and 12 as described in table 3. All data is to be recorded on the case report form (CRF) in an anonymised format against a unique participant number.

Data will be transferred to a computer database without patient identifiable data and analysed once all results have been collected. The trial database will have built in measures to assess data quality at time of input and stored securely.

Metabolic profiling

We will use both untargeted (1 hour NMR) and targeted quantitative approaches such as high-performance liquid chromatography-mass spectrometry to analyse a panel of gut microbial cometabolites involved in cell signalling, namely SCFAs, bile acids, indoles and cresols and branch

chain amino acids. This will include a novel eicosanoid assay[36] for precision measurement of pro and anti-inflammatory regulators and the use of a bile acid assay.[37] Metabolome data will be analysed by several multivariate ordinations including principal component analyses, non-metric multidimensional scaling Kruskal-Wallis independent tests, and multivariate analysis of variance with Bonferroni correction. We will create receiver operating curves for both multivariate models and individual metabolites for key clinical outcomes. Metabolic reaction networks of metabolites found differentially expressed between different transplants will be created using the MetaboNetworks software.[38]

Participant rights and confidentiality

The chief investigator will be the custodian of the data. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, National Health Service Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

There will be no patient identifiable data on the CRF and a unique participant number will be allocated. The principal investigator will hold the key to the coded number of the participants only. Only the principal investigator will have access to the patient identifiable information.

Statistical analysis

Both descriptive and exploratory data analysis will be performed. For each group, we will calculate the number of participants approached and/or assessed for eligibility, randomised and received the treatment. Thus, we will calculate the recruitment and retention rate along with the rate of adverse events. Descriptive statistics (mean, SD, 95% CI) for continuous outcomes (eg, CUCQ-32 Score, Mayo score) and raw count (n, %) for categorical outcomes (eg, renal profile, liver profile, histological grading) will be reported as per the clinical endpoints.

All these summary statistics will be provided as per baseline and other follow-ups (as appropriate to the outcome measure) and with respect to the three treatment arms. All the analysis and data preparation will be performed using SPSS v.22.0 as a validated statistical software for clinical trials.

Safety measures

An adverse event (AE) is defined as any untoward medical occurrence in a patient after administration of the study intervention (FMT) that does not necessarily have to have a causal relationship with this treatment. Serious adverse event (SAE) is any adverse experience occurring during or after FMT that results in either death, life-threatening experience or requiring inpatient hospitalisation, persistent or significant disability or incapacity. SAEs will be notified to the study sponsor within 24 hours and to the Research Ethics Committee (REC) within 15 days. AEs that are expected for patients undergoing FMT, and symptoms expected from UC, are specified in the protocol and will not require to be reported as adverse events. FMT-related AEs are procedure-related symptoms such as bloating, transient fever or abdominal discomfort as reported by previously reported studies.

Quality assurance

The research and development quality assurance officer has performed a monitoring prioritisation assessment to assess the impact of trial participation on the rights and safety of participants and the reliability of trial results. This has guided the development of procedures in the trial with respect to informed consent, confidentiality and trial monitoring. Monitoring visits to the site will be made every 3 months during the study to ensure that all aspects of the protocol are followed. The quality assurance officer will also monitor the study after the first participant has been recruited. The monitoring visit timeframe can be changed depending on the monitoring findings. A quality assurance programme is also in place to ensure adherence to the study protocol. Major and minor deviations will be collected.

Endosocopy: One of several JAG accredited gastroenterologists or colorectal surgeons from hospitals of the Abertawe Bro Morgannwg University's Health Board will perform the sigmoidoscopy assessment at baseline and week 12. The study team will ensure that the endoscopist performing the 12-week assessment is blinded to the intervention that the patient has received. Endoscopic photographs taken at baseline and at final assessment will be independently assessed by a blinded expert to provide quality assurance for this outcome measure.

Pathology: A standardised protocol based on RCPath guidelines will be used for histological assessment of the disease as per standard of care by consultant pathologists.

Patient and public involvement

Patients with UC were surveyed during the trial design stage to ascertain willingness to participate in the trial as described. All seven patients approached indicated by return of questionnaire their willingness to be recruited into the trial.

The investigators will invite IBD-specific charitable organisations and their patient representatives to help disseminate the findings of the feasibility trial and to design phase III.

Ethics and dissemination

The chief investigator will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments. Written informed consent will be obtained from all participants. SAEs will be reported to the study sponsor and the regional ethics committee.

Table 4 Uncertainties for the optimal application of faecal microbiota transplantation (FMT) in ulcerative colitis (UC)

Human gut microbiota	► Responsible pathogens and their roles. ► Microbiome profiling techniques.
FMT preparations	► Frozen versus fresh. ► Donor screening protocol. ► Preparation methodology.
Donors	► Related versus unrelated. ► Single donor versus multiple donors.
Pre-medications/preparation	► Bowel preparation. ► Antibiotics versus non-antibiotics.
FMT in clinical application	► Dose. ► Administration routes. ► FMT alone versus with other traditional medications. ► Durability of engraftment. ► Who to treat—active, remission, refractory. ► Adverse effects. ► Long-term effects and safety. ► Long-term effects after transplant.
Clinical remission	► How to assess clinical response. ► How to define clinical remission. ► When to stop FMT treatment. ► Maintenance dose required for remission. ► Postremission dietary modification.

Trial results will be disseminated through oral presentations at national conferences and through peer-reviewed publication, which will include named members of the Trial Management Group (TMG) who meet the three criteria of scholarship (design, execution, analysis and/or interpretation of the data), authorship (drafting, reviewing and revision of the manuscript) and approval (approving the manuscript to be published). Participants in the study will be given a copy of the results and a final report will be written by the TMG for the funding body and the REC. Results will be used to aid in the development of a definitive phase III trial.

DISCUSSION

A recently published systematic review on the usage of FMT in IBD concluded that overall 36% of patients with UC achieved clinical remission (a total of 41 studies and four randomised controlled trials (RCTs)).[39] Meta-analysis, which included 4 RCTs (a total of 140 individuals), demonstrated that FMT was significantly linked to clinical remission with a pooled OR of 2.89, 95% CI of 1.36 to 6.13 and p-value of 0.016.

The number of FMT studies with high methodological quality has increased of late, yet the optimal conditions for durable FMT engraftment and maximal remission are presently unclear for UC. Table 4 summarises the current knowledge gaps in the application of FMT in UC.

Current studies are difficult to interpret as there is no universally agreed definition of remission as an endpoint in UC clinical trials to date.[40] Furthermore, a lack of homogeneity of clinical trial protocols makes comparison of such studies more difficult to comprehend and these clinical trials are no exception. Moreover, different clinical trials use different patient groups, donors, treatment dose, routes, frequency and pretreatment medications. These multiple variables make the comparison of studies very challenging, although all studies appear to demonstrate promising results for the usage of FMT in active UC. Finally, and most importantly, patients recruited in published RCTs had been on previous conventional medical therapy until given the FMT treatment if not being assigned to further medical treatment. This makes the interpretation of the magnitude of treatment response to FMT very difficult.

Although the efficacy of FMT in UC appears to be promising, more clarity is required around optimal treatment conditions through a rigorous study. This study will estimate the efficacy of rectally administered FMT in treatment naïve patients towards the design of a definitive trial. This phase II study allows us not only to estimate the magnitude of treatment response to FMT in UC, but also to determine the changes and durability of engraftment of the gut microbiota after FMT treatment. Furthermore, we will study the dose response by comparing one dose only and five daily doses towards establishing the optimum dosage of rectally administered FMT treatment for UC. There is a fundamental lack of mechanistic data to support the use of FMT in clinical practice. Bacteria represent a diverse and highly active chemical engine that creates a suite of biologically active small molecules through secondary metabolism. The critical function of these target metabolites in the initiation and maintenance of systemic inflammation remains poorly defined and this trial will provide a detailed insight into the role

of the gut microbiome in UC therapy that have the potential to stratify care in the future and improve the precision of this intervention.

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Contributors DAH and ADR are responsible for the idea for the trial. MJ, ALC, ADR, MDH, SI, JK, APD, PER, TSW, GJJ, JGW and DAH have drafted and the manuscript and/or provided critical revision. ADR, MDH, SI, JK, APD, PER, TSW, GJJ, JGW and DAH have made substantial contributions to the conception and design of the work and subsequent protocol revisions. MJ, ALC, ADR, MDH, SI, JK, APD, PER TSW, GJJ, JGW and DAH all agree to be accountable for all aspects of work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent Not required.

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