Safety and efficacy of faecal microbiota transplantation in patients with acute uncomplicated diverticulitis: study protocol for a randomised placebo-controlled trial

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Abstract

Background: Little is known about the involvement of gut microbiota in the disease course of diverticulitis and the potential benefits of manipulating the gut milieu. We propose to conduct a randomised placebo-controlled feasibility trial of faecal microbiota transplantation (FMT) given as capsules to patients with acute uncomplicated diverticulitis.

Objectives: The objective is primarily to investigate the feasibility of clinical safety, explore efficacy associated with FMT in this patient population, and examine changes in patient-reported quality of life and the composition and function of the gut microbiota.

Design: Study protocol for a randomised placebo-controlled trial.

Methods and analysis: Participants with acute, uncomplicated diverticulitis, as confirmed by computed tomography (CT) scan, will be recruited from Odense University Hospital (Denmark) and randomly assigned to either the intervention group or the control group. The intervention group will consist of 20 patients who receive encapsulated FMT. The control group will also consist of 20 patients, receiving placebo capsules. *Primary safety endpoint*: Patient safety is monitored by (a) the number of re-admissions and (b) the number of adverse events within 3 months of FMT/placebo; *Primary efficacy endpoint*: Reduction in the proportion of patients treated with antibiotics within 3 months following FMT/placebo; *Secondary outcome*: Change from baseline to 3 months in the GI-QLI questionnaire. Results will be analysed using an intention-to-treat approach. Adverse events or unintended consequences will be reported.

Ethics and discussion: This is the first study to investigate the safety and efficacy of FMT in patients with acute uncomplicated diverticulitis. The project has the potential to broaden the knowledge and literature on the role of the intestinal microbiota in diverticulitis, and we believe it will elevate our understanding of cause and effect.

Trial registration: Informed consent is obtained from all participants. The study is approved by the regional ethics committee (ref. S-20230023) and the Danish Data Protection Agency (ref. 24/2435). The trial was registered on clinicaltrials.gov (NCT06254625) on 10th February 2024.

Keywords: acute uncomplicated diverticulitis, faecal microbiota transplantation, placebo, randomised controlled trial

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Introduction

Diverticula are protrusions of the mucosal wall,[1] and appear predominantly on the left side of the colon in the Western world.[2] Colon diverticulosis (CD) is a prevalent condition, and its global incidence appears to be rising due to an ageing population, an increasing number of younger individuals affected[3,4] and improved diagnostic modalities.[5] Of the general population, 17.5% are estimated to have CD,[6] with 70% of individuals over 80 years of age having CD,[7] and the lifetime prevalence is estimated up to 72%.[8,9] Symptoms may include abdominal pain, changes in bowel habits and bloating. The prevailing hypothesis suggests that CD arises from chronic constipation, resulting in heightened intraluminal pressure, colonic muscular hypertrophy and mucosal herniation.[3] However, the aetiology remains incompletely understood, involving complex interactions involving genetic factors, gut microbiota, diet, obesity and smoking.[10–17] Fewer than 5% of individuals with diverticulosis progress to acute diverticulitis.[6,18] The reason for this remains unclear.[19] The path from CD to diverticulitis occurs when a diverticulum becomes inflamed and is believed to involve diverticular obstruction and micro-trauma, alterations in the gut microbiome, local tissue ischaemia and micro-perforations.[11,20,21] Acute diverticulitis is one of the most common conditions encountered by surgeons in the acute setting[22] and typically, patients with acute diverticulitis present with acute pain, tenderness in the left lower quadrant, fever and elevated inflammation parameters.[23] Acute diverticulitis is episodic, but can, however, become complicated by perforation and formation of abscesses,[14,24,25] leading to disease progression to a chronic or complicated state.[6] Therefore, the disease is classified as either uncomplicated diverticulitis or complicated diverticulitis,[22,26] depending on the findings on computed tomography (CT) scan, with over 70% of the acute presentations of diverticulitis being uncomplicated.[3] Traditionally, diverticulitis has been treated with antibiotics due to its association with bacterial overgrowth in the large intestine.[25] However, recent studies are exploring the clinical evidence supporting the use of antibiotics for uncomplicated diverticulitis.[20,27]

In healthy individuals, the gut microbiota forms a balanced community of bacteria, viruses, archaea and eukaryotes crucial for maintaining host homeostasis.[28] It plays an influential part in regulating colonic mucosal defences and both local and systemic inflammation.[29] Various research has looked into the association between different pathologies and the impact of the gut microbiota.[30–32] However, the role of microbiota in diverticula formation is still debated. Dysbiosis in diverticulosis may lead to mucosal barrier breakdown and microbial dislocation, possibly causing diverticulitis.[33,34] Recent studies provide evidence supporting the role of altered colonic microbiota, showing compositional changes in diversity and abundance, as well as localised imbalance, in the microbiome of inpatients with diverticulitis compared to controls.[29,35]

Rationale

If the alterations in the gut microbiota can initiate the pathway to diverticulitis in patients with diverticulosis, then modifying the colonic microbiota could be a potential treatment option. Currently, faecal microbiota transplantation (FMT) has emerged as a novel therapeutic approach to restore the balance of intestinal microbiota.[36] FMT is considered a safe and effective strategy to restore a healthy diversity of the gastrointestinal microbiota in patients with recurrent *Clostridioides difficile* infections (CDI),[37] with >90% demonstrating clinical resolution.[38] Furthermore, positive responses of FMT in the treatment of inflammatory bowel disease (IBD) have been observed,[39–41] and FMT is also being tested in various other gastrointestinal as well as non-gastrointestinal diseases.[42] To the best of our knowledge, no study has yet investigated the efficacy and safety of FMT in patients with diverticulitis.

Objective

The objective of this study is primarily to evaluate the feasibility in terms of clinical safety of one FMT or placebo administered via capsules in patients with acute uncomplicated diverticulitis at Odense University Hospital (Odense/Svendborg). In addition, efficacy will be explored as well as changes in patient-reported quality of life and the composition and function of the gut microbiota.

We hypothesise that FMT could be a safe and feasibly administered treatment for diverticulitis by restoring pathogenic alterations in the colonic

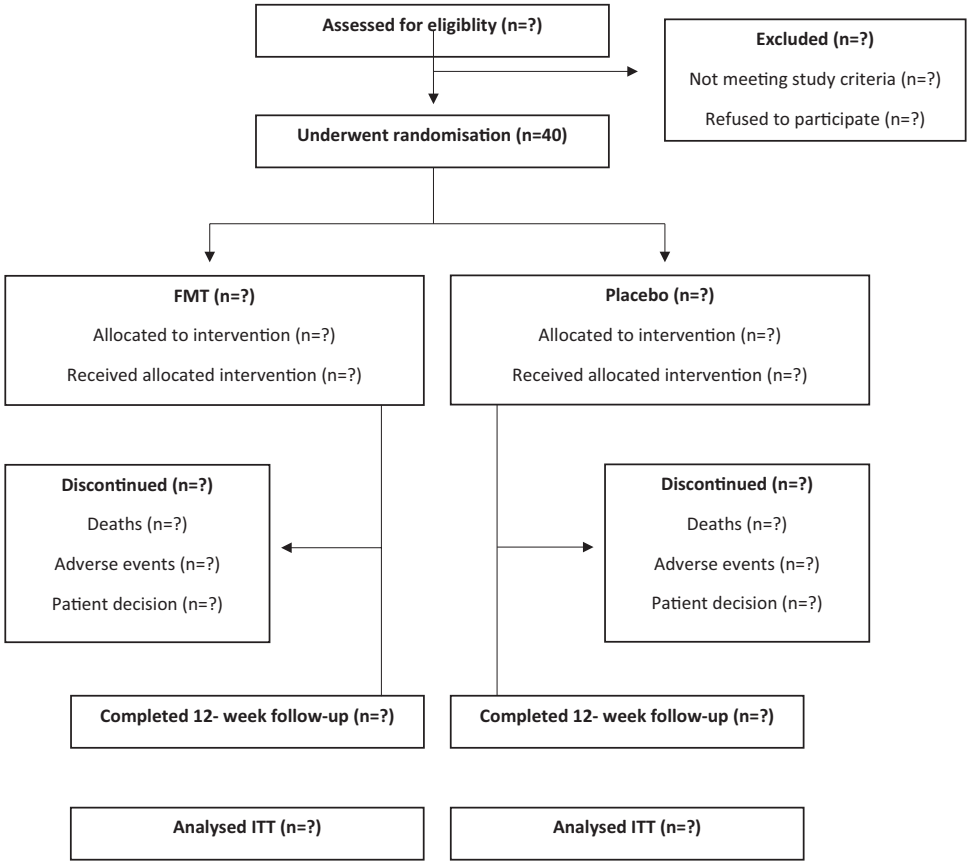

Figure 1. Flow diagram of the randomised, placebo-controlled trial.
FMT, faecal microbiota transplantation; ITT, intention-to-treat.

microbiome, and thereby could prevent recurrent diverticulitis (Figure 1).

Methods and analysis

Trial registration

Clinicaltrials.gov, NCT06254625. Registered 10th February 2024.

Trial design

This is a randomised, placebo-controlled, patient, physician and outcome-assessor blinded, 3-month trial. Patients are assigned randomly in a 1:1 ratio to receive FMT or placebo. The primary outcome assessment will occur after 3 months at the primary endpoint evaluation. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline was consulted when preparing the manuscript for this clinical trial protocol (Supplemental Material).

Participants

The study population will consist of patients with acute uncomplicated diverticulitis admitted to the Surgical Department at Odense University Hospital (Odense/Svendborg). Eligible patients will be identified during hospital admission and assessed for inclusion in the study. To be eligible, the patients must have uncomplicated diverticulitis, as confirmed by CT scan.[43] After hospital discharge, eligible patients will be offered the opportunity to participate in the study. All participants will be required to provide both verbal and written informed consent before they are included in the study. Invitees will also be informed that they have the option to decline FMT treatment on the day of intervention. Patients who do not want to participate will be treated according to the treatment guidelines in the department. The recruitment started in April 2024 and will continue until a total of 40 patients are included (Figure 2).

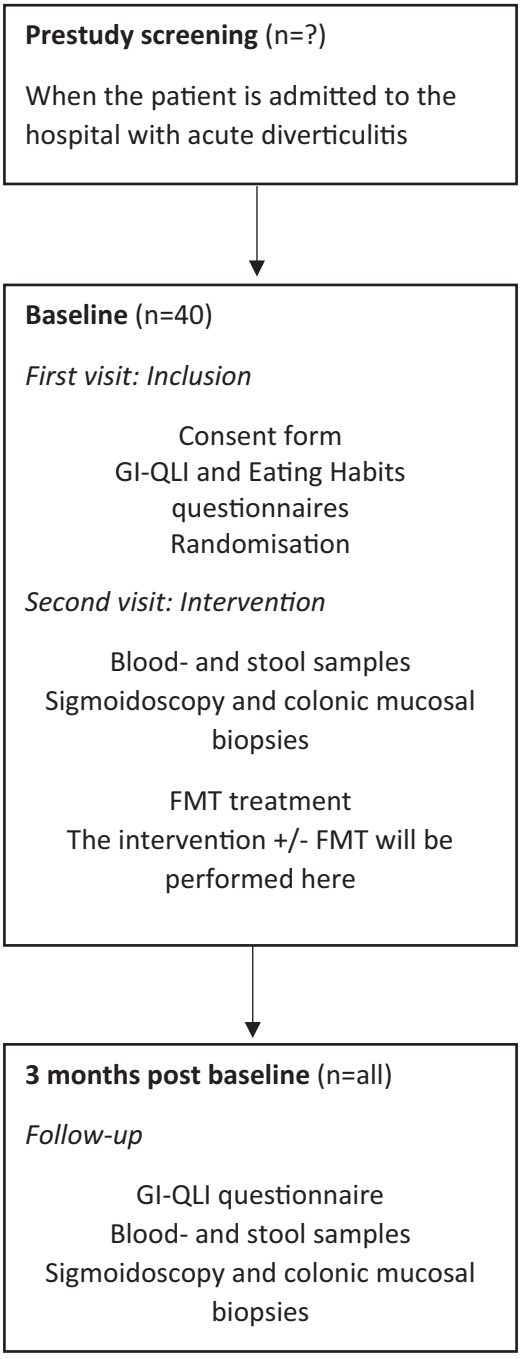

Figure 2. Timeline and characteristics of each participation visit.
FMT, faecal microbiota transplantation; GI-QLI, Gastrointestinal Quality of Life Index.

Inclusion criteria

The study will include a total of 40 patients, all of whom have CT scans confirmed acute uncomplicated diverticulitis, and fulfil the following eligibility criteria:

1. Age above 18 years of age at the time of enrolment.
2. Confirmed diagnosis of acute uncomplicated diverticulitis based on in-hospital CT scans. The condition is defined as an inflammation limited to the colon, not extending to the peritoneum, and findings of diverticula, increased density of pericolic fat or thickening of the colonic wall.[22] To ensure that patients are comparable, the diagnosis of uncomplicated diverticulitis is chosen on the CT scans for inclusion, rather than the patient's symptoms, need for antibiotic treatment, c-reactive protein (CRP) levels or white blood cell counts, as these features are not specific for diverticulitis alone, and clinical suspicion alone is only correct in 40%–65%.[26,44]
3. Participants must be admitted to Odense University Hospital in Odense or Svendborg for the diagnosis and initial management of acute uncomplicated diverticulitis.

Exclusion criteria

- Unable to comprehend the study information and provide informed consent due to cognitive impairment, language barriers or any other reason.
- Patients with disabilities that hinder their ability to comply with the study procedures, either cognitively or physically.
- Complicated diverticulitis, as defined by the presence of abscesses, fistulas, perforations or other severe complications on the CT scan.
- CT findings indicating the need for colonoscopy to perform biopsy (e.g. suspected cancer) or for polyp removal.
- Other gastrointestinal diseases, for example, IBD.
- Known immunodeficiency disorders or undergoing immunosuppressive therapy.
- Impaired renal function.
- Previous treatment with FMT.
- Breastfeeding individuals.
- Known allergies to the active substances administered in the trial, for example, bowel preparation before sigmoidoscopy.
- Individuals currently participating in other clinical trials involving investigational drugs or interventions.

Stool donors

The recruitment of stool donors will occur from the South Danish Transfusion Service & Tissue Centre, Department of Clinical Immunology, Odense University Hospital. All donors are voluntary and no compensation fee is offered.

Stool donors must be active members of the Danish blood donor corps, age 25–55 years, body mass index of 18.5–25 kg/m^2 and have an average alcohol intake of <7 (women) and <14 (men) units per week. The donors cannot drink alcohol within a week of the donation, eat any extremely low-calorie or high-calorie diets, have any intake of systemic medication (including antibiotics and non-steroidal anti inflammatory drugs (NSAIDs) 6 months prior to donation) or be in a stressful life period.[45,46] The donors must be healthy, both mentally and physically, as assessed by a screening questionnaire and through conversation with a doctor. Each potential donor will go through a thorough and careful screening process including stool analyses for faecal calprotectin, enteric pathogens, parasites, *Entamoeba histolytica/dispar* (DNA), *Cryptosporidium* (DNA), *Giardia* (DNA), sapovirus (RNA), rotavirus (RNA), human astrovirus (RNA), human adenoviruses (DNA) and noroviruses (RNA).[45] Furthermore, the donor's blood will be tested for CRP, white blood cell count, haemoglobin, albumin, alanine aminotransferase, estimated glomerular filtration rate, Epstein-Barr virus (IgM), cytomegalovirus (IgM), hepatitis A, B, C and E, tuberculosis (QuantiFERON-TB Gold test), syphilis, HIV and human T-lymphotropic virus 1/2 (HTLV1/2).[45] Lastly, the process includes a faecal *Helicobacter pylori* antigen test, and a urine test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (DNA/RNA).[45] If the donor passes the screening tests, they will donate stool for the next month, and then have to pass the screening program once more before the stool can be released for transplantation.[45,46] Each patient in the active treatment group will only receive FMT from one donor.

Interventions

Overall study interventions. The FMT will be a stand-alone strategy for patients with acute uncomplicated diverticulitis, as they otherwise only would receive conservative pain management as treatment, according to the guidelines from the Surgical Department.

Active and placebo comparator. Patients will be randomised into two study arms with an allocation ratio of active-to-placebo treatment of 1:1. The active treatment group ($n=20$) will receive encapsulated FMT with healthy donor faeces suspension. The control group ($n=20$) will receive identical appearing placebo capsules, containing brown coloured glycerol.

Preparing the FMT suspension. Donors will collect stool at home and within 1 h transport faeces in a cooling bag to the Department of Clinical Immunology where the FMT products are processed and stored. The donor stool is processed by dilution with a sterile saline solution, homogenisation and sieve to create a homogenous suspension. The stool suspension is centrifuged to separate the microbiota fraction from the remaining suspension and glycerol is added to maintain the viability of the microorganisms until it is ready for administration. The FMT suspension is then filled into empty capsules (1–2 g per capsule). The FMT capsules will be stored at −80°C until use.[46,47]

The FMT procedure. The FMT will take place within 4 weeks of the inclusion. The patients will meet at the out-patient clinic after a 6-h fast. They will be offered one dose (10 mg) of metoclopramide 30 min before ingesting the capsules. The use of capsule-based FMT is a clinically effective approach to restore intestinal microbiota composition in CDI and capsules are now the preferred form of administration. This non-invasive oral delivery provides an easy route of administration for clinicians and patients. Fifteen to thirty FMT capsules are ingested with apple juice or Coca-Cola Light. The capsules must be ingested within 4 h of thawing. Each transplant, comprising 25–30 capsules, is prepared from 50 g of faeces originating from one donor. The placebo group receives placebo capsules. The patients will only receive one treatment with FMT or placebo capsules.

Outcomes

Primary outcome measure. Primary efficacy endpoint: Reduction in the proportion of patients treated with antibiotics within 3 months following the experimental intervention (FMT/placebo).

Primary safety endpoint: Patient safety is monitored by (a) the number of re-admissions and (b) the number of adverse events (AEs) within 3 months of FMT. AEs will be monitored and noted as the number of AEs in each group; the number of AEs in each group leading to withdrawal; the number of patients with a least one AE in each group and the number of serious AEs.

If the patients present with unacceptable disease activity during the 3-month trial period, they will, depending on the clinical presentation, be handled according to the department's guidelines for diverticulitis, and be characterised as FMT treatment failure according to the primary efficacy endpoint and primary safety endpoint.

Secondary outcome measure. Secondary endpoints: Change from baseline to 3 months in the Gastrointestinal Quality of Life Index (GI-QLI) questionnaire.

The GI-QLI is a 36-item multidimensional scale questionnaire, covering symptoms, and physical, emotional and social dysfunction relating to gastrointestinal diseases or their treatments. It is an appropriate and validated tool to assess health-related quality of life in clinical studies in patients with gastrointestinal disease. Each of the 36 items is scored on a five-point Likert scale and summed to get an overall GI-QLI score (Table 1).[48]

Collection of data on demographics. At the baseline inclusion, data will be noted about the patient's age, sex, BMI, possible comorbidities, current use of medication, number of admissions to the hospital with diverticulitis, ASA score and blood sample laboratory findings at the current admission with acute uncomplicated diverticulitis.

The eating habits questionnaire is filled out by the patients at baseline, to detect potential differences in the eating habits of the patients, and map out food that potentially could influence the disease and its progression.

Biological samples (biobank) and planned laboratory analyses. The patients will collect fresh stool samples, using the EasySampler stool collection kit within 24 h prior to the visit. Samples will be stored in the patient's freezer until transported to the study site. During transportation, the samples will be kept on ice, and on arrival be transferred to the biobank and stored at −80°C immediately. The same material for biobanking will be collected at both baseline and 3 months follow-up. We will investigate the faecal microbial composition and microbial activity using metagenomics, culturomics, proteomics and metabolomics. As antibiotics are known to influence and alter the gut microbiota, we will take into account if the patients have received this in the 3 months follow-up period, when analysing the faecal samples, and consult the existing literature on the subject, when investigating the changes in faecal microbial composition.[49] Faecal samples will also be collected if the patient is admitted in need for antibiotics, prior to the treatment.

At baseline, patients will have blood tests taken, and this will be done also at the 3-month follow-up. We will investigate markers of intestinal permeability such as plasma/serum zonulin, zonulin-related protein, calprotectin, intestinal fatty acid binding protein (I-FABP), CD14 and lipopolysaccharide (LPS)-binding protein. Furthermore, we will conduct analyses of inflammation-related plasma proteins using the OLINK 92 inflammation panel (link) or a similar protein assay.

The patients will have the opportunity to undergo a sigmoidoscopy at baseline and at the 3-month follow-up, where a biopsy (0.1 g/1 mm × 1 mm) will be obtained from the gastrointestinal mucosa of the patient's colon. The purpose of this procedure is to examine the microenvironment in the diverticula, focusing on inflammation or other microbiological abnormalities. Both paraffin-fixed tissue for immunohistochemistry and tissue stored in RNALater for proteomics will be collected. All brush biopsies, blood samples and faecal samples will be stored in a research biobank for current and future research with the patient's consent.

Safety

The treatment that is being offered here is identical to the treatment that is given as a routine to patients with CDI. It is the same product, amount and procedure. This treatment has been used routinely at Odense University Hospital for the last 7 years since 2017. Short-term minor AEs related to FMT are common and appear immediately following FMT, and include abdominal discomfort, vomiting, flatulence, transient fever and

Table 1. Protocol schedule and procedures.

Activity/assessment	Pre-study screening	Baseline	3 Months post-baseline
Patients	*n* = ?	*n* = 40	*n* = all
Screening log	x		
Inclusions/exclusion criteria	x		
Collection of data on demographics		x	
Informed consent form		x	
Randomisation		x	
GI-QLI questionnaire		x	x
Eating habits questionnaire		x	
C-reactive protein (mg/L)	x		
Faecal calprotectin		x	x
Faecal microbiota analysis		x	x
Sigmoidoscopy and mucosa brush biopsy		x	x
Intervention (±FMT)		x	
Stool and blood samples (biobank)		x	x
Intestinal permeability analysis (zonulin, LPS-binding protein, etc.)		x	x
Serious AE forms	x		

AE, adverse events; FMT, faecal microbiota transplantation; GI-QLI, Gastrointestinal Quality of Life; LPS-binding protein, lipopolysaccharide-binding protein.

diarrhoea.[50] The AEs of FMT have been investigated in several systematic reviews; one searched over a 20-year period and found a total incidence rate of 19% FMT-related AEs, in 129 relevant studies with a total of 4241 patients, and 5688 FMT courses. Diarrhoea (10%) was the most frequently reported AE, followed by abdominal discomfort (7%), and the rates of FMT-related serious adverse events (SAEs) were 1.4%, and all were in patients with mucosal barrier injury.[51] Another systematic review of 61 studies, with a total of 5099 patients and 5551 FMTs found an overall rate of SAEs related to FMT of only 0.65%. The individual SAEs were sepsis or sepsis-like conditions (0.19%), aspiration pneumonia (0.27%) and bowel perforation (0.20%).[52] This study also pooled the minor AEs and found constipation reported in 1.03%, abdominal pain in 1.66%, nausea in 0.92%, vomiting in 0.34%, flatulence in 0.70% and febrile episodes in 0.33%.[52]

Although most of the knowledge on FMT-related AEs is from patients who have suffered from CDI and/or IBD, these findings show that FMT is in general considered safe, especially with a strict screening of donors, and even elderly patients with poor medical conditions as well as immunosuppressed patients have been proven to tolerate the procedure well.[52–56]

In the present study, safety will be monitored and evaluated through open assessment of AEs. Observed or reported AEs are recorded by the investigators and the patients will be monitored until the AE is resolved, stabilised or it is shown

that the study intervention was not the cause. The severity of AEs will be graded by The National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03 (NIH publication #09-7473). If the patients experience any gastrointestinal side effects (nausea, vomiting, abdominal pain, number of stools per week, stool type (Bristol Stool Chart) blood or mucus in stool), they will be registered once a week for the first month, and weeks 8 and 12, following the randomised intervention. Based on the system organ class and preferred term, the occurrence rates of all treatment-related AEs will be organised into tables, and additionally, all fatal and/or serious AEs, significant treatment-emergent AEs and AEs leading to withdrawal from the study, will also be provided in tables.

Statistical considerations

When designing this trial, no prior data for FMT efficacy in patients with diverticulitis were available. As this study mainly focuses on the feasibility of FMT in patients with uncomplicated diverticulitis, no formal power calculation has been performed.[57] The sample size of 20 individuals in each group has been a consensus estimate within the author group aiming to balance the risk of AEs, available logistics and the economy. The study will be terminated when 40 patients have been included in total, which is anticipated to be achieved within a 12-month period.

Randomisation, allocation concealment and blinding

The randomisation, (1:1) to receive either FMT or a placebo, will be managed by the randomisation tool in the REDCap database hosted by Odense Patient Data Explorative Network (OPEN) at Odense University Hospital. The eligible patients will sign the informed consent form and then be assigned randomly in permuted blocks of varying sizes of 2 and 4, according to computer-generated random numbers, to which the trial team is blinded. They will furthermore be stratified on age and divided into five groups, to ensure comparability between randomisation groups. Outcome assessors, care providers and patients will be unaware of the group assignments, and the participants will be linked by de-identified codes to their data during the study, to ensure confidentiality. A designated coordinator will implement the randomisation of each patient and the allocation will be concealed. The coordinator will arrange with The Department of Clinical Immunology, which will then deliver the products, along with the transplantation journal (whether FMT or placebo), to the core department of the patients. If a circumstance arises where it is essential for further management of the patient to know of the treatment allocation, the designated coordinator will reveal the assigned intervention to the treating doctor, but as far as possible the outcome assessors, trial care providers and patients will remain blinded. Any cases of unblinding will be reported and registered.

Data collection, management and confidentiality

Data on participants will be collected from electronic patient files, questionnaires and through conversations with the patients. Only relevant information for conducting the study is extracted. Data are entered into a central OPEN REDCap database via a secure web-based electronic clinical report form. Questionnaires are sent out from the database directly to the patients and therefore filled out directly into the database. Any data obtained during the examination for inclusion will be entered directly into the database. Study data access will be restricted, and to control the access a password system will be used. Information will be covered by confidentiality, for example, about the patients' health, private matters and biobank materials. The information will continue to be so after the project ends, this also includes material that will continue to be stored in one of the research biobanks. Gathered information on participants is protected according to the 'Legislation on the Processing of Personal Data' and the 'Danish Health Care Act'. The authorisation from Danish Data Protection Agency has been secured (ref. 24/2435).

Statistical methods

All randomised participants will be included in the intention-to-treat (ITT) analysis set population. This set will be analysed according to the ITT principle: participants assigned to a randomised treatment group will be monitored, evaluated and analysed within the context of that group, regardless of their compliance with the planned treatment. Both the efficacy analysis and the safety analyses will primarily be performed on the full analysis set (FAS) population, defined as

all patients who were randomly allocated to a group, underwent baseline measurements and received transplants (independent of the group). Subjects will contribute to the FAS analyses as randomised. If the FAS and ITT populations differ, then the efficacy analyses will be repeated using the ITT population. While random assignment helps to prevent selection bias, it will not ensure that the groups have identical baseline characteristics. Therefore, the study groups will be compared and presented at baseline in terms of demographics and clinical features, allowing readers to evaluate their similarities. The summaries of continuous variables will include *N*, mean, SD, median, interquartile range and range, and summaries of frequencies and incidences will include counts, percentages and the total number of participants in the corresponding arm. As this is a feasibility study with no formal sample size calculation and no formal primary null hypothesis, only descriptive statistics without formal statistical testing will be presented.

Our strategy for ITT analysis with incomplete observations aligns with White et al.[58] recommendations:

1. Aim to follow up on all randomised participants, even if they withdraw from allocated treatment.
2. Primary analysis performed using all observed data.

The exploratory efficacy endpoints will be discussed based on descriptive summaries of those who received the allocated treatment. During follow-up, any medical treatments that potentially could modify the intestinal microbiota will be reported, but not affect the statistical analysis. Differences in demographics between the groups will be discussed based on the summary of characteristics. Participants can be lost to follow-up, and this will be participants who are not examined at the follow-up, and the reason will be registered. Data will be analysed with the STATA statistical package (V.18; StataCorp).

Patient and public involvement

Before study initiation, we discussed the content of the trial protocol and participation information with the patient representative associated with our research unit. According to the received feedback, there were made corrections and clarifications.

Ethics and dissemination

This clinical trial was designed as a proof of concept and will be performed in agreement with Good Clinical Practice (GCP) standards, in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration (64th, 2013). The trial has been registered with ClinicalTrials.gov (NCT06254625) and important protocol modifications will be updated here. The study has been approved by the regional ethics committee (ref. S-20230023) and the Danish Data Protection Agency (ref. 24/2435), and data are handled in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act.

As the FMT procedure is not classified as a medical intervention by the Danish Health and Medicines Authority, no GCP auditing is legally required. We will, however, report any potential side effects and AEs to the Ethics Committee yearly, and any Suspected Unexpected Serious Adverse Reactions will be reported to the Ethics Committee within 7 days so that the Ethics Committee can choose to terminate the trial early, based on these reports. Patients injured in connection to a medical clinical trial will be compensated by the Danish Patient Compensation Association. Although donor faecal microbiota is not yet classified as tissue by the Danish Health Authorities, all steps of the stool donor recruitment, stool donation and FMT preparation will be in accordance with the Danish Tissue Law to ensure that the quality and safety standards laid down in the Danish Legislation BEK nr 764 of 26 May 2015 (implementing Directive 2004/23/EC) are met. Frozen stool components will be clearly labelled with a unique donation code based on the ISBT 128 coding and labelling system, and the release of the final product will adhere to the standards for tissue and blood donation.[46]

Due to uncomplicated diverticulitis being a common disease, and no treatment with convincing clinical evidence, the identification of new treatment modalities is essential. Recent studies have shown that the use of antibiotics in this patient group no longer holds any clear evidence,[3,44] and all patients with acute uncomplicated diverticulitis, who are participating in this study, would not receive any other treatment. Furthermore, the role of gut microbiota in the disease course of diverticulitis and whether manipulation of the gut

milieu can be beneficial in this condition is still relatively unknown. The findings will contribute to the advancement of knowledge in the aetiology and treatment of diverticulitis, and a more thorough understanding of how the intestinal microbiota influence our health. Furthermore, the study will establish a research biobank, which will contribute as a valuable resource for current and future microbiome and gastrointestinal research. Consequently, when considering the advantages and disadvantages, it is essential to conduct this trial from a scientific and ethical perspective. Dissemination will occur through publications in international peer-reviewed journal(s) and presentations at conferences. Positive as well as negative results will be published.

Discussion

In recent years, there has been a growing interest in the underlying cause of colon diverticulitis, onset and management of the disease. The hypothesis of aetiology is that acute inflammation arises in a diverticulum due to lesions caused by faecolith obstruction, leading to bacterial infection and micro-perforations.[7] This theory is being challenged by the hypothesis of multifactorial pathogenesis, including the important impact of the gut microbiota.[59] This involvement has been described as a breakdown of the mucosal barrier and displacement of microbes within the diverticulum, particularly in areas that are compromised by inflammation, which can lead to thinning or perforation of the epithelium.[33,34] This has led to the investigation of whether microbiota analysis could predict the development of diverticulosis and/or diverticulitis, and hereby result in a quicker intervention, prevention of complications and perhaps even targeted therapies for microbiota modulation.[21] We expect that our double-blind, randomised, placebo-controlled trial will shed light on this highly relevant topic.

A recent case–control study comparing the microbiome of acute diverticulitis patients with controls found lower diversity in the microbiome of acute diverticulitis compared to control samples, as well as an increase in *Fusobacteria*, *Prevotella* and *Paraprevotella*, and a lower abundance of commensal bacterial families like *Lachnospiraceae*, *Ruminococcus* and *Faecalibacterium*.[29] *Prevotella* has shown pathogenic impact, like increased cytokine production and chronic colonic inflammation observed in HIV individuals,[60,61] whereas both *Fusobacterium* and *Paraprevotella* have been linked to colorectal cancer pathogenesis.[62–64] The genera decreased in abundance including species producing short-chain fatty acids (SFCAs), which are essential molecules that fulfil 70% of the energy needs of colonocytes, the cells lining the colon.[65,66] An abundance in their presence is crucial for the metabolic requirements of the cells, which then upholds the intestinal barrier, facilitating improved tight-junction integrity and production of mucin, thereby ensuring effective protection against harmful substances from the gut lumen to the bloodstream, thus contributing to overall gut health and homeostasis.[67,68] One study found depletion of these microbiota members in both diverticulosis and symptomatic uncomplicated diverticular disease patients, compared to controls[33]; furthermore, studies have described the depletion in the pathogenesis of inflammatory bowel syndrome (IBS),[69] in patients with diverticulitis,[70] and IBD,[71,72] as well as an association with lower dietary fibre and slower stool transit time.[73] Furthermore, SFCAs increase lymphocytes by enhancing metabolism, thereby supporting antibody production and plasma-cell differentiation[74], which is linked to anti-lipogenic, anti-inflammatory and anti-carcinogenic actions, hence the impracticality of depletion.[33] On the whole, the combination of increased and decreased microbiota genera and their by-products suggests that alterations in the intestinal barrier, anti-inflammatory protective agents, the immune system and pathogenic interactions can lead to a pro-inflammatory state, allowing for microbiota–host interactions and the potential development of diverticulitis.[29]

Furthermore, a recent systematic review investigated whether alterations in the microbial composition could be involved in the pathophysiology of diverticulosis.[73] The highest taxa-level differences were found in the *Enterobacteriaceae* family, showcasing a higher diversity of microbiota between diverticulitis and control samples,[59] this was supported in another study with significantly higher ($p = 0.043$) levels of *Enterobacteriaceae* in colonic mucosa of diverticular disease versus controls.[75] However, one study, comparing diverticulitis cases to IBD and IBS controls, found that *Firmicutes* and *Ruminococcaceae* were twice as high, but *Enterobacteriaceae* and *Porphyromonadaceae* were almost absent,[76] and another study saw no differences in the

microbiota of diverticulosis and controls; however, patients were assessed on whether they later developed acute diverticulitis (2.8%) and these cases now showed abundance increase in *Comamonas* genus ($p=0.027$) compared to the asymptomatic remainders.[73,77] Consequently, the review concludes no clear evidence linking diverticular disease to changes in microbial abundance, as the identified differences were diverse, primarily from variations in the methodological approaches used in the reviewed studies. These differing methodologies limit direct comparison, and there are ongoing speculations on the best sample collection as well as the best technique for analysis.[73]

This is the first time that the efficacy and safety of FMT are being investigated in patients with acute uncomplicated diverticulitis, and there is little literature about FMT and diverticulitis. One case report described a patient with multiple admissions with acute diverticulitis, resulting in two colectomies, but still continued admissions with the disease, resulting in treatment with antibiotics, and the development of CDI. In this case, treatment with FMT resulted in full remission of both diverticulitis and CDI.[78] This evokes both the possible positive effects of FMT in this patient group but also the question of antibiotics. This is an ongoing debate, and recently expert panels have adjusted their recommendations, looking to selective antibiotic usage over routine administration,[79,80] after findings showing no difference in time to recovery or episodes of recurrence.[20,27] Therefore, this patient group would not receive any other treatment, and would, on an individual basis, benefit the most from participating in new experimental clinical trials.

As this will be the first time FMT is performed on patients with diverticulitis, only patients with acute uncomplicated diverticulitis will be included. We acknowledge that patients with complicated diverticulitis represent a more affected patient group. However, we do not differ between patients with a new onset of the disease or patients with a long history of diverticulitis and many re-admissions, thus hoping to detect treatment effects of clinical importance. As of now, it is unknown whether one FMT will be sufficient or whether it should be repeated to normalise the alterations of the microbiota. However, in the present proof-of-concept clinical trial, the FMT is the implementation of a new treatment, and therefore it has been decided to perform only one FMT (or placebo treatment) in each patient, from a pragmatic and ethical point of view. We are well aware that this may not be adequate to achieve long-lasting effects, and studies on patients with recurrent CDI have shown that FMT administered multiple times increased the likelihood of clinical response, as well as a rise in efficacy from 84% with a single FMT to 91% with repeated FMT.[40,41,81,82] Nevertheless, we hope that one FMT procedure will be sufficient to document the effects on the participants.

The selection of stool donors is a critical issue, considering the mapping of normal microbiota composition,[83] and identifying the optimal donor microbiota for the treatment of diseases remains a challenge. The microbial content of the stool may differ between each FMT procedure, and it cannot be fully standardised due to variability; however, to meet this challenge, samples from each donation will be collected and stored to determine the composition of microbiota in each donation, in case some prove more effective than others. Furthermore, the lifestyle of the recipient may also be of importance in the interactions between the received microbiota and the microbiota of the host, with factors like pathogenic and commensal microbes and environmental variables playing a role. There is, however, uncertainty about how to define the optimal lifestyle and a lack of knowledge on how different lifestyles may interfere with the microbiota, so no predefined lifestyle regime has been made for the participants after the FMT. Interestingly, it is speculated how diet may influence the disease course of diverticulitis,[3,15] so we decided that all participants fulfil an eating habit questionnaire at the beginning of the trial, to further analyse this hypothesis.

In conclusion, this trial has the potential to substantially expand the growing body of literature on the role of intestinal microbiota in diverticulitis, and we further anticipate that it will enhance our understanding of cause and effect.

Declarations

Trial status

Protocol version number 1.3. Recruitment began on the 29th of April 2024 and will approximately be completed in march 2025.

Ethics approval and consent to participate
Approved by the regional ethics committee (ref. S-0230023). Written informed consent to participate will be obtained from all participants.

Consent for publication
Not applicable.

Author contributions
Camilla Thorndal: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Maja Skov Kragsnaes: Methodology; Project administration; Supervision; Validation; Visualisation; Writing – original draft; Writing – review & editing.

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Dorte Kinggaard Holm: Conceptualisation; Methodology; Project administration; Resources; Supervision; Visualisation; Writing – original draft; Writing – review & editing.

Rene dePont Christensen: Methodology; Supervision; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author, CT. The data are not publicly available due to restrictions, for example, their information could compromise the privacy of research participants.

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Supplemental material
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Appendix

List of abbreviations

AE	adverse event
CDI	*Clostridioides difficile* infections
CD	colon diverticulosis
CT	computed tomography
CI	confidence interval
FMT	faecal microbiota transplantation
GDPR	General Data Protection Regulation
GI-QLI	Gastrointestinal Quality of Life Index
GCP	Good Clinical Practice
ITT	intention-to-treat
IBD	inflammatory bowel disease
OR	odds ratio
OPEN	Odense Patient data Explorative Network
SCFA	short-chain fatty acid