A randomised, placebo-controlled cross-over study of the effect of chronic feeding of methylcellulose and inulin on inulin fermentation in people with IBS-C

Final version 1.0
17 February 2025

Short title: Effect of methylcellulose on inulin fermentation in IBS-C

Acronym: TEMPO

Trial Registration: ISRCTN (entry coming soon)

IRAS Project ID: 349409

Trial Sponsor: University of Nottingham

Sponsor reference: *25001*

Funding Source: MRC

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SYNOPSIS

Title	A randomised, placebo-controlled controlled cross-over study of the effect of chronic feeding of methylcellulose and inulin on inulin fermentation in people with IBS-C
Acronym	TEMPO
Short title	The effect of methylcellulose on inulin fermentation in people with IBS-C
Chief Investigator	Prof Robin Spiller
Objectives	(A) To test the effect of methylcellulose given over 3 weeks in people with IBS-C on measures of intestinal function using MRI, inulin fermentation pathways and microbiota compared to maltodextrin. (B) To test whether 3 weeks chronic inulin and methylcellulose (or maltodextrin) ingestion in people with IBS-C causes an adaptation to intestinal function as assessed by MRI, inulin fermentation pathways and gut microbiota.
Statistical methods	Baseline differences between the two arms will be compared to assess for any issues with randomisation. The differences in each measurement after the intervention period compared to baseline for each patient will be calculated and then summarised with mean and 95% confidence intervals. If differences are not normally distributed median and interquartile ranges will be used. The mechanistic primary analysis will compare colonic gas 0-6 hour AUC 3 week value in the MC compared to the placebo arm. Other differences including baseline AUC between the two arms will be assessed adjusted for repeated measures. The secondary end points will be tested in a similar approach. If differences are not normally distributed then non parametric methods will be used. The primary clinical analysis will compare BSFS after 3 weeks intervention on methylcellulose versus placebo.

ABBREVIATIONS

AE Adverse Event

AUC Area under the curve

CI Chief Investigator overall

CRF Case Report Form

DMC Data Monitoring Committee

GCP Good Clinical Practice

IBS-C Irritable bowel syndrome with predominant constipation

ICF Informed Consent Form

MC methylcellulose

MRI Magnetic resonance imaging

NHS National Health Service

PI Principal Investigator at a local centre

PIS Participant Information Sheet

REC Research Ethics Committee

R&D Research and Development department

SAE Serious Adverse Event

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Low FODMAP (fermentable oligo-, di- and mono-saccharides and polyhydric alcohols) diets have revolutionised management of irritable bowel syndrome (IBS). FODMAPs cause abdominal discomfort, bloating and flatulence by their rapid colonic fermentation which produces gas and distends the colon. Low FODMAP diets, although widely adopted, are expensive, inconvenient and may have negative effects on health by excluding high fibre foods that protect against cardiovascular and metabolic diseases (obesity, type II diabetes, hyperlipidemia) and colon cancer. This project aims to use methylcellulose (MC) to trap FODMAPs, specifically inulin, in a gel, thereby limiting bacterial access and modifying fermentation to produce less gas.

We have previously shown this to occur acutely in IBS patients by co-administered psyllium, a viscous and gel-forming fibre, with the FODMAP inulin but whether this would work when consumed regularly is unclear[1]. We are using a specific form of MC which can form gels at body temperature and unlike psyllium is not fermentable. Furthermore it is a product widely used in food manufacturing and unlike psyllium can be easily modified and produced in very large amounts to precise composition and quality. We want to determine whether the effect of psyllium on trapping inulin, therefore making it less available for bacterial fermentation, is unique or will also be found with methylcellulose[2]. Previous studies have shown methylcellulose is non-inferior to psyllium in reducing colonic gas when given as a single dose but we want to determine its effect when given as a regular daily supplement.

Our previous studies point to the importance of habitual FODMAP intake which is likely to alter the microbiota, favouring those bacteria that can efficiently utilise fructans. We want to understand whether chronic feeding of inulin along with MC, a gel-forming dietary fibre which persists in the colon, will significantly alter the tolerance to inulin relative to chronic feeding of inulin with a placebo, maltodextrin. We have previously shown that maltodextrin is rapidly absorbed in the small bowel and does not alter colonic contents[3].

Initial experiments in healthy volunteers (HVs) with breath hydrogen response to inulin as the endpoint have co-administered MC to define the optimum cellulose for subsequent use (manuscript in preparation), which showed MC to be non-inferior to psyllium. We have further recently performed a pilot MRI study and a study using a gas-sensing capsule in HVs, which show methylcellulose reduces colonic gas while increasing small bowel water and speeding transit. All of these studies administered one dose of the fibre supplements only (15 g in 375 ml) and looked at acute effects. We are now investigating what effect a longer term use of the fibre will have. The study period of 3 weeks was deemed to be sufficient to enable changes in microbiota composition[4].

We plan to provide inulin and methylcellulose for daily consumption by people with IBS-C who will be randomised at the screening/consent visit to consume either active (methylcellulose) or placebo (maltodextrin) intervention for two periods of three weeks each. The intervention will be divided into 3 portions to be taken before breakfast, lunch and supper. In the first 10 days, the portions will contain 2.5 g of both inulin and intervention (active or placebo) in 62.5 mL water. In the remaining 11 days, the portions will contain 5 g of both inulin and the same intervention in 125 mL water. After a 4 week washout period participants will repeat the 3 week feeding schedule with the alternative intervention.

We will use MRI at baseline and at the end of the 3 week intervention to assess changes in colonic gas, volume, small bowel and colon chyme water, and whole gut transit utilising marker capsules with high MRI contrast, as previously published [35]. We will measure breath hydrogen and methane as measures of transit and of fibre fermentation by colonic

microbiota. We will collect stool samples at baseline and after 1 week and at the end of the 3 week intervention to monitor the expected changes in microbiota and to test fermentation properties *in vitro*. We assume that ingesting MC gels and the hypothesised reduction in colonic gas will be associated with relief of both constipation and gas-related symptoms, but this study is not powered for these outcomes. As an indication, symptoms will be assessed daily along with stool form and frequency documenting weekly average for the Bristol stool form score, number of daily bowel movements and number of complete spontaneous bowel movements (using the Study Day Symptom Questionnaires during study days and the Study Period Diary during the intervention periods). At baseline before the start of the intervention, the patient cohort will be characterised to confirm they are representative of other IBS patients using the IBS Symptom Severity Score (IBS-SSS) and Hospital Anxiety and Depression Scale (HAD-S).

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of the study is to determine whether incorporating inulin into a methylcellulose gel can reduce gas production in people with IBS-C as measured using MRI.

PRIMARY OBJECTIVE

To test the effect of methylcellulose given over 3 weeks in people with IBS-C on measures of intestinal function using MRI, inulin fermentation pathways and microbiota compared to maltodextrin.

SECONDARY OBJECTIVES

To test whether 3 weeks chronic inulin and methylcellulose (or maltodextrin) ingestion in people with IBS-C causes an adaptation to intestinal function as assessed by MRI, inulin fermentation pathways and gut microbiota. We will record gas-related symptoms but the study is not powered for this endpoint.

DETAILS OF PRODUCT(S)

Description

A) Interventions: Study participants will be given two food interventions in a randomised order, 1) a firm gel containing inulin and methylcellulose and 2) a liquid containing inulin and maltodextrin (placebo). They will be prepared in our food production facility (University of Nottingham) and stored at 4°C in our fridges and then the participants' fridges.

All interventions will be prepared to the same concentration of inulin and intervention (methylcellulose) or placebo (maltodextrin), which is based on a volume of 375 mL water with either;

1) 15 g inulin + 15 g methylcellulose in a pot providing a final firm texture after heating
2) 15 g inulin + 15 g maltodextrin in a pot for a final drinkable texture

For all fibre products, an identical base drink containing inulin (15 g / 375 mL), stevia sweetener (0.1875 g / 375 mL) and flavouring (0.0375 g / 375 mL) is prepared by addition of all ingredients to freshly boiled water and with continuous mixing until all ingredients are dissolved. For this 3 week intervention we are providing a range of flavourings for variety and to accommodate any specific dislike.

For methylcellulose gel: MC (15g / 375 mL) is added to the base drink while hot (above 70°C) with continuous mixing so as to ensure it disperses within the base drink. The mixture

is then allowed to cool to ambient temperature (20°C) where the solution thickens but remains pourable.
For maltodextrin drink: Maltodextrin (15 g / 375 mL) is added to the base drink while hot (above 70°C) with continuous mixing to ensure it disperses within the base drink. The mixture is then allowed to cool to ambient temperature (20°C) where the solution thickens but remains pourable.

During the first 10 days of the intervention, only half of the supplement will be given for each dose, i.e. 2.5 g of MC or maltodextrin and 2.5 g of inulin in 62.5 ml water t.d.s. for a total daily 7.5 g of each fibre in 187.5 ml water. The full dose (5g MC or maltodextrin and 5 g of inulin) will be given during the remaining 10 days omitting the doses on the last day before the MRI scans to ensure a similar low baseline breath hydrogen on each study day.

B) Transit markers: Study participants will also be receiving 5 transit markers before each of the 4 study days. These are inert plastic capsules filled with a low concentration gadolinium solution that enables them to be tracked on MRI. Capsules are produced by injection moulding and then filled at the SPMIC. They are stored at room temperature. Participants will be instructed to swallow the transit markers 24h before the first MRI scan. These markers are not CE-marked. We have used them repeatedly (314 times) over the last ten years without any adverse events.

C) Whole gut transit will additionally be compared using a recently introduced 'blue muffin' test. On day 18 of each intervention arm, participants will eat two 'blue muffins' and record the date and time of eating it as well as when they notice a discoloration of their stool. Blue muffins are simple muffins with a high amount of blue food dye baked in. They will be produced in our food production facility (University of Nottingham) and then stored frozen before dispensing to participants.

Manufacture

A) Interventions used for either on-site study days or at-home chronic feeding periods will be prepared at the Food Production Facility, School of Biosciences, University of Nottingham. Manufacture, packaging/labelling and storage will be overseen by Co-I food scientist Dr Joshua Reid and will be performed by staff with the relevant food safety training.

B) Capsules for the transit markers will be produced by injection moulding by Xometry (https://xometry.uk/injection-moulding/) out of inert acetal plastic, which is certified for biocompatibility (DuPont Delrin PC652 NC010). The capsule measures 20 mm long by 8 mm diameter, slightly smaller than the standard 00 pill size. Each capsule is filled with 0.4 mL gadolinium solution (15 µM Gadoteridol (ProHance, Bracco, Milan, Italy) diluted in distilled water with blue food dye (Sainsbury's)) and the filling hole closed with a small piece of acetal using histoacryl tissue adhesive (B. Braun, Sheffield, UK). All transit markers undergo a leak test in 37°C water for 48h where markers are discarded if any filling leaks out as made visible by the food dye included.

C) A vegan muffin recipe will be prepared at the Food Production Facility, School of Biosciences, University of Nottingham from standard supermarket ingredients. Manufacture, packaging/labelling and storage will be overseen by Co-I food scientist Dr Joshua Reid and will be performed by staff with the relevant food safety training.

Packaging and labelling

A) The mixture is poured into a plastic pot so that the contents of the pot are approximately 375 mL (or equivalent mass of 420 g). The pots are sealed using a thermal press. Labels

stating production date, flavour and whether MC or placebo supplement (coded as a dummy, e.g. A/B) will be stuck on each pot.

B) Transit markers will be disinfected for 15 minutes (Milton Sterilising Fluid, Milton, Nantes, France). Each dose of 5 markers will be sealed in a small ziplock food freezer bag (Tesco) and labelled including production date.

C) One portion, i.e. two muffins, will be packaged into each small ziplock food freezer bag (Tesco) and labelled including production date.

Storage, dispensing and return

A) Pots are then stored at 4°C and are to be consumed within four weeks. Participants will be given 10-12 days' supply of pots at a time. Any unused pots (due to unforeseen circumstances) are to be disposed in general waste and do not need to be returned.

B) Transit markers are stored at room temperature for up to four months. They will be dispensed to participants before each study day. Any unused markers (due to unforeseen circumstances) are to be disposed in general waste and do not need to be returned.

C) Muffins are stored at -20°C for up to 3 months. They will be dispensed to participants at the product pick-up halfway through the intervention period.

Known Side Effects

In some participants the intervention (MC as well as inulin itself) might cause mild bloating, some abdominal discomfort, and flatulence, especially at initiation of intervention. These symptoms are usually mild and quickly resolved. All gastrointestinal symptoms will be recorded in daily symptom questionnaires (using the Study Day Symptom Questionnaires during study days and the Study Period Diary during the intervention periods). IBS itself commonly presents as abdominal pain with bloating and flatulence, therefore it will be difficult to assign the symptoms' causation.

STUDY DESIGN

STUDY CONFIGURATION

Single centre, 2-way randomised control cross-over study. People with IBS-C will undergo both interventions (MC and placebo) in a randomised order. Outcomes will be compared in paired analyses.

Mechanistic outcomes

Primary endpoint

- Colon gas volume (ml) as analysed using MRI, area under the curve over 6 hours after a 15 g inulin challenge with or without MC (hereafter described as "AUC 0-6h") at the end of the 3 week intervention period

Secondary endpoints

- Colon gas volume (ml) as analysed using MRI, AUC 0-6h, comparing the endpoint before vs after the 3 week intervention

The following endpoints will be considered in the comparisons a) MC vs placebo at the end of the 3 week intervention and b) within each arm before vs after the 3 week intervention:

- Whole gut transit time (hours) of transit markers as analysed using MRI
- Small bowel and colon water (ml) AUC 0-6h as analysed using MRI
- Small bowel motility baseline and at 2 hours post ingestion
- T1 in AC AUC 0-6h (seconds) as analysed using MRI
- Colon volumes AUC 0-6h (ml) as analysed using MRI
- Breath hydrogen production (ppm) AUC 0-24h
- Oro-caecal transit time measured (hours) using breath hydrogen
- Breath methane production (ppm) AUC 0-24h
- Stool sample gas production (ml) over 48h after *in vitro* fermentation
- Stool sample short chain fatty acid production (mol/L) over 48h after *in vitro* fermentation
- Microbiota composition determined using 16S sequencing of stool samples.
- Intervention tolerability as recorded at the second study day of each arm
- Stool form and frequency - weekly average 1) Bristol stool form score (BSFS), 2) daily bowel movements, 3) complete spontaneous bowel movements to explore how the physiological outcomes relate to patient bowel habits
- Symptom severity to explore how the physiological outcomes relate to patient symptoms
- Participants will be characterised using IBS-SSS and HAD-S at baseline and by whole gut transit using blue muffin while on treatment.
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Safety endpoints

The intervention has been piloted in healthy volunteers and is not expected to cause significant side effects beyond flatulence and some abdominal discomfort, symptoms which IBS patients will already be experiencing. The study methods (i.e. the MRI and breath testing) are in routine clinical practice and in research. We will allow dose reduction in the event that the increase in dose after the first 10 days causes unacceptable side effects. Thus we do not expect serious adverse reactions anticipated from participation in the study and no specific safety endpoints.

Stopping rules and discontinuation

There are no specific stopping rules for the study.

Participants will be told that they are free to withdraw at any time, without giving a reason. It will be explained that data collected about them, in the form of images and questionnaires, will need to be retained and we will seek their consent to use those data in analysis of the study.

RANDOMIZATION AND BLINDING

We will use randomisation and double blinded allocation by a member of staff who is not part of the study team using a randomisation sequence generated from http://www.jerrydallal.com/random/permute.htm.

Maintenance of randomisation codes and procedures for breaking code

Fibre supplements will be labelled either A or B for MC or placebo according to the concealed randomisation code.

The staff member using the randomisation sequence will have a database showing each participant's intervention. Blinding will only be broken when data has been analysed. The

supplements are not expected to cause any medical emergencies but should any AE be recorded that requires treatment, the PI will be informed of the current intervention. It is in their discretion as a consultant gastroenterologist whether to unblind the participant and whether they should discontinue the study. The study team will not be unblinded in this case. Any code breaking will be recorded including the participant's ID, date and reason for unblinding.

TRIAL/STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: The study will start recruitment on 1/4/2025 or after this time point, when ethical approval has been obtained. It will close by 31/3/2027. The total duration is therefore a maximum of 24 months.

Participant Duration: Each participant will typically be enrolled for four months from recruitment, allowing time to schedule MRI scan days, 3 weeks of the first intervention arm followed by 4-8 weeks wash-out and another 3 weeks for the second intervention arm.

End of the Study

The end of the study will be when the participants have completed the study (expected end maximum of 18 months after starting) and all their samples have been analysed (expected to be at least 6 further months).

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The trial is an investigation of physiological mechanisms, rather than an assessment of efficacy, so the trial setting is in an academic environment, and participants will be selected to optimise interpretation of the mechanistic data and avoid confounding. We will exclude children, older people who are more likely to have confounding conditions such as diverticular disease, those with relevant co-existing conditions such as significant intra-abdominal pathology, and those whom the PI judges will be unable to complete all aspects of the study.

Potential participants will be identified through the Digestive Diseases services at Nottingham University Hospitals NHS Trust. These centres will be for identification only. The initial approach will be through a letter to all IBS-C patients who appear to fulfil eligibility criteria from a member of the patient's usual care team. In this letter, patients are invited to get in touch with the investigators. Information about the trial will be on display in the relevant clinical areas. We will also write to our large cohort of patients who have participated in previous studies and have indicated their willingness to be contacted again about future research.

General advertisement for participants will be done on all campuses of the University, including the Cripps Health Centre (primary care) by poster or e-poster. We will also publicise the study via the department's social media presence. Potential participants will be

advised to contact the Nottingham Digestive Diseases Centre or Sir Peter Mansfield Imaging Centre. They will then be called back by a member of the study team. If further recruitment is required we will engage with the Clinical Research Network as the trial will be eligible for adoption.

The investigator or their nominee from the research team will inform the participant of all aspects pertaining to participation in the study. They will provide a paper or electronic version of both the summary and the full version of the Participant Information Sheet (PIS), advising that they might read the summary PIS first, then the full PIS if they are still interested in taking part, to minimise time commitment. In all cases a paper copy of the full PIS will be provided prior to final consent. Potential participants will also be provided with the documents Restrictions Information and MRI scanning information and Volunteer Safety Screening Questionnaire.

This small mechanistic trial does not have the resources to support access to translation services throughout research days. Participants also need to interpret English language versions of questionnaires. On this basis we have stipulated a language requirement for entry into the trial. Since the intervention involved offers no therapeutic benefit, this does not disadvantage excluded parties.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Fulfilling Rome IV criteria for IBS-C for at least 3 months[6]
  Abdominal pain at least one or more days per week.
    - Pain associated with two or more of the following:
    - Related to defecation
    - Associated with a change in frequency of stool
    - Associated with a change in form (appearance) of stool
    - Abnormal bowel movements are predominantly (>25%) constipation, Bristol stool form scale Type 1 or 2 and <25% are Bristol stool form scale Type 6 or 7
- Has been given a diagnosis of IBS by a medically qualified doctor
- Aged 18 – 65 years
- Able to give informed consent
- Agrees to consume the meals provided
- Agrees to not smoke during the breath hydrogen sampling period
- Agrees not to change their diet during the study (being on a low FODMAP diet will not be an exclusion).

Exclusion criteria

- Pregnancy, lactating, or planning pregnancy during the course of the investigation declared by candidate
- History declared by the candidate of pre-existing gastrointestinal disorder other than IBS-C that may affect bowel function including but not limited to:
    - Inflammatory Bowel Disease

    - Coeliac Disease
    - Pancreatitis
    - Gallstone disease (biliary colic, cholecystitis; asymptomatic presence of gallstones permitted)
    - Complicated diverticulitis (asymptomatic presence of diverticula permitted)
    - Cancer of the gastrointestinal tract
    - Gastroparesis
    - Other functional gastrointestinal disorders will be permitted as they frequently co-exist with IBS.
- Reported history of previous resection of the oesophagus, stomach, or intestine (excluding appendix)
- Intestinal stoma
- Have contraindications for MRI scanning i.e. metallic implants, pacemakers, history of metallic foreign body in eye(s) and penetrating eye injury
- Unable to lie flat and relatively still for less than 5 minutes
- Any medical condition potentially compromising participation in the study e.g., diabetes mellitus, respiratory disease limiting ability to use breath hydrogen analyser, known intolerance to one of the test substances
- Has a body mass index (BMI) value less than 18.5 or greater than 35
- Will not agree to follow dietary and lifestyle restrictions required
- Unable to stop opiate use or planning to change medication which might alter GI motility.
- Mebeverine, calcium channel antagonists, selective serotonin reuptake inhibitors, low dose tricyclic antidepressants, antihistamines, and oral contraceptive pill will be recorded in the CRF but will not be an exclusion criteria provided no change in dosage is planned during the study period.
- Participants who have taken antibiotics or probiotics within the last 4 weeks
- Poor understanding of English language
- Participation in night shift work the week prior to the study day. Night work is defined as working between midnight and 6.00 AM
- Anyone who in the opinion of the investigator is unlikely to be able to comply with the protocol e.g., cognitive dysfunction, chaotic lifestyle related to substance abuse
- Having taken part in a research study in the last 3 months involving invasive procedures or an inconvenience allowance.

Expected duration of participant participation

Study participants will be participating in the study for 4 months.

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis. Withdrawn participants will be replaced and the study will end when 22 participants have completed it.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the

participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

STUDY TREATMENT AND REGIMEN

Overview

This is a randomised cross-over study in which 22 participants will receive both the methylcellulose and the placebo intervention in random order. Both arms are structured the same, with a baseline study day (SD1) followed by 3 weeks of study product intake and ending in a second study day, SD2 identical to SD1. For pragmatic reasons, SD2 will be 19-23 days after SD1, to facilitate scanner bookings. Every attempt will be made to have a 21d interval between SD1 and SD2. Participants will fill in questionnaires throughout the intervention periods. The two intervention periods will be separated by a 4-8 week wash-out period**.**

The study consists of up to 9 visits to the Sir Peter Mansfield Imaging Centre (SPMIC), University of Nottingham.

The first visit (in person or online as detailed below) will be to take consent, assess eligibility by the participant answering questions and record baseline covariates of interest. Four visits will be MRI study days, where participants will undergo a series of MRI scans and other assessments. Four visits are to drop off and pick up study materials, some of which can be done by mail (packaging and postage provided by the Research Team) if preferred.

We will send emails, text messages and/or schedule telephone calls

- To check eligibility at the end of the 7-day stool diary
- On the day before each study day: remind of study day appointment, to follow dietary restrictions and overnight fast, to take transit markers.
- After 10 days intervention to remind patients to take their supplements and to increase the dose
- with a further call 2-3 days later to confirm the higher dose is acceptable or to advise dose reduction if needed
- On Day 18 reminder to take blue muffins and omit supplements the day before the MRI scan.

Figure 1 demonstrates patient flow through the study. Figure 2 shows the activities that will take place on each study day.

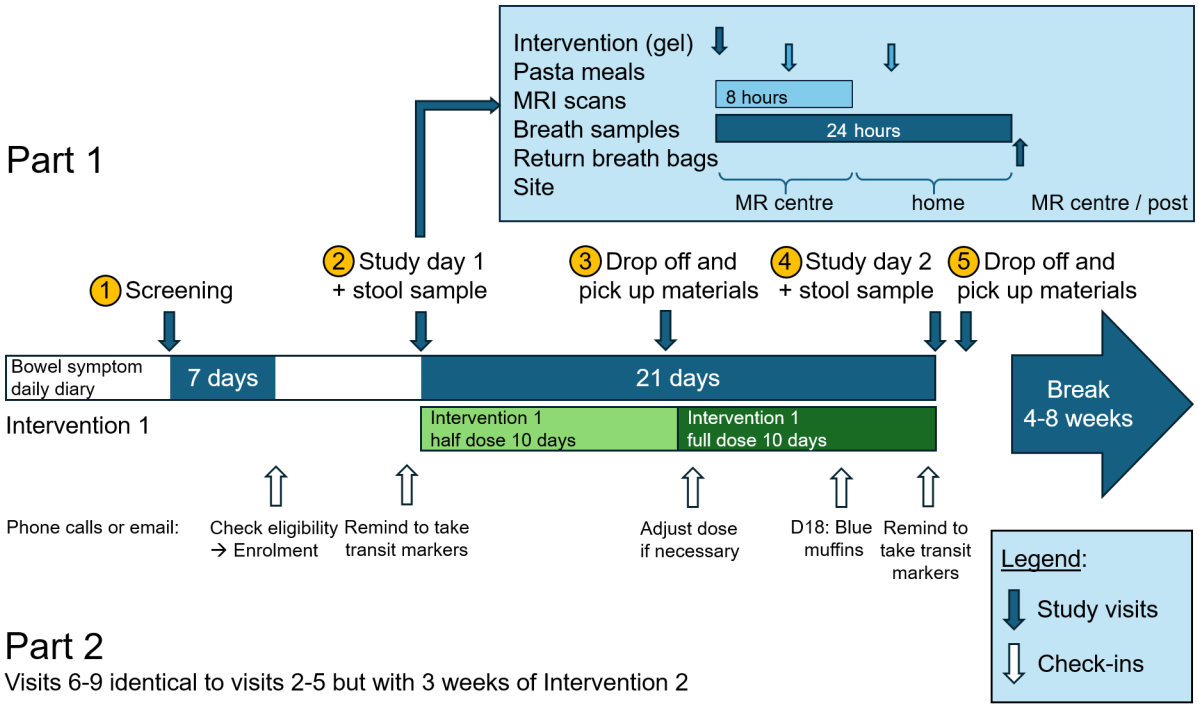


Figure 1: Study design overview.

Screening

The screening visit can be in person at the SPMIC or, if the participant prefers, online. If it occurs online, the participant will sign an online form (https://forms.office.com/e/bz0U8JrEbh) to indicate their consent to be screened for the study before history taking and the 7 day stool diary to confirm their eligibility. They will then sign the study consent form when they arrive for their first study day at the MRI centre. Any potential participants who were not eligible to take part in this study will not be enrolled. If their IBS is in remission at the time of completing the 7 day Screening Stool Diary and therefore do not fulfil the criteria for IBS (abdominal pain at least one day per week associated with at least two of the following: defecation; change in stool frequency; change in stool form; as well as >25% bowel movements are Bristol stool form scale Type 1 or 2 and <25% are Bristol stool form scale Type 6 or 7) they will be invited to repeat the Screening Stool Diary when their symptoms have returned.

The screening and consent visit will last around 30 minutes. The researcher will confirm that the potential participant has understood the information sheet and answer any remaining questions. Participants will be asked whether they consent to take part (written consent if this visit is in person; online form if this is an online meeting). If so, the participant will then be assessed for eligibility against the criteria previously set out. If eligibility is confirmed, then participants will be asked for details of current medication use including contraception, smoking status, and significant past medical history. Height and weight will be recorded. Participants will complete the IBS symptom severity scale (IBS-SSS) and the Hospital Anxiety and Depression Scale (HAD-S). This is needed to characterise the patients and confirm that they are representative IBS patients and that our findings can be generalised to other IBS sufferers. Participants will complete the MRI safety form to ensure safety in the scanner and will complete the Abnormal Scans form to provide the name of their GP to a radiologist, should their scans show any abnormalities. Participants will be given a link to a food frequency questionnaire provided by Monash University (see document CNAQ FFQ) to complete before the end of the

study, which will give information on their habitual FODMAP intake which may be relevant to their response to inulin.

At the end of the screening visit participants will be given a stool kit and a set of 5 transit markers. If the screening visit is online, these materials will be posted.

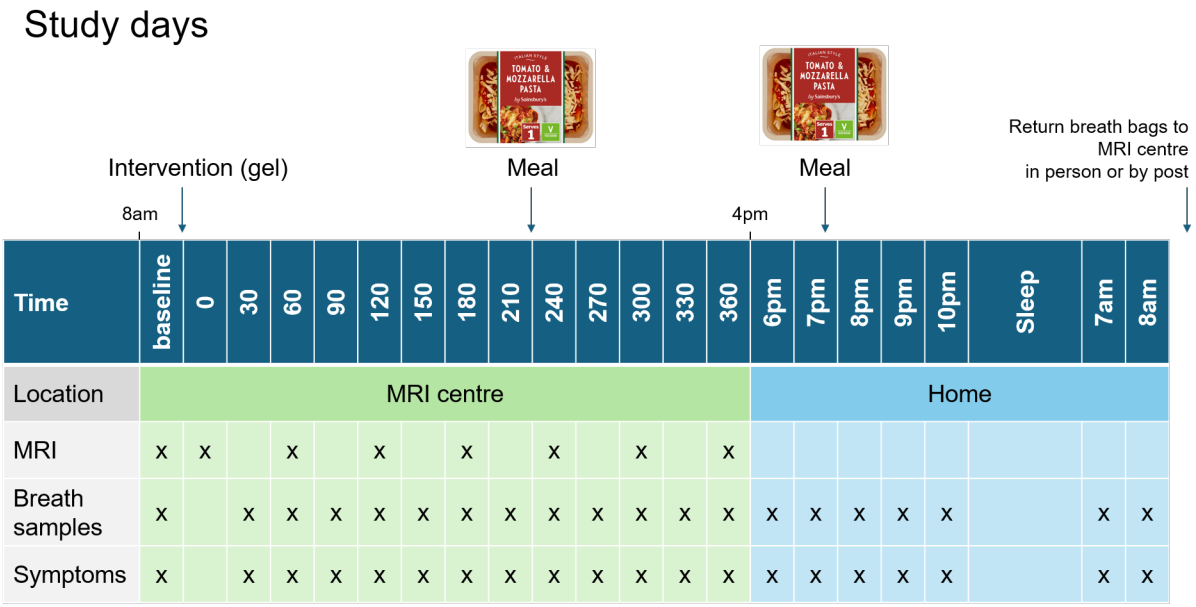
Participants will then begin a 7-day screening diary of bowel habit and symptoms. This will be used to confirm frequency of IBS symptoms and IBS subtype. Participants will complete the Rome IV diagnostic questionnaire as part of their eligibility assessment. If there is a discrepancy between diary data and participant report on the Rome IV questionnaire, then the PI may decide to repeat the 7-day diary or exclude the patient. To reduce participant burden, it will be acceptable to return completed diaries by post (prepaid envelope), by electronic communication (scan or photo), or in person.

Participants will also be informed that their GP will be contacted, both to inform them of the subject's participation and to confirm medical details where required.

Once eligibility has been confirmed, the Participant will be enrolled and randomised to a sequence of interventions. Participants will be asked to minimise their intake of fermentable carbohydrates on the day preceding each of these visits in addition to moderate tea and coffee and alcohol intake. This means that for the day before Study Day 2 they will omit the intervention. A dietary advice sheet will be provided.

MRI Study Days

MRI study days will take place in the SPMIC, University of Nottingham main campus. Participants will fast from 8 pm on the evening before the Study Day. Water will be permitted after 8 pm up to 3 hours before their scans. They will attend the study day for about 8 hours – 8am to 4pm. On the morning of the Study Day participants will not eat or drink, other than a few sips of water to assist swallowing of essential medicines. If any of the conditions on arriving (following dietary guidelines the day before the study day) have not been fulfilled it is in the discretion of the PI to decide whether to reschedule the study day visit. If the participant was not nil by mouth or had not taken their transit markers they would be rescheduled as the resulting data would not be comparable.



Time	baseline	0	30	60	90	120	150	180	210	240	270	300	330	360	6pm	7pm	8pm	9pm	10pm	Sleep	7am	8am
Location	MRI centre														Home							
MRI	x	x		x		x		x		x		x		x								
Breath samples	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Symptoms	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Figure 2: Summary of the study day procedures for both SD1 and SD2.

It will be confirmed that participants remain safe, eligible and willing to take part. If the participant's initial screening visit was online, they will now sign the study consent form. They will change into surgical scrubs, in line with scanning policy. They will then complete the first set of assessments ("baseline").

The assessments will be:

1) An MRI scan including various scan sequences (See MRI Analysis section),
2) Measurement of breath hydrogen and methane content from a single forced exhalation, using the GastroCheck device (Bedfont, UK),
3) Report of gastrointestinal symptoms (Study Day Symptoms Questionnaire). Symptoms of wind/flatulence, bloating and abdominal pain will be scored on a 7-point scale, 0 - 3 in half-integer intervals.

After fasting assessment participants will ingest the challenge fibre. This will comprise 375 ml of the intervention (i.e. 15 g MC or maltodextrin with 15 g inulin) in line with the intervention provided during the intervention period.

The fibre will be administered in 3 x 125 ml portions within a total time of 20 minutes to standardise speed of intake.

Assessments will be repeated immediately after ingestion, then at intervals post-ingestion (see Figure 2). After 3 hours a meal (tomato mozzarella pasta ready meal, Sainsbury's) will be provided. This will stimulate gut motility and movement of small bowel content into the colon. The whole Study Day will last around 8 hours. Participants will collect a further 5 breath samples in the evening and 2 more the following morning, all accompanied by symptom questionnaires. They will take home a second portion of the pasta meal to eat in the evening again to standardise intake of fibre and specifically FODMAPs between participants.
They will record bowel symptoms using the daily diary documenting bowel movements and stool consistency using the Bristol Stool Form Score (BSFS). Patients will be called to remind them of their appointment and the need to take the transit markers before each study day.

In between assessments participants will be provided with a comfortable sitting area. They will be advised to bring material such as magazines, books or electronic devices for entertainment. Guest access to the university's wireless internet (wifi) network will be available.

Stool samples passed either the day before or on the study day will be delivered when attending for the study day or if this is not possible as soon as possible thereafter.

The table below outlines when participants will be given and will return study-specific items.

	Contact	**We will collect from participants**	**We will give to participants as part of visit**
1	Screening/consent		• stool kit (6 tubes) • 5 transit pills
2	Arm 1 Study day 1	• stool samples (6 tubes)	• Arm 1 study period diary • Pasta bake dinner • stool kit (2 tubes) • 5 transit pills • fibre supplements either for first week (half doses) or all 3 weeks if enough space in the fridge • bags to collect breaths in during the evening and morning after Study Day 1
3	Arm 1 after 1 week	• stool samples (2 tubes) • filled breath bags • symptom questionnaire from Study Day 1	• remaining fibre supplements if applicable • stool kit (6 tubes) • 2 blue muffins
4	Arm 1 Study day 2	• stool sample (6 tubes) • completed Arm 1 study period diary	• Pasta bake dinner • stool kit (6 tubes) for Arm 2 • 5 transit pills for Arm 2 • bags to collect breaths in during the evening and morning after Study Day 2
5	Soon after Arm 1 Study day 2 (can be by mail if participant prefers)	• filled breath bags • symptom questionnaire from Study Day 2	
Wash out period - no intervention			
6	Arm 2 Study day 1	• stool sample (6 tubes)	• Arm 2 study period diary (this document) • Pasta bake dinner • stool kit (2 tubes) • 5 transit pills • fibre supplements either for first week (half doses) or all

			3 weeks if enough space in the fridge • breath bags
7	Arm 2 after 1 week	• stool samples (2 tubes) • filled breath bags • symptom questionnaire from Study Day 1	• remaining fibre supplements if applicable • stool kit (6 tubes) • 2 blue muffins
8	Arm 2 Study day 2	• stool samples (6 tubes) • completed Arm 2 study period diary	• Pasta bake dinner • bags to collect breaths in during the evening and morning after Study Day 2
9	Soon after Arm 2 Study day 2 (can be by mail if participant prefers)	• filled breath bags • symptom questionnaire from Study Day 2	

Intervention at home

Participants will be provided with fibre supplement pots for the entire intervention time (in two batches per arm, to reduce difficulties with production and storage) and will be instructed to heat in the microwave and consume one portion (62.5 ml in the first 10 days, 125 ml in remaining 10 days) three times a day. Instructions on how to store and prepare the interventions at home will be provided in the Study Period Diary. In the same document, they will be provided with symptom and stool diaries to record daily (wind/flatulence, bloating and abdominal pain; stool frequency and Bristol stool form scale). The diaries will also contain a field in which the participant confirms daily compliance with the intervention. Participants will be instructed to 'catch up' on any missed interventions to ideally consume three portions of the intervention each day. If portions are missed repeatedly it will be in the discretion of the PI to decide on whether to withdraw a participant from the study.

Wash-out period

Participants do not have any instructions for this 4-8 week period apart from continuing with their usual diet and any medications while avoiding antibiotics and probiotics.

Compliance

There is no formal way of ensuring compliance to the intervention other than self-assessment as the daily intake of fibre intervention occurs at the participant's home.

Criteria for terminating trial

The trial will be terminated if it fails to recruit 12 participants within 12 months of opening. Only one centre is involved.

MRI ANALYSIS

Subjects will be scanned on a research dedicated 3T Philips MRI scanner, using a parallel imaging SENSE 16-element torso coil. A range of MRI sequences will be used to image the abdomen.

Colonic Morphology

Colonic volume will be calculated following the method described by Pritchard et al.[7]. Individual regional colon volumes will be manually segmented from the coronal data on each image slice using MIPAV software (NIH, Bethesda, MD, USA). Each colon region will be identified within each coronal image slice, building a 3D representation of the morphology from which the volume of each region is measured. Information from axial data will be used to guide definition of the regions where anatomy is ambiguous.

Colonic gas will be calculated using methods described by Murray et al.[8]. Colonic gas will be determined after measuring colonic volumes. The in-phase and out-of-phase coronal images are summed using in-house software written in C. Regions of interest are manually traced around the ascending, transverse, and descending segments of the colon on each image slice using MIPAV software (as above) and the regions summed across the slices. Colonic gas is qualitatively identified as regions that are completely black on the sum of the in-phase and out-of-phase images. Their total volume is assessed using histograms generated across the entire colon, with a maximum cut-off threshold level for gas determined as the mean + 1 s.d. of the gas regions manually identified.

Small Bowel Water Content

Small bowel water content will be calculated using the method validated by Hoad et al[9]. In brief, a threshold was set on data from the RARE sequence described above based on the signal from cerebro-spinal fluid. Signal below that threshold is removed as unwanted and the remaining signal from non-luminal areas such as gall bladder, large blood vessels and the urinary tract is manually discarded.

Transit

Speed of gastrointestinal transit will be tracked and scored according to progress of MRI-visible transit markers through stomach, small intestine and colon. Transit markers are made in our laboratory from medical grade plastic and are the size of 00 capsules which are widely used for oral medication. Marker capsules of a similar size containing radio-opaque markers have been used in clinical practice since the 1970s to assess transit times without problems. They pass unaltered through the gut and their position in the colon can be assessed on MRI scans from which we can calculate the average transit time. They are similar in size and profile to Smart Pills and other measuring devices which are widely used in clinical practice. We have used them routinely now for over a decade on more than 314 separate occasions in both patients and healthy volunteers without adverse effects. Whole gut transit will also be assessed on day 18 of the intervention using the time of stool to change colour after ingesting the blue muffin, typically 1-2 days.

TRANSPORT AND STORAGE OF THE TISSUES

Samples will be stored in a linked anonymised format and labelled using a combination of study reference, unique study identifier and date of collection to permit accurate linkage to study data and the consent form.

Stool samples will be collected at the participant's home and stored in aliquots at -20C, then transported to the University of Nottingham on frozen ice packs, then stored at -80C. All materials will be supplied in a kit with instructions (see document Stool Collection Advice).

The master database will be held by Dr Dellschaft in a password encrypted file.

The analysis of samples will take place at the Quadram Institute, Norwich. Appropriate transfer agreements will be in place.

Samples will be transferred on dry ice from the Nottingham Digestive Diseases Centre to the Quadram Institute in one shipment by courier at the end of the study with relevant transfer agreements in place. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples.
Where samples are not used up as part of the analysis they will be transferred to a Biobank if the participant agrees during the consent process or else destroyed in accordance with the Human Tissue Act, 2004.

STATISTICS

Methods

Statistical analysis will be performed by Dr Colin Crooks using R Foundation for Statistical Computing, Vienna, Austria on UoN computers and backed up to the UoN servers.
There are no interim analyses planned. This a pilot study.
Baseline differences between the two arms will be compared to assess for any issues with randomisation.

The differences in each measurement after the intervention period compared to baseline for each patient will be calculated and then summarised with mean and 95% confidence intervals. If differences are not normally distributed median and interquartile ranges will be used.

The mechanistic primary analysis will compare colonic gas 0-6 hour AUC 3 week value in the MC compared to the placebo arm. Other differences including baseline AUC between the two arms will be assessed adjusted for repeated measures. The secondary end points will be tested in a similar approach. If differences are not normally distributed then non parametric methods will be used. The primary clinical analysis will compare BSFS after 3 weeks intervention on methylcellulose versus placebo.

Sample size and justification

This is a pilot study and there are no directly comparable data. However our previous MRI study using 22 healthy volunteers and similar doses of inulin and methylcellulose was able to show a reduction in colonic gas during acute administration of methylcellulose and psyllium so we propose to use 22 participants.

Assessment of efficacy

Mechanistic outcomes

Primary endpoint

- Colon gas volume (ml) as analysed using MRI, area under the curve over 6 hours after a 15 g inulin challenge with or without MC (hereafter described as “AUC 0-6h”) at the end of the 3 week intervention period

Secondary endpoints

- Colon gas volume (ml) as analysed using MRI, AUC 0-6h, comparing the endpoint before vs after the 3 week intervention

The following endpoints will be considered in the comparisons a) MC vs placebo at the end of the 3 week intervention and b) within each arm before vs after the 3 week intervention:

- Whole gut transit time (hours) of transit markers as analysed using MRI
- Small bowel and colon water (ml) AUC 0-6h as analysed using MRI
- T1 in AC AUC 0-6h (seconds) as analysed using MRI
- Colon volumes AUC 0-6h (ml) as analysed using MRI
- Breath hydrogen production (ppm) AUC 0-24h
- Oro-caecal transit time measured (hours) using breath hydrogen
- Whole gut transit time of blue muffin colouring
- Breath methane production (ppm) AUC 0-24h
- Stool sample gas production (ml) over 48h after *in vitro* fermentation
- Stool sample short chain fatty acid production (mol/L) over 48h after *in vitro* fermentation
- Microbiota composition determined using 16S sequencing of stool samples.
- Intervention tolerability as recorded at the second study day of each arm
- Stool form (Bristol scale) and frequency per day (both of all bowel movements and complete spontaneous bowel movements) recorded daily during the 3 week intervention periods
- Symptom severity as recorded in IBS-SSS (standardised questionnaire used in clinical settings) on study days and a shortened version for acute symptoms every day of the 3 week intervention periods

Assessment of safety

There are no specific safety endpoints.

Procedures for missing, unused and spurious data

Where a data point is missing at any one time point, due to technical failure or human error, then the mean of the two adjacent time points will be imputed. Missing baseline data will be imputed from the mean of baseline data during other study days. Where two consecutive data points are missing the whole dataset for that parameter on that study day will be excluded.

Definition of populations analysed

Safety set: All randomised participants who receive at least one intervention.
Full Analysis set: All randomised participants, who participated in at least two interventions and for whom at least three post-baseline assessments of the primary endpoint is available.
Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

Given the mechanistic nature of the study, participants' data will only be included for analysis if adequate data is available to test one of the comparisons set out in the 'Hypotheses' section:

- inulin + MC vs inulin + maltodextrin after both interventions
- before vs after inulin + MC
- before vs after inulin + maltodextrin

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

In this study specific gastrointestinal symptoms are an endpoint, and other gastrointestinal symptoms are expected in this patient group in a mechanistic trial. As such, these will not be recorded as adverse events unless a specific underlying diagnosis is made. Otherwise standard definitions will apply.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the intervention that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment / intervention administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment / intervention is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Trial Treatment / Intervention Related SAEs
A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at screening, for use on samples, CRFs, other trial documents and the electronic database. Samples, the documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of study visit.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

CRFs are used to record clinical trial data and are an integral part of the study and subsequent reports. The CRFs, therefore, must be legible and complete.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance of claims made by research subjects.

TRIAL CONDUCT

This is a small study and there will be no independent audit. The PI and Research Team will hold regular meetings to review progress and study documentation including trial data.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY
Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Results will be published in peer reviewed journals and presented at National and International meetings. They will also be disseminated through the University's and Departmental social media platforms. Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

We have convened a Patient and Public advisory group who have reviewed and approved the details of project. They have also provided advice about wording of patient facing documents and the feasibility of the various interventions and procedures.

STUDY FINANCES

Funding source

This study is funded by an MRC Experimental Medicine Challenge Grant MR/N026810/1

Participant stipends and payments

Participants will be paid an inconvenience allowance of £600 to participate in the study made up of £200 per arm of study with a final £200 for completing both arms of the study since this will be essential for interpretation of the data. Travel and other approved expenses will be offered for any visits required.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Prof Robin Spiller

Signature: 

Date: 17/02/2025

Co- investigator: (name) _____

Signature:_____

Date: _____

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