STUDY LONG TITLE- A Proof-of-Concept Study to Assess the Efficacy of Symprove Probiotics in Managing Persistent Gastrointestinal Symptoms in Adult Coeliac Disease Patients in Histological Remission

STUDY SHORT TITLE- Efficacy of Symprove Probiotics in Coeliac Disease

Sponsor Representative: Jemima Clarke, Clinical Research & Innovation Office, D Floor Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust

Funded by: Investigators account

Chief/Principal Investigator: Professor David S Sanders, Consultant Gastroenterologist, Sheffield Teaching Hospitals NHS Foundation Trust,
Telephone: 01142713412, Email: david.sanders1@nhs.net

Co-Investigators: Dr. Arkadeep Dhali, NIHR Academic Clinical Fellow in Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Telephone: 07471323814, Email: Arkadeep.Dhali@nhs.net

Table of Contents

1. Study Synopsis/Profile

Study title	A Proof-of-Concept Study to Assess the Efficacy of Symprove Probiotics in Managing Persistent Gastrointestinal Symptoms in Adult Coeliac Disease Patients in Histological Remission
Study short title	Efficacy of Symprove Probiotics in Coeliac Disease
Study design	Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
Study participants	**Inclusion criteria:** • Adults aged 18–65 with biopsy-confirmed coeliac disease (CD). • Normal duodenal biopsy within the last 12 months. • Adherence to a gluten-free diet (GFD) for at least 6 months. • Persistent gastrointestinal (GI) symptoms for ≥6 months. • Ability to provide written informed consent. **Exclusion criteria:** • Active gluten ingestion or non-adherence to a GFD. • Use of antibiotics or probiotics in the past 3 months. • Known comorbidities affecting GI function (e.g., Crohn's disease, IBS with severe diarrhoea). • Pregnancy or lactation.
Planned sample size	24
Planned study period	03/12/2025-31/12/2026
Planned recruitment period	03/12/2025-31/08/2026
Study assessments	**Timepoint** / **Assessments** Baseline: GI symptom score, EQ-5D, stool sample Month 1: GI symptom score, EQ-5D Month 2: GI symptom score, EQ-5D Month 3 (end): GI symptom score, EQ-5D, stool sample
Objectives	***Primary*** To determine whether Symprove reduces persistent gastrointestinal (GI) symptoms in coeliac disease patients with histological remission, via rebalancing of gut microbiota dysbiosis, confirming its hypothesized mode of action as a food supplement. ***Secondary*** • To characterize changes in gut microbial composition (diversity and abundance of pro-/anti-inflammatory taxa) following Symprove intervention. • To assess the correlation between microbiota rebalancing and improvements in GI symptom severity (GSRS-IBS) and quality of life (EQ-5D). • To confirm the association between baseline dysbiosis and residual symptoms in treated coeliac disease.

Primary outcome	A reduction of ≥50 points on validated GI symptom assessment scales from baseline to the end of the intervention period (3 months), indicating clinically meaningful improvement in GI symptoms.

2. Research Questions

1. Main Research Question (Hypothesis):
Does Symprove, a multi-strain probiotic, reduce persistent gastrointestinal symptoms in adults with coeliac disease who are in histological remission, compared to their baseline symptom status?

2. Secondary Research Questions:
a) Does Symprove intervention lead to a significant change in gut microbial composition and diversity in this patient population?
b) Is the reduction in gastrointestinal symptom severity associated with restoration of a healthy gut microbiota profile?
c) Is baseline gut microbiota dysbiosis associated with the presence and severity of persistent symptoms in treated coeliac disease?

3. Abstract/Summary

Background
Coeliac disease is a chronic autoimmune condition affecting about 1 in 100 people, in which eating gluten damages the small intestine. Most patients feel better and their gut heals after following a strict gluten-free diet (GFD). However, up to 20% of people with coeliac disease continue to suffer from gut symptoms like bloating, pain, and diarrhoea despite a healed intestine and good dietary adherence. These symptoms greatly impact quality of life, and their cause is often unclear. Recent research suggests that, even after a GFD, the community of gut bacteria (microbiota) can remain imbalanced, a state called dysbiosis. This imbalance may cause ongoing symptoms similar to irritable bowel syndrome (IBS). Probiotics—beneficial live bacteria—have shown promise in improving gut health in IBS and may help rebalance the gut microbiota in coeliac disease. However, high-quality evidence in this area is lacking.
Methods
This proof-of-concept study will recruit 24 adults aged 18–65 with biopsy-confirmed coeliac disease who are in histological remission but still have persistent gut symptoms. Participants must have followed a GFD for at least six months and have a normal gut biopsy in the past year. All participants will take the probiotic Symprove daily for three months. We will monitor their gastrointestinal symptoms and quality of life monthly using standard questionnaires. Participants will also provide stool samples at the start and end of the study to assess changes in gut bacteria.
Results
We will analyse whether taking Symprove leads to a clinically meaningful reduction in gut symptoms (primary outcome) using validated symptom scores. Secondary analyses will include changes in quality of life and gut microbiota composition, with statistical tests comparing before and after treatment. The study will also explore whether improvements in symptoms are linked to restoration of a healthier gut bacteria balance.

4. Aims of the Study

Primary

To determine whether Symprove reduces persistent gastrointestinal (GI) symptoms in coeliac disease patients with histological remission, via rebalancing of gut microbiota dysbiosis, confirming its hypothesized mode of action as a food supplement.

Secondary

- To characterize changes in gut microbial composition (diversity and abundance of pro-/anti-inflammatory taxa) following Symprove intervention.
- To assess the correlation between microbiota rebalancing and improvements in GI symptom severity (GSRS-IBS) and quality of life (EQ-5D).
- To confirm the association between baseline dysbiosis and residual symptoms in treated coeliac disease.

5. Background

Coeliac disease (CD) is a chronic autoimmune disorder triggered by dietary gluten in genetically predisposed individuals, affecting ~1% of the global population (Lebwohl et al., 2015). While strict adherence to a gluten-free diet (GFD) typically induces clinical remission and mucosal healing, up to 20% of CD patients continue to report persistent GI symptoms (e.g., bloating, abdominal pain) despite histological normalization (Roos et al., 2019; Shahbazkhani et al., 2015), a prevalence far exceeding rates in the general population. These symptoms, which overlap with irritable bowel syndrome (IBS), significantly impair quality of life and resist resolution through gluten avoidance alone (Pedersen et al., 2017), implicating non-gluten mechanisms.
Emerging evidence highlights gut microbiota dysbiosis as a plausible contributor to persistent inflammation and symptom generation in CD. Untreated CD patients exhibit reduced microbial diversity, elevated pro-inflammatory Proteobacteria, and depletion of beneficial taxa (e.g., Lactobacillus, Bifidobacterium), patterns that often persist post-GFD (De Palma et al., 2010; Wacklin et al., 2014). Dysbiosis may perpetuate intestinal barrier dysfunction, immune activation, and visceral hypersensitivity (Tojo et al., 2014), mirroring mechanisms observed in IBS. Critically, microbiota alterations correlate with residual symptoms in CD (Cenit et al., 2015; Wacklin et al., 2014), suggesting that microbial imbalance rather than gluten exposure could underpin ongoing morbidity in a subset of patients.
Probiotics represent a logical therapeutic strategy to target dysbiosis, given their capacity to modulate microbial composition, enhance barrier integrity, and dampen inflammation (Ford et al., 2018). In IBS, probiotics like Symprove a gluten-free, dairy-free formulation containing live Lactobacillus and Bifidobacterium strains have demonstrated efficacy in rebalancing microbiota and alleviating symptoms (Sisson et al., 2014). In CD, preclinical studies suggest specific probiotics mitigate gluten-induced inflammation (Smecuol et al., 2013), yet clinical evidence remains scarce (Francavilla et al., 2019). Importantly, probiotics such as Symprove function as food supplements, exerting effects through microbial modulation rather than pharmacological mechanisms (Hill et al., 2014), aligning with their intended use.
This study addresses a critical gap by evaluating whether Symprove alleviates persistent GI symptoms specifically via rebalancing of the gut microbiota in histologically remitted CD patients. By directly linking microbial changes to clinical outcomes, the study will test the causal role of dysbiosis in symptom persistence and validate microbiota restoration as a therapeutic target.

6. Plan of the Investigation

6.1. Methodology

Participants will receive a daily dose of 70 mL Symprove for 3 months, with an optional fourth month if they complete all study assessments. Symprove will be provided free of charge.

Study Timeline
1. Baseline: GI Symptom scores, EQ-5D, and stool collection.
2. Follow-ups: Questionnaires administered monthly (months 1, 2, and 3).
3. Endpoint: Final stool sample collected at 3 months.
4. Optional Fourth Month: Symprove provided contingent on month-3 questionnaire completion.

Outcome Measures

- ·Primary Outcome: Reduction in GI symptom scores by ≥50 points, assessed monthly.

· Secondary Outcomes:
- Changes in EQ-5D scores from baseline to month 3.
- Stool microbiota diversity and taxonomic composition changes at months 0 and 3

6.2. Design

Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

6.3. Intervention (if applicable)

Participants will receive a daily dose of 70 mL Symprove for 3 months, with an optional fourth month if they complete all study assessments. Symprove will be provided free of charge.

Sympove is commercially available, off-the-shelf, liquid food supplement obtainable to the public in health food shops and online.

Ingredients: Water, extract of germinated barley (gluten free), fermented with cultures* of: L. rhamnosus NCIMB 30174, E. faecium NCIMB 30176, L plantarum NCIMB 30173, L acidophilus NCIMB 30175; acidity regulators: ascorbic acid, trisodium citrate; preservative: potassium sorbate; natural flavourings. *Relative proportions will vary.

Nutritional Information (per 70ml serving):
- Sugar - 2.5g
- Carbohydrates - 2.5g
- Protein - <0.5g
- Fat - <0.5g
- Fibre - 0g
- Sodium - Trace
- Calories - 10kcal
- Vitamin C - 185mg per 70ml dose (231% of Reference Intake). Sourced from Ascorbic acid, an approved food ingredient

Symprove is:
- Gluten free. The malted barley extract used in the fermentation process has been produced using techniques that remove the gluten. This enables Symprove to meet the gluten free standard of <20ppm.
- Dairy free and suitable for those following vegan/vegetarian diets.
- Free from artificial colours and flavours

Symprove should be taken a minimum of 10 minutes before eating or drinking to allow it to pass through the stomach.
Unopened bottles of Symprove should be kept in a cool, dark place until they're opened, once opened the bottle needs to be stored in a fridge and consumed within 10 days. Each pack has a shelf-life of three to 4 months.

6.4. Safety Assessment

Symprove is a widely available probiotic with a favourable safety profile. Potential risks include mild GI discomfort, which typically resolves within a few days. Benefits include improved GI symptoms, quality of life, and a better understanding of probiotics in CD management.

6.5. Pregnancy (if applicable)

NA

6.6. Subject Withdrawal, Breaking the Blind and Trial Discontinuation rules

Participants will be informed that their involvement in the study is entirely voluntary and that they may withdraw from the study at any time, without needing to provide a reason and without any impact on their clinical care. If a participant chooses to withdraw, any data already collected will be retained and analysed only with their explicit permission; otherwise, it will be removed from the analysis. At each monthly follow-up and contact point, a member of the research team will confirm ongoing willingness to participate.

As this is a non-randomised, open-label proof-of-concept study, there is no blinding or placebo control, and therefore, no breaking the blind process is required.

Criteria for Trial Discontinuation:

- The trial may be discontinued prematurely for significant safety concerns, ethical reasons, insufficient recruitment, or at the discretion of the Sponsor or Principal Investigator (PI).
- In the event of early discontinuation, all participants and relevant ethics bodies will be informed, and appropriate arrangements will be made for participant follow-up and data handling in line with ethical standards.

6.7. Justification of Measures

- **GI Symptom Rating Scale (GSRS-IBS):** This is a validated, widely used questionnaire for measuring gastrointestinal symptom severity. It is sensitive to clinical change and suitable for assessing response to interventions in both IBS and coeliac disease populations.
- **EQ-5D Quality of Life Questionnaire:** The EQ-5D is a well-validated, standardised instrument for measuring health-related quality of life in clinical trials, with established sensitivity to detect meaningful variations in chronic GI disorders.
- **Stool Sample Microbiota Analysis:** 16S rRNA gene sequencing is an internationally accepted, high-sensitivity technique for characterising changes in gut microbiota diversity and composition. It enables the detection of both broad and specific bacterial changes pre- and post-intervention.

6.8. Setting

The patients will be seen at the Gastroenterology clinic at the Royal Hallamshire Hospital/Northern General Hospital; all outcome measures will be collected at their routine clinical appointment.

6.9. Participants

Inclusion Criteria:

- Adults aged 18–65 years with biopsy-confirmed coeliac disease (CD).
- Normal duodenal biopsy within the last 12 months.
- Adherence to a gluten-free diet (GFD) for at least 6 months.
- Persistent gastrointestinal (GI) symptoms for ≥6 months.
- Ability to provide written informed consent.

Exclusion Criteria:

- Active gluten ingestion or non-adherence to a GFD.
- Use of antibiotics or probiotics in the past 3 months.
- Known comorbidities affecting GI function (e.g., Crohn's disease, IBS with severe diarrhoea).
- Pregnancy or lactation.

6.10. Sample Size

Sample Size Calculation
Assumptions:
1. Primary Outcome: Reduction in GI symptom scores. 2. Effect Size: 75% response rate (Rej et al. 2022) in the intervention group (Symprove) and 20% response rate in the placebo/natural variation group. 3. Significance Level (α): 0.05 (two-tailed). 4. Power (1−β): 0.80 (to detect a significant effect with 80% probability). 5. Allocation Ratio: 1:1 (equal intervention and control groups if randomized; this proof-of-concept study will guide the total estimate).

The sample size for comparing proportions between two groups is calculated as: n = (2 × (Zα/2 + Zβ)^2 × [p1(1-p1) + p2(1-p2)]) / (p1 - p2)^2 Where: - Zα/2: Z-score corresponding to the significance level (α = 0.05, Zα/2 = 1.96). - Zβ: Z-score corresponding to the power (β = 0.20, Zβ = 0.84). - p1: Proportion of responders in the intervention group (assumed to be 0.75 or 75%). - p2: Proportion of responders in the placebo/natural variation group (assumed to be 0.20 or 20%).

Step-by-Step Calculation:
1. Responder Rates:
- p1 = 0.75 - p2 = 0.20
2. Effect Size:
p1 - p2 = 0.75 - 0.20 = 0.55
3. Variances:
p1(1 - p1) = 0.75 × (1 - 0.75) = 0.75 × 0.25 = 0.1875 p2(1 - p2) = 0.20 × (1 - 0.20) = 0.20 × 0.80 = 0.16
4. Z-Scores:
Zα/2 = 1.96 Zβ = 0.84
5. Z-Scores Sum (Squared):
(Zα/2 + Zβ)^2 = (1.96 + 0.84)^2 = 2.8^2 = 7.84
6. Variance Sum:
p1(1 - p1) + p2(1 - p2) = 0.1875 + 0.16 = 0.3475
7. Effect Size Squared:
(p1 - p2)^2 = 0.55^2 = 0.3025
8. Numerator for Formula:
2 × (Zα/2 + Zβ)^2 × [p1(1 - p1) + p2(1 - p2)] = 2 × 7.84 × 0.3475 = 5.44616
9. Sample Size Per Group:
n = 5.44616 / 0.3025 = 17.99 Rounded up to the next whole number: n = 19
Adjusting for Dropouts:
Considering a 20% dropout rate based on prior clinical trials: n_adjusted = n / (1 - dropout rate) = 19 / 0.80 = 23.75
Rounded up = 24

6.11. Recruitment

Potential participants will be identified by a member of the research team (who are also the patients direct care team) through review of clinic lists and electronic health records of adult patients with coeliac disease who are under the care of Sheffield Teaching Hospitals NHS Foundation Trust. The

identification process will take place at the coeliac clinics at the Royal Hallamshire Hospital and Northern General Hospital by members of the direct care team.

Potential participants will first be approached by the direct care team either during a routine clinic appointment or by receiving an invitation letter sent by post/email. The invitation letter will include a participant information sheet that describes the study in accessible language. Those who are approached in person will also be provided with the information sheet and given an opportunity to discuss the study privately with a member of the research team at the clinic.

Interested individuals will be given as much time as they require to consider their participation, discuss the study with family or friends, and ask questions. If they wish to take part, a member of the research team will confirm their eligibility and provide another copy of the information sheet, before offering the opportunity to provide informed consent either in person during the clinic visit or at a subsequent appointment, as preferred by the participant.

We do not anticipate significant difficulties in recruiting the required sample size of 24 participants, as there is a large pool of eligible patients attending specialist coeliac clinics, and patients with persistent symptoms often express interest in non-drug management options.

If participants express interest but are unable to provide consent at the initial approach, they will be followed up by a member of the research team at a later date (by telephone or in person) to answer further questions and offer the opportunity to provide consent at their next visit to clinic.

6.12. Outcome Measure(s)

Primary Outcome Measure:
Clinically significant reduction in gastrointestinal symptom severity, assessed by a validated GI symptom rating scale (GSRS-IBS).

- **When and how measured:** Participants will complete the GSRS-IBS questionnaire at baseline (Month 0), and at Months 1, 2, and 3. A clinically meaningful response is defined as a reduction of ≥50 points from baseline to Month 3.
- **Rationale:** This outcome directly addresses the main research question regarding the efficacy of Symprove in reducing persistent GI symptoms in coeliac disease.
- **Validity:** The GSRS-IBS is a widely used, validated instrument sensitive to changes in GI symptoms in both irritable bowel syndrome and coeliac disease populations.

Secondary Outcome Measures:

1. **Quality of Life,** measured using the EQ-5D questionnaire.
    - **When and how measured:** EQ-5D will be completed by participants at baseline and at Month 1,2, and 3.
    - **Rationale:** This assesses the impact of the intervention on broader health and daily functioning, linked to the secondary research objective of improving quality of life.
    - **Validity:** EQ-5D is a validated, generic quality of life measure sensitive to change in chronic GI disorders.
2. **Gut microbiota composition and diversity,** analysed from stool samples using 16S rRNA gene sequencing.
    - **When and how measured:** Stool samples will be collected at baseline (Month 0) and Month 3, and analysed in an accredited, commerciallaboratory.

- **Rationale:** This addresses secondary research questions regarding whether symptom improvement is associated with restoration of a healthy gut microbiota profile.
- **Validity:** 16S rRNA gene sequencing is the gold standard technique for characterising gut microbiota and detecting compositional changes relevant to GI disease.

Figure 1: Study Schedule for Outcome Measures

Visit/Month	GSRS-IBS	EQ-5D	Stool Sample
Baseline (0)	✓	✓	✓
Month 1	✓	✓	
Month 2	✓	✓	
Month 3 (end)	✓	✓	✓

7. Data and Sample Management

7.1. Statistical Analysis

All analyses will be conducted using statistical software (e.g., R or SPSS). The primary analysis will involve within-subject comparisons of gastrointestinal symptom scores (GSRS-IBS) from baseline to the end of intervention (Month 3). For data that are normally distributed with equal variance and without extreme outliers, paired t-tests will be used to compare pre- and post-intervention symptom scores. If the assumptions of normality or equal variance are not met, the Wilcoxon signed-rank test (non-parametric) will be used.

For secondary outcomes:

- Changes in EQ-5D quality of life scores will also be compared between baseline and Month 3 using paired t-tests or Wilcoxon signed-rank tests as appropriate.
- Microbiota data will be analysed for alpha diversity (within-sample diversity) using indices such as Shannon or Simpson, and for beta diversity (between-sample) using principal coordinates analysis (PCoA) and PERMANOVA. Differential abundance of specific taxa will be assessed using DESeq2 or similar tools. Correlations between changes in microbiota and symptom improvement will be explored using Spearman's correlation or linear regression.

All tests will use a two-sided significance level of 0.05.

7.2. Statistical Opinion

This a pilot study which hopes to form the basis of further grant funding for a larger study. Statistical advice has been received through the University of Sheffield in regards to the sample size, however further statistical advice would be sought should further funding be granted for future study.

7.3. Confidentiality

Participant will be given a unique study number, pseudo-anonymising all patients and allowing no identifiable data to be kept within the study data. The identifier log will be kept in a locked draw separate from all study data.

7.4. Data and Sample Collection, Handling and Storage Record Keeping

To ensure data integrity, all data will be entered into secure, password-protected databases, with dual data entry and regular cross-checks for consistency and completeness.

Laboratory analyses (microbiota sequencing) will be performed in accredited commercial Laboratory with strict sample tracking and quality controls. The Sponsor will enter into a Service and Materials Transfer Agreement with the third-party provider of the analysis. The samples will be collected by the participants in their home, returned to the hospital by courier and stored locally in -80oC freezers within dedicated and monitored facilities.

Samples will only be labelled with study ID and timepoint (e.g. Baseline, Month 3) and no corresponding clinical or personal data will be transferred to the external Laboratory.

Samples will be batch shipped at the end of the study to the Sponsor's preferred Laboratory, (currently this is a commercial, third-party Laboratory located in Norway, Europe). A service level and material transfer agreement will be executed prior to shipment. Once the required microbial genetic material has been extracted, the remaining stool sample will be disposed of by the commercial Lab.

Minimising and Managing Missing Data:
Missing data will be minimised by regular participant reminders (e.g., for questionnaire completion and stool sample submission), flexible options for questionnaire return (in person, by post, or online via email), and close follow-up from the research team. Based on similar studies, it is anticipated that less than 10% of outcome data may be missing at study end. Reasons for missing data will be documented.

Where feasible, sensitivity analyses will be performed, and if missing data exceed 10%, multiple imputation methods may be used to minimise bias. The impact of missing data on study power and risk of reporting bias will be considered in interpreting results. All analyses and reporting will comply with the CONSORT guidelines.

The analysis will take place on a STH computer

The PI will check all source documents and eCRF input before submitting to minimise the chance of any data errors.

7.5. Data Storage

All data for this study will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR). Paper copies of source data, such as signed consent forms and original case report forms, will be stored in a locked cupboard within the Clinical Research & Innovation Office at the Royal Hallamshire Hospital, Sheffield. Access will be strictly limited to authorised members of the study team.

Electronic data—including questionnaire responses and laboratory results—will be entered onto a secure, password-protected database within the Sheffield Teaching Hospitals NHS Foundation Trust (STH) computer network. The electronic database will only be accessible to members of the research team and trust-approved research and governance auditors.

All identifiable personal data will be anonymised or pseudonymised as soon as practical, and stored separately from study data. The data custodian for this study will be Professor David S. Sanders, Chief Investigator, based at Sheffield Teaching Hospitals NHS Foundation Trust.

Data will be retained for five years following study completion, as per institutional and regulatory requirements, after which all data will be securely destroyed or fully anonymised if further retention is necessary for future research purposes. Data archiving will take place within the STH archiving facility, ensuring full compliance with data protection principles, including secure access control, encryption, and regular auditing.

8. Study Management

8.1. Project Plan

Activity	Time Frame
Ethical Approvals	November 2025 – December 2025
Recruitment	January 2026 – February 2026
Closed to Recruitment, In Follow-up	March 2026 – April 2026
Follow-up Complete	April 2026
Data Analyses	May 2026
Write-up	May 2026
Dissemination (presentations/publications, feedback to participants)	May 2026 – July 2026

8.2. End of Trial definition

End of Trial is defined as the date of database lock (DBL), i.e., when all protocol-defined assessments are completed for all participants (including those who undertake the optional 4-month extension), all data have been entered, data queries resolved, and reconciliation/monitoring are complete.

8.3. Project Management

The Chief investigator will have overall responsibility for the study and will supervise, monitor and review any work undertaken by the research team. They will also be responsible for the data collection and analysis of the outcome measures.

9. Expertise

The team are the foremost department in the UK for coeliac disease. We are the designated NHS England National centre and have extensive experience over 25 years of RCT's including commercial work.

10. Ethical Issues

10.1 Ethical Considerations:

All participants will be informed, both verbally and in writing, that participation in this study is entirely voluntary and that their decision will not affect their clinical care or legal rights in any way. The Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be provided to each potential participant, who will be given adequate time to consider the information, discuss with others if desired, and ask questions before giving consent. Participants will be clearly informed of their right to withdraw from the study at any time, without the need to give a reason, and with assurance that this will not impact their medical care. Throughout the study, all participant rights—including consent, confidentiality, and privacy—will be fully respected and maintained.

Anticipated Ethical Issues:
No major ethical concerns are anticipated, as this is a low-risk, non-drug interventional study involving a widely available probiotic supplement.

10.2 Declaration of Helsinki

The CI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

10.3 Guidelines for Good Clinical Practice

The CI will ensure that this study is conducted in accordance with relevant regulations and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-Good Clinical Practice.

All research active staff will have completed the GCP training or re-fresher training within the last 3 years (in line with STH Trust Requirements).

10.4 Expenses and Benefits

There is anticipated benefit of gastrointestinal symptom reduction to participants, and it is hoped that the information obtained will help to identify a possible management option for the above described condition.

11. Service Users and Patient and Public Involvement

Service users and patient representatives have been actively involved in the design and development of this project. Input was sought from members of local coeliac disease patient support groups, who contributed to the identification of key research questions and outcome measures most relevant to individuals living with coeliac disease. Their feedback emphasised the need for interventions targeting persistent gastrointestinal symptoms despite adherence to a gluten-free diet, and the importance of using patient-friendly language in study documents.

Drafts of the Participant Information Sheet (PIS) and consent form were reviewed by patient representatives and PPI leads within the Trust. Feedback from these groups led to improvements in the clarity and readability of participant-facing documents, including the use of lay terminology and the addition of clear explanations of study procedures and the right to withdraw at any time. Patients also highlighted the value of receiving a summary of study results and recommended offering both email and postal options for study communications.

Ongoing involvement will include offering study updates to patient groups and involving them in the dissemination of results, such as through patient newsletters or information events. This approach ensures that the study remains aligned with patient priorities and maximises the acceptability and impact of the research.

12. Dissemination

The findings of this study will be disseminated through multiple channels to ensure broad reach and impact. Results will be submitted for publication in peer-reviewed scientific journals. The outcomes will also be presented at local, national, and international conferences—including meetings of the British Society of Gastroenterology (BSG) and the European Society for the Study of Coeliac Disease (ESsCD).

Final reports will be submitted to the research sponsor (Sheffield Teaching Hospitals NHS Foundation Trust) and Research Ethics Committee/ HRA. Details of the research will also be published as part of the Trust's R&D programme and will be included in national clinical trial and research registers, such as clintrials.gov.

Study results will be shared with service users and patient groups through accessible summaries, patient newsletters, and dedicated feedback events, both in-person and online. Participants will receive a lay summary of the findings via their preferred method of communication.

The study team will also provide training updates and research briefings to clinical and academic staff within the Trust, ensuring integration of new knowledge into clinical practice and ongoing professional education. If the results provide a foundation for larger-scale studies or grant applications, patient and public input will be sought for future research development and dissemination planning.

13. Taking the Work Forward

Depending on the findings of this proof-of-concept study, there may be a strong rationale for undertaking an extension study. If the results demonstrate that Symprove probiotics are effective in reducing persistent gastrointestinal symptoms and/or beneficially modifying gut microbiota in patients with coeliac disease in remission, a larger, multicentre randomised controlled trial (RCT) would be warranted.

Further Questions for an Extension Study:

- Does Symprove's efficacy persist over a longer duration (e.g., 6–12 months)?
- Are improvements maintained after discontinuation of the probiotic?
- What is the comparative efficacy of Symprove versus placebo or other probiotic interventions?
- Are there particular subgroups (e.g., based on baseline microbiota profile) that benefit most from the intervention?
- What are the health economic implications of long-term probiotic use in coeliac disease?

14. Intellectual Property

STH arrangements for IP are set out in the Policy for the Management of Intellectual Property. IP generated by Trust researchers is managed by Medipex Ltd (NHS Innovation Centre for the Yorkshire & Humber region). The Service Level Agreement with the commercial Laboratory analysing the Gut microbiota composition of the stool samples contains appropriate clauses regarding the ownership of IP in relation to results.

15. Costing Schedule

NA

16. Funding Arrangements

The study is being funded via the CI's investigator account, managed by the Gastroenterology Directorate Accountants.

17. References

Lebwohl, B., et al. (2021). Functional gut symptoms in celiac disease. Clinical Gastroenterology and Hepatology, 19(12), 2626–2633.e1. DOI: 10.1016/j.cgh.2021.07.026

2. Zanini, B., et al. (2013). Persistent non-celiac gluten sensitivity with gastrointestinal symptoms: The role of a gluten-free diet. Nutrition Research, 33(7), 535–541. DOI: 10.1016/j.nutres.2013.07.005

3. Hansen, T., et al. (2013). The gluten-free diet: Simple rule or complex challenge? Compliance and quality of life in adults with coeliac disease. BMC Gastroenterology, 13, Article 40. DOI: 10.1186/1471-230X-13-40

4. Muir, J. G., et al. (2019). Gluten-free and low FODMAP diets for treating functional gastrointestinal symptoms in patients with celiac disease: A randomized trial. Clinical Gastroenterology and Hepatology, 17(4), 788–796.e3. DOI: 10.1016/j.cgh.2018.05.015

5. De Palma, G., Nadal, I., Collado, M. C., Sanz, Y. (2009). Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. British Journal of Nutrition, 102(8), 1154–1160. DOI: 10.1017/S0007114509371767

6. Cenit, M. C., Olivares, M., Codoñer-Franch, P., Sanz, Y. (2015). Intestinal microbiota and celiac disease: Cause, consequence or co-evolution? Clinical Gastroenterology and Hepatology, 13(6), 922–933. DOI: 10.1016/j.cgh.2015.02.006

7. Smecuol, E., et al. (2013). Gastrointestinal permeability and gluten metabolism in celiac disease patients on a long-term gluten-free diet. Clinical Nutrition, 32(4), 571–577. DOI: 10.1016/j.clnu.2012.1

Sisson G, Ayis S, Sherwood RA, Bjarnason I. Randomised clinical trial: A liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome--a 12 week double-blind study. Aliment Pharmacol Ther. 2014 Jul;40(1):51-62. DOI: 10.1111/apt.12787.

9. Freedman, A., et al. (2021). How the microbiota may affect celiac disease and what we can do. Journal of Immunology Research, 2021, Article 9943678. DOI: 10.1155/2021/9943678

10. Ford, A. C., Harris, L. A., Lacy, B. E., Quigley, E. M. M. (2018). Systematic review with meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Clinical Gastroenterology and Hepatology, 16(5), 635–648.e3. DOI: 10.1016/j.cgh.2017.08.030

11. Rej A, Sanders DS, Shaw CC, Buckle R, Trott N, Agrawal A, Aziz I. Efficacy and Acceptability of Dietary Therapies in Non-Constipated Irritable Bowel Syndrome: A Randomized Trial of Traditional Dietary Advice, the Low FODMAP Diet, and the Gluten-Free Diet. Clin Gastroenterol Hepatol. 2022 Dec;20(12):2876-2887.e15. doi: 10.1016/j.cgh.2022.02.045.