Manchester University
NHS Foundation Trust

Study Name: **A pilot study exploring the use of Symprove for the management of gastroesophageal reflux symptoms.**

Acronym: **SPACER** (***S**ymprove, a **P**ilot **A**ssessment of its **C**linical **E**ffect on **R**eflux)*

Exploring **Symprove** product for the management of GORD symptoms

Amendment History

Research Reference Numbers

IRAS Number	364448
Sponsor Reference	B02663
Funder Reference	N/a

HRA Protocol Compliance Declaration

This protocol has regard for the HRA guidance.

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

Signature Page

The sponsor signature on the IRAS form, acts as documented acceptance that the sponsor approves the protocol.

The Chief Investigator should sign below to confirm the following:

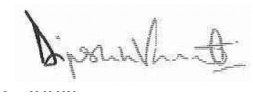
The Chief Investigator confirms the protocol has been agreed and accepted and agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date:



12/12/25...

.....

Name: (please print): .Dr Dipesh H Vasant

List of Contents

Full/Long Title of The Study 1
Research Reference Numbers 1
HRA Protocol Compliance Declaration 1
Signature Page 2
List of Contents 3
Key Study Contacts 5
Study Summary 6
Funding 7
Role of Study Sponsor and Funder 7
Study Flow Chart 8
1. Background 8
2. Rationale 9
3. Research Question/Aim(s) 9
3.1 Objectives 9
3.2 Outcome Measures 9
3.2.1 Primary Outcome Measure 9
3.2.2 Secondary Outcome Measure(s) 9
4. Study Design 10
5. Study Setting 10
6. Participant Eligibility Criteria 10
6.1 Inclusion Criteria 10
6.2 Exclusion Criteria 10
7. Sample Size 11
8. Study Procedures 11
8.1 Participant Identification and Recruitment 11
8.2 Consent 11
8.3 Study Assessments 12
8.4 Schedule of Procedures 14
8.5 Samples 14
8.6 Participant Withdrawal 14
8.7 End of Study 14
8.8 Participant Compensation 15
9. Safety Reporting 15
10. Statistics and Data Analysis 15
10.1 Data Analysis 15
11. Data Management 16
12. Monitoring 16

13. Ethical and Regulatory Considerations 16
13.1 Risks and Burdens to Participants and Researchers 16
13.2 Research Ethics Committee (REC) and Other Regulatory Review & Reports 16
13.2.1 NHS REC Reviewed Research 16
13.3 Amendments 17
13.4 Peer Review 17
13.5 Patient & Public Involvement 17
13.6 Protocol Compliance 17
13.7 Data Protection and Participant Confidentiality 17
13.8 Indemnity 18
13.9 Access to the Final Study Dataset 18
14. Dissemination 18
14.1 Dissemination Policy 18
14.2 Authorship Eligibility Guidelines and Any Intended Use of Professional Writers 18
15. Archiving 18
16. References 18

Key Study Contacts

Chief Investigator	Dr Dipesh Vasant Consultant Gastroenterologist & Honorary Senior Lecturer University of Manchester Neurogastroenterology Unit Manchester University NHS Foundation Trust, Manchester, UK Tel: 0161 291 2702 Email: dipesh.vasant@mft.nhs.uk
Study Contact for Enquiries	Sharon Archbold, GI Physiologist, Neurogastroenterology Unit, Manchester University NHS Foundation Trust, Manchester, UK Tel: 0161 291 4293 Email: sharon.archbold@mft.nhs.uk
Sponsor	Dr Lynne Webster Manchester University NHS Foundation Trust The Nowgen Centre 29 Grafton Street Manchester M13 9WU research.sponsor@mft.nhs.uk 0161 276 4125
Funder(s)	Phil Thomas, HCP Engagement Director Symprove Ltd Sandy Farm Business Park, Sands Road, Farnham, Surrey GU10 1PX Tel: 01252 413600 Email: phil@symprove.com
Statistician	Emma Barrett, Statistician Manchester University NHS Foundation Trust, Manchester, UK Email: emma.barrett-2@manchester.ac.uk
Key Protocol Contributors and Study Coordinators	Sharon Archbold, GI Physiologist, Neurogastroenterology Unit, Manchester University NHS Foundation Trust, Manchester, UK Tel: 0161 291 4293 Email: sharon.archbold@mft.nhs.uk Sorela MaziluWood Research Nurse Neurogastroenterology Unit Manchester University NHS Foundation Trust, Manchester, UK Tel: 0161 291 4188 Email: Sorela.MaziluWood@mft.nhs.uk

Study Summary

Study Design	6-week, remote, single-arm real world pilot study
Study Participants	Patients with symptoms of gastro-oesphageal reflux disease (GORD) who are undergoing routine care at a single recruiting site in the UK (Manchester University NHS Foundation Trust)
Planned Size of Sample	70
Recruitment Period	Rolling recruitment over 3-4 months
Follow Up Period	6 weeks
Overall Study Duration	6 months
Research Question/Aim(s)	The aim of this study is to evaluate changes in symptoms of GORD following 6 weeks of Symprove treatment in patients with proven pathological gastroesophageal reflux and those with Rome IV Functional Heartburn or Rome IV Reflux hypersensitivity.

Primary Objective	**Primary Outcome Measure**
To quantify the change in GORD symptoms following 6 weeks of Symprove treatment.	Absolute change in RESQ-7 score from baseline to 6 weeks.
Secondary Objective(s)	**Secondary Outcome Measure(s)**
To estimate differences in the change in GORD symptoms between patients with pathological acid reflux and those with oesophageal DGBI.	Difference in absolute change in RESQ-7 score from baseline to 6 weeks.
To estimate differences in the change in GORD and IBS symptoms between patients with and without Rome IV DGBI IBS or Functional Dyspepsia.	Difference in absolute change in RESQ-7 score and IBS-SSS score from baseline to 6 weeks.
To explore trajectories in change in GORD and IBS symptoms during Symprove treatment, and investigate differences by subgroup i) oesophageal DGBI, ii) DGBI IBS or Functional Dyspepsia.	Weekly RESQ-7 and IBS-SSS scores over the 6-week treatment period.

Funding

Funder(s)	Financial And Non-Financial Support Given
Phil Thomas, HCP Engagement Director Symprove Ltd Sandy Farm Business Park, Sands Road, Farnham, Surrey GU10 1PX Tel: 01252 413600 Email: phil@symprove.com	£51,138 (GBP) grant to run the study, including protocol design, ethical approval, participant recruitment, managing participants, statistical analysis and manuscript development.

Role of Study Sponsor and Funder

Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

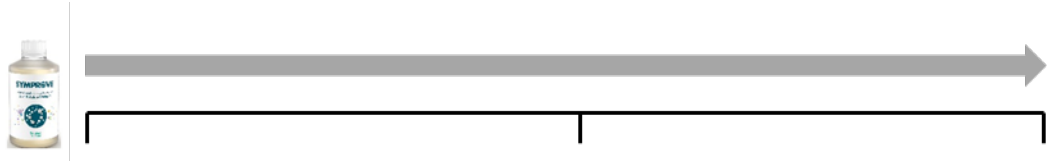
Symprove Ltd is the funder and will not have any input into study design, statistical analysis, manuscript development or access to participant results.

Key Words: Symprove, probiotics, gastro-oesphageal reflux disease, GORD, gut microbiome

Abbreviations

Abbreviation	Definition
AE	Adverse Event
CRF	Case Report Form
DGBI	Disorders of Gut Brain Interaction
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GORD	Gastro-oesophageal Reflux Disease
H2RA	Histamine Type-2 Receptor Antagonist
ICF	Informed Consent Form
MFT	Manchester University NHS Foundation Trust
PPI	Proton Pump Inhibitors
REC	Research Ethic Committee
RESQ-7	Reflux Symptom Questionnaire 7day recall
TMF	Trial Master File
UK	United Kingdom

Study Flow Chart



0 weeks (Baseline)	Weekly follow-up (telephone calls)	6 weeks (Endpoint)
• Demographics • Rome IV diagnostic questionnaire for DGBI – functional heartburn, reflux hypersensitivity, functional dyspepsia and irritable bowel syndrome • RESQ-7 • IBS-SSS	• RESQ-7 • IBS-SSS • Data collected on adverse events, rescue medications, and/or changes in usual anti-reflux medications	• RESQ-7 • IBS-SSS • Data collected on adverse events, rescue medications, and/or changes in usual anti-reflux medications

1. Background

Gastro-oesophageal reflux disease (GORD) affects 15-20% of the UK population and continues to increase, particularly in younger patients (30-39 years old).[1] Prescriptions for proton pump inhibitors (PPIs) are widespread and have doubled in the UK. Notably, omeprazole makes up for about four fifths of all prescriptions. PPIs are first-line therapy yet a large proportion of patients with GORD report persistent symptoms.[3] Despite the risks associated with long-term use of PPIs, long-term PPI use is common.

More recently, the gut microbiome has been implicated in GORD-related disease risk. Additionally, research suggests GORD is linked with fundamental compositional and functional shifts in the gut microbiome.[4] Given the gut microbiome exhibits a high level of plasticity and is modifiable, gut microbiome targeted therapies, such as probiotics, may be considered a novel strategy for symptom management that warrants further exploration.

Symprove is a four-strain liquid-based probiotic (food supplement) with efficacy across several clinical groups including irritable bowel syndrome and Parkinson's disease, as well as vulnerable clinical groups, including children.[5-8] Symprove is well tolerated and has a very good safety profile.[5-10]

With modern advances in GI physiology diagnostics and classification systems, it is recognized that not all people with gastro-oesophageal reflux symptoms have objective evidence of pathological reflux on 24-hour oesophageal pH impedance testing. The role of oesophageal physiology testing in guiding reflux diagnoses and treatments is now well established, and the Rome IV diagnostic criteria incorporate Functional Heartburn and Reflux Hypersensitivity.11 Functional Heartburn is defined by Rome IV criteria as symptoms of burning retrosternal discomfort or pain, with no symptom relief despite optimal anti-acid medication, and absence of objective pathological reflux or symptom reflux association on oesophageal pH testing. Reflux hypersensitivity is defined by Rome IV criteria as heartburn and chest pain, with normal endoscopy, and evidence of triggering of symptoms by reflux events despite normal acid exposure on pH impedance testing.11 The treatment approaches for pathological reflux and disorders of gut-brain interaction (DGBI) such as reflux hypersensitivity and functional heartburn are different, with the latter requiring symptomatic treatments to improve visceral sensitivity as opposed to reflux.

2. Rationale

Given the overlapping symptoms in people with pathological reflux and those with Functional Heartburn and Reflux Hypersensitivity, and the positive evidence of efficacy of Symprove in people with other disorders of gut-brain interaction (DGBI) such as IBS, it would be important to understand if an intervention such as Symprove benefits people with reflux symptoms, or whether it only benefits subsets either with reflux hypersensitivity or functional heartburn.

3. Research Question/Aim(s)

The hypothesis of this study is that symptoms in people with PPI dependent reflux may be contributed to by unbalanced microbiota, dysbiosis and probiotic-driven restoration of microbial balance will mediate clinical improvements.

The aim of this study is to evaluate changes in symptoms of GORD following 6 weeks of Symprove treatment in patients with proven pathological gastroesophageal reflux and those with Rome IV Functional Heartburn or Rome IV Reflux hypersensitivity.

3.1 Objectives

Primary objective:

- To quantify the change in GORD symptoms following 6 weeks of Symprove treatment in patients with proven pathological gastroesophageal reflux and those with Rome IV Functional Heartburn or Rome IV Reflux hypersensitivity

Secondary objectives:

- To estimate differences in the change in GORD symptoms between patients with pathological acid reflux (according to Lyon Consensus on 24-hour oesophageal pH testing or wireless oesophageal pH testing) and those with oesophageal DGBI (Rome IV functional heartburn or Reflux Hypersensitivity)
- To estimate differences in the change in GORD and IBS symptoms between patients with and without Rome IV DGBI IBS or Functional Dyspepsia
- To explore trajectories in change in GORD and IBS symptoms during the treatment period in patients with proven pathological gastroesophageal reflux and those with Rome IV Functional Heartburn or Rome IV Reflux hypersensitivity.

3.2 Outcome Measures

3.2.1 Primary Outcome Measure

- Absolute change in Reflux Symptom Questionnaire 7-day recall (RESQ-7) score from baseline to 6 weeks.

3.2.2 Secondary Outcome Measure(s)

- Difference in absolute change in RESQ-7 score from baseline to 6 weeks between patients with pathological acid reflux and oesophageal DGBI.
- Difference in absolute change in RESQ-7 score and IBS-SSS score from baseline to 6 weeks between patients with and without DGBI IBS or functional dyspepsia.

- Weekly RESQ-7 and IBS-SSS scores from baseline to 6 weeks for analysis of trend over time.

4. Study Design

This will be a 6-week, remote, single-arm real pilot study to assess the effect of Symprove on symptoms of GORD. We aim to recruit a minimum of 70 patients (allowing for 20% dropout) through a single recruiting site in the UK (Manchester University NHS Foundation Trust). Based on previous audit data in the department, we anticipate that there will be an even split between people with pathological reflux on 24-hour pH testing or wireless oesophageal pH testing and those that will have a Rome IV disorder (Functional Heartburn or Reflux Hypersensitivity).

All participants will receive Symprove to take once a day for 6 weeks and will be asked to complete validated questionnaires (RESQ-7 and irritable bowel syndrome symptom severity scale (IBS-SSS) about their symptoms every week for 6 weeks (i.e. baseline, week 1, week 2, week 3, week 4, week 5 and week 6 (endpoint).

5. Study Setting

This is a single centre study only and recruitment will take place at the Reflux Clinic at Wythenshawe Hospital, part of MFT, in line with routine care.

6. Participant Eligibility Criteria

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

This will be assessed using Inclusion and Exclusion Criteria.

6.1 Inclusion Criteria

To be eligible to participate in this study all of the following criteria must be met:

1. Referred for and completed oesophageal pH/impedance testing or wireless oesophageal pH testing (Bravo capsule), OFF PPI or H2RA at the Neurogastroenterology Unit at Wythenshawe Hospital.
2. Have had a recent endoscopy or Barium swallow as part of routine care in line with the British Society of Gastroenterology guidelines on oesophageal manometry testing[12]
3. People between 18 -65 yrs old

4. Willing and eligible to provide consent and comply with protocol and product intake

6.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

1. Use of products marketed as prebiotics or probiotics within 4wks of study entry
2. Systemic antibiotic or antifungal treatment within 4wks prior to study entry
3. An unstable dose of PPI or H2RA prior to entry into the study
4. An unstable antidepressant/antipsychotic treatment regimen within 3months prior to study entry (i.e treatment should be stable for 3months prior to entry)
5. Severe illness(es) or medical condition(s) including gastrointestinal pathologies:
   - G.I ulcers, coeliac disease, inflammatory bowel disease, bowel cancer, bowel resection, bariatric surgery

6. Surgical operations in the mouth or G.I tract within 4weeks prior to study entry or planned during the study
7. Pregnancy or lactation, or plan to become pregnant during the study
8. Advanced pulmonary, cardiac, liver or renal disease
9. Already taking part in a research study

7. Sample Size

A minimum of 70 patients will be recruited, allowing for an anticipated dropout rate of 20%, in line with previous recommendations13. As this is a pilot study, the sample size has been chosen based on feasibility and to provide estimates of change in symptom score and variability. Based upon previous data from our department, we estimate that approximately 50% of recruited participants with reflux symptoms will have pathological reflux and approximately 50% will have an oesophageal DGBI (Reflux Hypersensitivity or Functional Heartburn)14. A cohort of 56 completing the 6-week assessment, with subgroup sizes of around 28, will allow for exploratory estimation of within-group changes and between-group differences to inform the design of a future study.

8. Study Procedures

8.1 Participant Identification and Recruitment

Patients investigated for reflux symptoms will be recruited from the neurogastroenterology unit at Wythenshawe hospital which is a regional referral centre for gastro-oesophageal reflux testing.

Initial contact with potential patients will be via the direct care team at Manchester University NHS Foundation Trust. The clinical team will identify patients who may be eligible from clinic visits or clinic lists. If the participant is interested in the study, the researcher will determine if they fit the study criteria by asking specific questions (pre-screening) in clinic (either via telephone or face-to-face). If criteria are fulfilled, participants will be provided with a participant information leaflet and consent form and have at least 24 hours to become familiarised with the requirements of the study before providing consent.

8.2 Consent

Signed and dated informed consent will be obtained at V1.0 11/12/2025 before any study procedures are undertaken. The study coordinator will explain the nature of the study to the patient and answer any questions the patient may have in relation to the study. The patient will be informed that their participation in the study is voluntary and if they choose not to participate or withdraw from the study it will not affect the standard of care they receive at the hospital. The statement of informed consent that the patient will sign has met the requirements of local regulation; ICH guidelines and the IEC of the study centre. Should the ICF be updated during the patient participation in the study the patient will be reconsented using the most current approved version of the ICF. A copy of the ICF will be provided to the patient. The original signed and dated ICF will be stored in the ISF for monitoring, auditing and inspection purposes. Patient medical record will be updated stating that the informed consent process was performed, written informed consent was obtained, a copy of the informed consent was provided to the patient before the patient was enrolled in the study together with the date the written informed consent was obtained. The study coordinator will also sign the ICF. A copy of the consent form will be uploaded to the patients' medical records alongside a copy of the patient information sheet. The participant will also be given a copy of the completed consent form and patient information sheet to keep.

All personal data will be pseudonymised and will be stored using password protected computers. From the beginning of their involvement, participants will be given an identification number and only that will be added to the completed questionnaires and other paperwork. All data will be kept confidentially under the UK Data Protection Act 1998 including the General Data Protection Regulation (GDPR), and

participant names will not appear anywhere in any publication or description of our findings. Personal data and unidentifiable research data will be kept for 10 years on a password protected research database.

8.3 Study Assessments

Baseline:

At baseline visit, the eligibility of the patients will be assessed based on the inclusion and exclusion criteria and informed consent given by the patient. Each study participant will have an unique study number. The study co-ordinator will provide the patient with instructions on how to request the study product securely on www.symprove.com. The patient will provide their name, home address, email address and phone number with Symprove. This is required for delivery purposes only. The patient will select from four different flavours of product on the website: Original, Strawberry & Raspberry, Mango & Passionfruit or Pineapple. The study site will be supplied with codes that will be inputted when the 12 week pack of product is added to the shopping cart on website. The product will automatically get shipped within 1-2 working days.

Symprove is shipped as a 12wk pack to all customers and why participants for this study will also be receiving a 12wk pack.

The baseline questionnaire will be completed electronically in Manchester University NHS Foundation Trust during the first visit which will be in person.

At baseline, all recruited participants will complete 3 questionnaires;

- Rome IV diagnostic questionnaire for DGBI relevant to the present study – functional heartburn, reflux hypersensitivity, functional dyspepsia and irritable bowel syndrome (Palsson et al Gastroenterology 2016).
- RESQ-7 questionnaire to assess 7-day recall of reflux symptoms (Ryden et al. Scand J Gastroenterol 2013).
- IBS symptom severity score (IBS-SSS) questionnaire (Francis et al APT 1997).

Data on baseline participant demographics and weight, height and body mass index (BMI) will be checked during the initial study visit, as well as a list of patient's medications to be collected on patient CRF.

Intervention:

Participants will be asked to take a daily dose of 70 mL Symprove for 6 weeks first thing in the morning on a empty stomach. A 70ml measuring cup will be provided in the box. Symprove will be provided free of charge.

Follow-up:

During the study patients will have contact with a member of the research team weekly via telephone for six weeks. During the telephone contact with the study team the patient and research team member will complete follow up questionnaires.

Follow-up questionnaires via a phone call at weeks 1, 2, 3, 4, 5 and 6 (endpoint). During the telephone follow-up calls the RESQ-7 questionnaires will be completed as well as the IBS-SSS questionnaire. The research team will read out the questions over the telephone and record patient responses. During these weekly follow-up calls data will be collected on any adverse events, and any rescue medications, or changes in usual anti-reflux medications and how many days of seven they took Symprove.

8.4 Schedule of Procedures

Procedures	Screening and Baseline*	Wk 1 (+/-1 day)	Wk 2 (+/-1 day)	Wk 3 (+/-1 day)	Wk 4 (+/-1 day)	Wk 5 (+/-1 day)	Wk 6 (+/-1 day)
Inclusion/ Exclusion Criteria	x						
Informed Consent	x						
Demographics	x						
Weight, height, BMI	x						
Rome IV diagnostic questionnaire for DGBI	x						
RESQ-7	x	x	x	x	x	x	x
IBS-SSS	x	x	x	x	x	x	x
Concomitant medications	x						
Capture data on adverse events, rescue medications or changes in usual anti-reflux medications		x	x	x	x	x	x

*Only screening and baseline completed in-person at reflux clinic. Weekly questionnaires completed (Weeks 1-6) are via telephone.

8.5 Samples

No samples will be collected during this study.

8.6 Participant Withdrawal

Participants can withdraw from the study at any time by contacting the Study co-ordinators (Sharon Archbold and Sorela MaziluWood). Any data collected before withdrawal will be included in the analyses, but no further data will be collected. It will be optional for participants to provide a reason for their withdrawal. Standard of care will not be affected in any way by patient withdrawal.

If the Chief Investigator is concerned about the safety of any patient then they will be withdrawn from the study. However, this is very unlikely as Symprove is a food supplement that is widely available and taken by thousands of people every day.

Patients who withdraw from the study will not be replaced. Withdrawal has already been factored into the target sample size of 70, with expectation of 20% dropout.

8.7 End of Study

The end of the study for each participant will be the completion of the 6-week questionnaires via telephone. The full study will be completed once the final participant of the n=70 initially recruited has completed the 6-week questionnaire.

8.8 Participant Compensation

There is no participant monetary compensation for taking part in the research. They are receiving Symprove at no cost. Participants who complete the study will be offered a free additional 12-week course of Symprove.

9. Safety Reporting

Safety reporting will follow the standard processes of the Trust, HRA and REC for a non-CTIMP study as outlined below.

The Trust requires that all Serious Adverse Events (SAEs) occurring in Trust-sponsored research studies are reported to the Sponsorship Team within 24 hours of the research team becoming aware using the adverse.events@mft.nhs.uk email. Safety reporting for non-CTIMP studies should also follow the HRA and REC reporting guidance here.

Reports of Serious Adverse Events (SAEs) that are:

- Related to the study (i.e., they resulted from administration of any of the research procedures) and
- Unexpected (i.e., not listed in the protocol as an expected occurrence)

should be emailed to the REC using the Non-CTIMP safety report to REC form. Such reports should be sent within 15 days of the Chief Investigator becoming aware of the event.

SAEs are not expected based on Symprove being a food supplement that's widely available for public consumption with thousands of people taking it each day, and no SAEs reporting previous studies.

10. Statistics and Data Analysis

10.1 Data Analysis

Descriptive statistics will be reported as mean and standard deviation (SD) or as median and interquartile range (IQR) for continuous variables, and as counts and percentages for categorical variables. Change in questionnaire scores will be calculated as absolute change and relative change at each time point and summarised for the cohort overall and by subgroup as mean (SD) with 95% confidence intervals (CI).

A two-sided one-sample t-test at the 5% significance level will be used for the primary analysis of absolute change in RESQ-7 score from baseline to 6 weeks for the cohort. Between-group differences in absolute change in RESQ-7 and IBS-SSS from baseline to 6 weeks will be reported as difference in mean change between groups with 95%CI estimated using Welch's unequal-variance method. As a non-parametric alternative, between-group differences will be summarised using the Hodges-Lehmann estimator with 95%CI.

Linear mixed-effects regression will be used to explore the change in RESQ-7 and IBS-SSS over the 6-week treatment period, with raw score as the outcome and fixed effects for time, subgroup and their interaction, and random intercept for participant, with coefficient estimates being reported alongside 95%CIs.
All analyses will be conducted in R statistical software v4.4.2 or later.

Pathological acid reflux will be defined according to Lyon Consensus 2.0 on 24-hour oesophageal pH testing with total oesophageal acid exposure time >6.0% (Gyawali et al. Gut 2024). Functional

reflux will be defined as oesophageal DGBI by the Rome IV diagnostic criteria for functional heartburn or reflux hypersensitivity. The first part of the secondary analyses will compare treatment response in the pathological vs functional reflux subgroups.
IBS and functional dyspepsia will be defined according to the Rome IV diagnostic criteria, and the second part of the secondary analyses will compare treatment response in the subgroups with and without IBS/functional dyspepsia.

11. Data Management

All participant data will be pseudonymized and stored securely in compliance with GDPR. Participants will receive a unique participant identifier to maintain confidentiality. Data collected by the researcher on patient outcomes for all study visits will be stored securely in an anonymized Excel spreadsheet. This Excel Spreadsheet will be located on a shared research drive on the Trust network which will only be accessible to members of the research team. There will be a separate password protected spreadsheet which will link study IDs to patient hospital numbers for additional security.

Study documents will be stored both as paper in the Site File and electronically on the Drive

Once enrolled into the study, patients will be provided with a link to the Symprove website and will enter their name, address, select their preferred flavour and enter their code at checkout which will bring the cost to zero. The product will be shipped within 24-48 hours.

No additional participant details or results will be shared with Symprove.

12. Monitoring

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

13. Ethical and Regulatory Considerations

13.1 Risks and Burdens to Participants and Researchers

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 may include improved GI symptoms, quality of life, and a better understanding of probiotics in GORD management.

13.2 Research Ethics Committee (REC) and Other Regulatory Review & Reports

13.2.1 NHS REC Reviewed Research

Before the start of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC) for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The study team will be responsible for the maintenance of a study site file or TMF, in which all current and superseded study documents will be retained. Also contained in the site file/TMF will be the approval documentation including correspondence with relevant authorities such as the HRA and REC.

The study team are responsible for producing progress reports throughout the study, as required. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications/abstracts, to the REC within 12 months of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

No participants will be enrolled into this research study prior to the study being reviewed by the relevant regulatory authorities and receiving HRA and REC approvals, as well as approval from the R&D office at Manchester University NHS Foundation Trust.

13.3 Amendments

Any amendments to the study shall be reviewed by the Sponsorship Team prior to submission. Any non-substantial amendments shall be notified to the HRA and any substantial amendments, along with amended documentation, shall be approved by the REC, and HRA, prior to implementation as per nationally agreed guidelines. The Chief Investigator or designee will work with the R&I department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

13.4 Peer Review

This study protocol has been Grade 2 reviewed by an internal Trust clinical academic reviewer independent to the study team.

13.5 Patient & Public Involvement

It is appreciated that patients and the public can improve both the quality and relevance of this research. Therefore, a patient advisory group will be involved in the following activities;

- Review of participant information sheet and consent form
- Co-production of the summary of findings to be sent to participants

13.6 Protocol Compliance

The research team will be vigilant in protocol deviations and will record them on a study specific deviation log which will be regularly assessed by the PI.
Deviations that may affect the safety, physical or mental integrity of participants or scientific value of the study will be reported to the study sponsor via research.sponsor@mft.nhs.uk by the research team.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach and should also be reported to the sponsor without delay.

13.7 Data Protection and Participant Confidentiality

All participant data will be pseudonymised and stored securely in compliance with GDPR. Participant codes will be created to maintain confidentiality. All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles. Only the Research team will have access to participant clinical data and this will be kept on password-protected Excel spreadsheets.

Patients provided with a link to the Symprove website will enter at checkout when in clinic. They will enter address and product will be shipped within 24-48 hours. No personal patient details beyond the above will be shared with Symprove.

The data custodian will be the CI who is substantively employed by MFT. As sponsor, MFT own the data from the study. Data will remain on site at MFT or within secure archived storage in line with R&I SOPs (see R&I SOP 'Retention of Data, Off–Site Archiving and Destroying Documents').

13.8 Indemnity

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer, and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

13.9 Access to the Final Study Dataset

Only the CI and Research team will have access to the final study dataset. If a statistician is used for data analysis, only fully anonymised data will be shared with them. The final data set will be stored using study codes, so it is considered pseudonymised and stored on a single data spreadsheet at MFT. A record of patient's names and their unique subject identifier will be stored for the study separately on a single data spreadsheet at MFT behind a Trust's firewall, password protected PC to allow for the study investigators, if needed, to query original records. The study statistician should not have access to the patient identification record or any identifiable patient data, they should receive an anonymised data set for analysis. No final data will be shared with Symprove.

14. Dissemination

14.1 Dissemination Policy

This study aims to establish Symprove's efficacy in reducing persistent GI symptoms in patients with gastroesophageal reflux symptoms. The results could provide a foundation for larger, randomized controlled trials and potentially introduce probiotics as a complementary therapy for this patient group.

The results from this study will be published in a peer-reviewed journal. Results will also be disseminated through gastroenterology conference proceedings.

14.2 Authorship Eligibility Guidelines and Any Intended Use of Professional Writers

Only the CI, Research team (and statistician, if used) will be granted authorship on the final study report. Each author will be listed in line with standard practice as outlined in The International Committee of Medical Journal Editors.

15. Archiving

The study files and documents will be stored in locked filing cabinets within the department for 10 years after the study has ended.

16. References

1. Yamasaki T et al. Journal of Neurogastroenterology and Motility 2018; 24(4): 559-569.
2. Hassan SA. BMJ 2019;367:l6483.
3. Delshad SD et al. Gastroenterology 2020;158(5):1250-61.
4. Wang K, et al. Front Immunol. 2024;15:1327503.
5. Sisson G, et al. Aliment Pharmacol Ther 2014;40(1):51–62.
6. Leta V, et al. Mov Disord. 2023; 38 (suppl 1).
7. Hassan H, et al. Arch Dis Child 2022;107(3):259–64.

8. Yerlett N, et al. Clin Exp Dermatol 2022;00:1-5.

9. Kvasnovsky CL, et al. Inflammopharmcology 2017; doi:10.1007/s10787-017-0363-y.

10. Bjarnason I, et al. Inflammopharmacology 2019;27(3):465–473.

11. Aziz Q, et al. Gastroenterology 2016:S0016-5085(16)00178-5.

12. Trudgill NJ, et al. Gut 2019;0:1–2013. Teresi JA, et al. Med Care 2022;60(1):95–103.14 Doyle R, et al. BMJ Open Gastroenterology 2021;8(1):e00810.