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Trial of alginates in throat symptoms: protocol for a pragmatic, multicentre, placebo controlled, double blind, parallel, randomised controlled trial of liquid alginate (Gaviscon Advance) for the treatment of persistent throat symptoms

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ABSTRACT

Introduction Persistent throat symptoms (PTS) are indicators for over 60 000 new patient referrals to NHS secondary care annually. PTS have been attributed to manifestation of gastro-oesophageal reflux disease (GORD) with the hypothesis that gastric refluxate damages and irritates the mucosa of the upper aerodigestive tract. Symptoms of PTS and GORD are commonly treated with proton pump inhibitors (PPIs) or alginates are often, incorrectly, advocated. The Trial of PPIs in Throat Symptoms trial definitively demonstrated that lansoprazole is no more effective than placebo in treating symptoms of PTS, indicating that empirical PPI treatment for PTS should be discouraged. The impact of this is an anticipated increase in prescriptions of alginates for PTS, however, there is a lack of evidence of the efficacy of alginates in treating this condition. Trial of alginates in throat symptoms aims to compare symptomatic response of the symptoms of PTS in liquid alginate (Gaviscon Advance) in comparison to a near matched placebo over an 8-week period to provide definitive evidence of the use of alginates in treating PTS.

Methods and analysis This is a multicentre, pragmatic, double blind, parallel, randomised controlled trial. 250 adults with PTS will be recruited from NHS secondary care sites and randomised to either liquid alginate (Gaviscon Advance) or near matched placebo in a 1:1 ratio. The primary objective is to compare the symptomatic response in patients with PTS to liquid alginate (Gaviscon Advance) compared with placebo using the outcome measure of total Reflux Symptom Index questionnaire score at 8 weeks.

Ethics and dissemination Favourable ethical opinion was received from the East Midlands—Leicester South Research Ethics Committee (reference: 22/EM/0205). All participants will provide informed consent prior to any trial specific activity taking place. Results will be disseminated in peer reviewed publications, at national and international conferences, in peer reviewed journals and to participants and the public (using lay language).

Trial registration number ISRCTN13949559

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large randomised controlled trial to provide an evidence basis for treatment.
⇒ Remote trial delivery.
⇒ Pragmatic trial design conducted over multiple sites in the UK.
⇒ Patient waiting times and referral routes differ across the country post-COVID-19, which has required adaptation to trial design to ensure inclusivity.

INTRODUCTION

Symptoms such as a feeling of a lump in the throat, the need to clear the throat, excess mucus/post nasal drip, hoarseness or cough constitute a significant proportion of referrals from primary care into secondary care ear, nose and throat and speech and language therapy clinics, with conservative estimates being 60 000 new patients being referred in the National Health Service (NHS) annually.[1]

Manifestations of gastro-oesophageal reflux disease (GORD) have been described as the major cause of these symptoms for at least 20 years, the hypothesis being that gastric refluxate causes damage in the mucosa of the upper aerodigestive tract. The symptoms grouped together are commonly referred to as 'laryngopharyngeal reflux' (LPR). Treating patients who present with these symptoms for underlying reflux with proton pump

inhibitors (PPIs) or alginates is very common practice;[2] however, the evidence basis for this is limited.[3] The Trial of PPIs in Throat Symptoms (TOPPITS) trial has demonstrated definitively that that the common PPI lansoprazole is no more effective than placebo in treating these symptoms, indicating that empirical PPI treatment for these patients is discouraged.[4] In light of this evidence, it is likely that specialists will advocate alginates for symptom management. The term persistent throat symptoms (PTS) is preferred to describe the presenting symptoms in Trial of alginates in throat symptoms (TALGiTS) rather than LPR. This is because LPR carries with it the connotation that the symptoms are conclusively caused by underlying reflux and may promote the ineffective use of PPIs for treatment of these symptoms.

PPIs and alginates have different mechanisms of action; PPIs reduce gastric acid and alginates act as a physical barrier to refluxate. Alginates may bind to oesophageal mucosa providing protection from pepsin and gastric acid erosive effects[5]; this is supported by in vitro evidence of Gaviscon Advance preserving epithelial barrier function in oesophageal and vocal cord cells when exposed to pepsin and acid, compared with placebo.[6] Additionally, alginates may displace the pocket of acid which forms on top of stomach contents following meals,[7] may inactivate pepsin (the digestive enzyme produced by gastric mucosa) at the gastro-oesophageal junction[8] and may reduce reflux episodes.[9] Though PPI treatment is not an effective treatment for PTS,[10] the physiological differences in how PPIs and alginates may act to physically reduce reflux justify further investigation to define treatment effectiveness of alginates on the PTS patient population.

Studies of alginates as treatment for PTS are limited. An observational study (n=100) suggested that PTS improved equally in patients treated with an alginate alone as in patients treated with combined alginate and PPI treatment,[11] one small randomised clinical trial (RCT) (n=49) showed that a liquid alginate (Gaviscon Advance) improved PTS compared with no treatment[12] and a larger RCT (n=80) showed that a different alginate preparation was no more effective than placebo[13]; however, uneven baseline symptoms in this trial were a concern indicating need for a larger definitive trial.

The TALGiTS trial aims to provide the first definitive evidence for the effectiveness of alginates in the treatment of PTS. The alginate used is liquid Gaviscon Advance, chosen due to the higher concentration of alginate and the availability of a placebo. The trial design aligns with the TOPPITS trial so that the results in combination with the comparative TOPPITS results, will define the management of the PTS patient population. However, knowledge gained from the TOPPITS trial (specifically, where no relationship was demonstrated between presenting symptoms and the endoscopic appearance of the larynx and pharynx; and the primary outcome findings at 16 weeks were evident at 12 months) has allowed refinement of the current trial design to avoid unnecessarily long follow-up and provided justification for a remote approach without physical examination so that the trial can be performed prior to a standard secondary care consultation.

METHODS AND ANALYSIS

Trial methods and analysis are reported as per Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[14]

Trial design and setting

TALGiTS is a pragmatic multicentre, placebo-controlled, two-arm, parallel design, double blind, randomised controlled trial. It will be conducted at up to 15 secondary care NHS sites with phased activation of recruitment over 6 months, following which there will be 16 months of recruitment at all sites.

The intention is for the trial to have a remote delivery coordinated by the trial sites. Participants may complete consent electronically and trial follow-ups via electronic patient reported outcomes (ePRO), and these participants will be sent electronic invites by email or text message containing a link to complete follow-up assessments on an electronic device. Trial medication will be delivered to participants from a Central Distribution Centre (CDC) via a courier. Though remote delivery is intended, the protocol is flexible permitting different methods of participant contact including telephone, post and in person contact.

The trial aim is to recruit 250 participants presenting with PTS, each site having a target to recruit 1–2 patients per month. Participants will be randomised 1:1 to receive either Gaviscon Advance or near-matched placebo. 125 participants will be recruited to each trial arm. Following the end of their participation in the trial, participants will continue with standard NHS care. The trial will end following the last participant follow-up or the completion of trial questionnaires, whichever occurs last.

The trial is sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust (tnu-tr.sponsormanagement@nhs.net) and has independent oversight from a Data Monitoring and Ethics Committee (IDMEC) and a Trial Steering Committee (TSC). The IDMEC and TSC consist of independent experts in the field and patient and public representatives. Each committee has a charter, agreed by the independent members, defining their roles and responsibilities.

Patient eligibility: inclusion and exclusion criteria

Patients are eligible for the trial if all of the following inclusion criteria apply:

1. Aged ≥18 years.
2. ≥ 6 week history of PTS (hoarse voice, lump in throat sensation, throat clearing, cough, post-nasal secretions/catarrh, throat discomfort) as evidenced by a total RSI score omitting the ninth item (heartburn symptoms (HB) ‘heartburn, chest pain, indigestion or stomach acid coming up’ —that is, RSI – HB) ≥ 13.

3. Ability to comprehend trial information and complete trial questionnaires.
4. Willing and able to provide informed consent prior to any trial procedures taking place.

Patients are excluded from the trial if any of the following apply:

1. Any symptoms that meet the The National Institute for Health and Care Excellence guidance for 2 week wait suspected head and neck cancer referral, that is, persistent unexplained hoarseness or unexplained neck lump, except for those patients who have had these symptoms reviewed and no underlying malignancy found.
2. Any symptoms that when entered into the head and neck cancer risk calculator (ORLHealth.com | HaNC-RC v2, 2019) lead to a recommended urgent suspected cancer referral, except for those patients who have been clinically assessed face to face and no underlying malignancy found.
3. Prior to screening, intake of:
   systemic glucocorticosteroids within 28 days of screening;
   prokinetics (eg, cisapride) or drugs with prokinetic function, such as macrolide antibiotics, during the preceding 5 days and initiated in the previous 2 weeks of screening;
   anticholinergic drugs, sucralfate or any other drugs that in the investigator's opinion may affect the baseline measurements for the patient within 7 days of screening.
4. Female participants with a known pregnancy.
5. Known chronic kidney diseases. Patients with a history of chronic kidney disease will be specifically asked about: reduced kidney function, controlled potassium diet, hypophosphataemia, phenylketonuria, hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi.
6. Patients with known or suspected hypersensitivity to the active substances (sodium alginate, potassium hydrogen carbonate), or active substance excipients (methyl parahydroxybenzoate (E128), propyl parahydroxybenzoate (E216), sodium hydroxide, saccharin sodium, carbomer, calcium carbonate) or placebo excipient ingredients (hydrogenated glucose syrup, xanthan gum, titanium dioxide, caramel).
7. Administration of an investigational medicinal product (IMP) within 30 days of the first dose of IMP.
8. Any current or prior head and neck or gastro-oesophageal malignancy.
9. Current or prior malignancy not in complete remission within 3 years of screening with the exception of adequately treated basal cell carcinoma of the skin or in situ carcinoma of the uterine cervix.
10. Inability, in the opinion of the investigator, to be able to complete the clinical trial visits or procedures.
11. Any condition which, in the opinion of the investigator, would exclude the patient from participation in the trial.

Objectives and outcomes

The primary and secondary objectives for the trial are described in table 1.

Table 1 Objectives and outcome measures

Objectives		Outcome measures
Primary	To compare the symptomatic response in patients with persistent throat symptoms (PTS) at the end of 8 weeks of treatment with liquid alginate (Gaviscon Advance) versus placebo	► Total Reflux Symptom Index (RSI) at 8 weeks
Secondary	To compare the symptomatic response in patients with PTS at the end of 8 weeks of treatment with a liquid alginate (Gaviscon Advance) versus placebo	► RSI omitting the heartburn item at 8 weeks ► Comprehensive Reflux Symptom Score and its oesophageal, upper airway and pharyngeal subscales at 8 weeks
	To compare the symptomatic response in patients with PTS at 2, 4 and 6 weeks of treatment.	► Total RSI at 2, 4 and 6 weeks ► RSI omitting the heartburn item at 2, 4 and 6 weeks
	To assess investigational medicinal product compliance at the end of 8 weeks of therapy	► Participant reported trial medication compliance at 8 weeks
	Participants' view on which medication they received	► Direct question of the participants opinion of whether they were taking Gaviscon Advance or placebo as part of the trial, asked at 8 weeks
	Satisfaction with the trial	► Overall Satisfaction Score Questionnaire at 8 weeks ► Direct question of whether the participant would recommend the trial to family or friends, asked at 8 weeks

The primary objective is measured using the RSI, a nine-item, self-administered, validated questionnaire which captures LPR symptoms experienced by patients and the symptom severity (via a 6-point scale of 0–5 with 0 being no problem and 5 being severe).[15] An RSI score of≥13 is considered abnormal.

RSI is the most frequently used primary outcome measure in throat symptoms research. It was chosen as the primary outcome measure for TALGiTS to allow comparison in the literature and to mirror methodology of the TOPPITS trial,[4] allowing direct comparison between two commonly used medications in PTS. However, the RSI has limitations, in particular the absence of a throat pain score and traditional GORD symptoms being grouped together in the single, polysymptomatic, nineth item ('heartburn, indigestion, chest pain and stomach acid coming up'). To address this the comprehensive reflux symptom score (CReSS) questionnaire[16] is included in secondary outcome measures for the trial. This is a 34-item, self-administered, questionnaire which includes the RSI items but with the nineth item separated into four distinct items, 15 items from the GORD Symptom Assessment Scale (GSAS) and 10 symptoms originally included in the GSAS. Each item is scored using a 6-point scale of 0–5 with 0 being no problem and 5 being severe problem.

Identification, consent and screening of patients

Patients will be identified and recruited to the trial from one of two referral pathways: Referral Pathway 1 and Referral Pathway 2.

Referral pathway 1

The population for Referral Pathway 1 is patients who have been newly referred to secondary care NHS trial sites via a non-urgent referral for PTS. The aim is to deliver the trial remotely between the patients' referral and their first clinic appointment. All referral letters at trial sites will be triaged, those deemed as 'appropriate to screen for TALGiTS' will be contacted by the site team to explain the trial. Interested patients will be sent the patient information sheet (PIS) (online supplemental information). Each potential participant will have time to read and consider the PIS before having an opportunity to discuss the trial further with a member of the research team. Written, informed consent (online supplemental information) will be obtained by a medically qualified member of the research team prior to any trial specific screening activity, this will either be by remote eConsent or paper-based consent. Patients will then be screened for eligibility via the inclusion and exclusion criteria.

The following assessments will be completed as part of screening:

- Head and neck risk calculator.
- Demographics, medical history and medication history.
- RSI questionnaire.
- CReSS questionnaire.

To mitigate the risk of recruiting a patient with symptoms suggestive of a head and neck cancer, especially given the remote nature of the trial, clinicians will be required to complete the head and neck cancer risk calculator (ORLHealth.com | HaNC-RC v2 2019) in conversation with participants at screening/baseline. This assessment calculates an estimated probability of head and neck cancer and gives a recommendation of a referral timeframe, these are:

- Urgent, ≥ 7.1% risk, recommends a 2 week referral.
- Moderate, 2.2–7.09% risk, recommends a referral for an appointment within 6 weeks.
- Routine, <2.2% risk, recommends a routine appointment.

Patients with a risk score of 7.1% or above will not be recruited and will instead be directed towards a suspected head and neck cancer 2 week wait referral.

The calculator was assessed on over 3500 newly referred patients in Scotland; this showed that the prevalence of subsequent head and neck cancer in the routine risk category (47% of the 3500 patients) is less than 1% and in the moderate risk category (25% of the 3500 patients) is 3%.[17] Another assessment of the risk calculator during the COVID-19 pandemic included over 4500 patients referred on the suspected head and neck cancer pathway. Patients' symptoms were graded as urgent or non-urgent (moderate and low risk categories). The rate of cancers was 9.7% in the 2424 patients graded as urgent and 0.9% in the 2131 patients graded as non-urgent.[18] Taken together, these studies support the use of the risk calculator to assess trial eligibility.

Referral pathway 2

Patients who have been seen face-to-face or remotely in Ear Nose and Throat (ENT) and/or Speech and Language Therapy (SaLT) department clinics, following referral from primary care, where no malignancy has been diagnosed but where PTS is a reasonable diagnosis to be made, may be considered for eligibility to take part in the trial. From here on all approach, consent and eligibility assessment are as per Referral Pathway 1 with the exception that the head and neck risk calculator does not need to be completed for those patients who have had a face-to-face examination with no malignancy identified.

Randomisation

Eligible patients will be randomised to one of two treatments arms; Gaviscon Advance or near matched placebo, in a 1:1 ratio. Treatment allocation is double blind. Randomisation will be carried out using the trial database, Sealed Envelope (London, UK), a central, secure, 24-hour, web-based randomisation system with concealed allocation.

The allocation sequence will be computer-generated, using a random permuted block design; blocks might vary in size. Block sizes will not be disclosed, to ensure concealment. Randomisation will be stratified by two

Table 2 Investigational medicinal product contents

Treatment	Appearance	Contents of each dose (10 mL)
Gaviscon Advance	Off-white, viscous suspension	► 1000 mg sodium alginate ► 200 mg potassium hydrogen bicarbonate
Placebo	Off-white, viscous suspension	► Near-matched placebo (ingredients include: purified water, hydrogenated glucose syrup, peppermint flavour, preservatives, colourant)

variables: total 9-item RSI score (<20 or ≥20) and age (<40, 40–70,>70).

Intervention

Treatment allocation is double-blind. Each bottle of IMP is identical in appearance, to maintain the blind, and the contents of each treatment are listed in table 2. Participants will receive one kit of trial IMP sent to them via courier from a CDC. Each kit will contain sufficient IMP for the 8 week treatment period with an additional two bottles of medication to account for any breakages.

Participants will take 10 mL of their trial medication, four times a day for a total of 8 weeks. Three of the daily doses will be taken after meals and one dose will be taken before bedtime. If any meals are missed, medication could be taken after a snack or at a suitable interval time period between the other doses. No dose modifications are permitted.

Developing a placebo to match an alginate which is gloopy but does not adhere and potentially protect oesophageal mucosa, and whose peppermint flavour does not reduce heartburn has been the challenge. The manufacturers of Gaviscon products, Reckitt, have devised and tested a liquid placebo for Gaviscon Advance. This placebo is indistinguishable in appearance (colour, viscosity, opalescence), odour and taste; however, the mouth feel is slightly different resulting in it being a near-matched rather than matched placebo. Due to the trial's parallel design, remote delivery and blinding, there is only a very low risk that the small difference in mouthfeel would break the blind. The trial has been designed with an effect size (small to medium) and sample size large enough to allow any meaningful difference between the active alginate and the near matched placebo to be observed.

Participant follow-up and assessments

Follow-up will take place remotely wherever possible at 2, 4 and 6 weeks. At week 8, participants can be seen at a face to face appointment in clinic, or this can be performed remotely, as detailed in the trial schedule of events (online supplemental table 1).

Participants will complete RSI and CReSS questionnaires, which records participant symptoms every 2 weeks throughout their 8 week participation in the trial.

In addition to RSI and CReSS questionnaires, participants will complete short questionnaires about any new medications that they may have started or stopped taking, any adverse events (AEs) that may have occurred and report how much medication they have used and have left so that compliance can be established.

Pharmacovigilance

All AEs occurring from consent to end of trial participation will be recorded. Participants will be asked to report any side effects either via ePRO at follow-ups 1, 2 and 3 or over telephone, video consultation or face to face visits. Side effects will be reviewed by the trial team and where appropriate reported as AEs on the trial database and recorded in the participant's medical records (with the exception of protocol specific reporting exclusions—symptoms (including worsening of symptoms) relating to PTS such as hoarse voice, sore throat, feeling a lump in the throat, cough, throat clearing, postnasal secretions and catarrh).

AEs meeting the seriousness criteria (serious AEs (SAEs)) will be reported within 24 hours of awareness. Suspected Unexpected Serious Adverse Reactions will be reported to the Medicines and Healthcare products Regulatory Agency and Research Ethics Committee (REC) within the required regulatory reporting timelines.

Emergency unblinding is available for valid medical or safety reasons where it is necessary for the treating clinician to know which treatment a participant has been receiving. Emergency unblinding should be carried out by the site principal investigator or another medically qualified delegated member of the research team by accessing the 24-hour web-based randomisation system.

In the event of a trial participant becoming pregnant during their participation in the trial, this will be reported within 24 hours of awareness. Due to Gaviscon Advance being licenced for use in pregnancy, participants who become pregnant/find out that they are pregnant during their participation in the trial (ie, post-randomisation) may continue to take part in the trial.

Discontinuation and withdrawal

Participants have the right to discontinue trial treatment or withdraw from the trial at any time without detriment to their care. Participants choosing to discontinue trial treatment will be invited to complete all trial follow-up visits and assessments. Participants choosing to withdraw from the trial will not take part in any further trial activity. Data collected up to the point of withdrawal will be retained and included in analysis, as per consent for the trial. Participants who withdraw from the trial after receiving IMP (full or part dose) will not be replaced.

Data management

Delegated site staff will enter participant data into the trial-specific Clinical Data Management System (CDMS); Sealed Envelope's Red Pill (Sealed Envelope, London, UK). CDMS users will have password limited access, restricted to their site and role based on their delegated duties. Each screened patient will be assigned a unique, sequential, trial identification number by the site staff. This unique identifier is used to add the patients to the CDMS and becomes their participant ID at the time of randomisation.

Overall responsibility for data collection, quality and retention lies with the chief investigator who is the custodian of the final trial dataset. Data will be handled, computerised, stored and archived in accordance with the General Data Protection Regulation (2018) and the latest Directive on GCP (2005/28/EC). Newcastle Clinical Trials Unit staff will monitor the trial conduct and data integrity in accordance with the trial monitoring plan. The trial specific data management plan and data validation plan include details of how data will be managed and validated.

Analysis

The primary analysis population will be the intention-to-treat (ITT) population where all ineligible and protocol violator participants will be included in the analysis on an ITT basis with participants kept in their randomised treatment group. In addition, a compliant ITT population will be analysed as for ITT population, where participants are included only if the primary endpoint data were collected within the compliance window of −6/+14 days around the primary endpoint 8 week clinic visit. Baseline demographics will be presented by treatment group.

The primary outcome measure is RSI score at 8 weeks. Descriptive analysis, including boxplots, of RSI scores at baseline and the follow-up timepoints, along with changes in scores from baseline to these time points, will be carried out. The primary analysis as specified in the protocol will be a mixed effects linear regression model. Specifically, the primary outcome measure (RSI score at 8 weeks) will be analysed as a continuous outcome using a mixed effects linear regression model in order to compare the 8 week RSI scores between the treatment groups while adjusting for RSI score at the time of randomisation (week 0) and also adjusted for stratification factors used at randomisation. These are categorical age group (<40, between 40 and 70, >70) and categorical baseline severity as defined by the binary baseline RSI-HB (mild, severe) as fixed effects covariates in the analysis along with the inclusion of recruiting centre (as a random effect). The primary analysis will be carried out on a complete case basis (only cases with complete data on the necessary variables will be included). The treatment effect will be estimated from the model and reported with a 95% CI. A two-sided level of statistical significance of 5% will be used.

Secondary analysis will be broadly similar to that described for the primary analysis and will consist of using Total CReSS scores as the response in the place of RSI scores in the analyses previously described.

Sample size calculations

The target sample size is 250 patients. Assuming a clinically meaningful standardised effect size of 0.4, with a power of 90% and set a two-sided type 1 error rate of 5%, 133 participants would be required per arm. Our primary analysis will adjust for baseline RSI, and assuming a correlation of 0.5 for RSI between baseline and 8 weeks post baseline (based on actual observations from TOPPITS trial between baseline and 16 weeks),[4] the sample size reduces to 100 participants per arm. With allowance for a 20% attrition rate, 125 participants will be recruited per arm.

Patient and public involvement

Patient and public involvement and engagement (PPIE) members were involved in the trial design and development of trial documentation. Independent PPI members have oversight of the trial and results dissemination as members of the TSC.

Trial status

TALGiTS opened to recruitment on 25 May 2023 and is currently actively recruiting participants. Recruitment is due to end by 31 March 2025 with participant follow-up to be completed by 30 June 2025. Analysis and reporting will take place in the 6 months following completion of participant follow-up. This manuscript is based on protocol V4.0 dated 28 June 2023.

ETHICS AND DISSEMINATION

Favourable ethical opinion was received from the East Midlands—Leicester South REC (reference: 22/EM/0205). Patients will be provided trial information, following reasonable time to consider participation; patients interested in taking part in the trial will be asked to provide informed consent prior to any trial activity. Consent will be taken by a medically qualified member of the delegated trial team and may take place by electronically (eConsent) or by paper-based written consent.

Trial results will be disseminated in peer reviewed publications, at national and international conferences, in peer reviewed journals and to participants and the public (using lay language).

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amendments and have revised the manuscript and given approval for the final version. TF and DT have advised on trial design and provided statistical oversight and analysis. HS provided IMP oversight. MM, RJ, LE, JT and RW provided trial and database design and management and trial monitoring.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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