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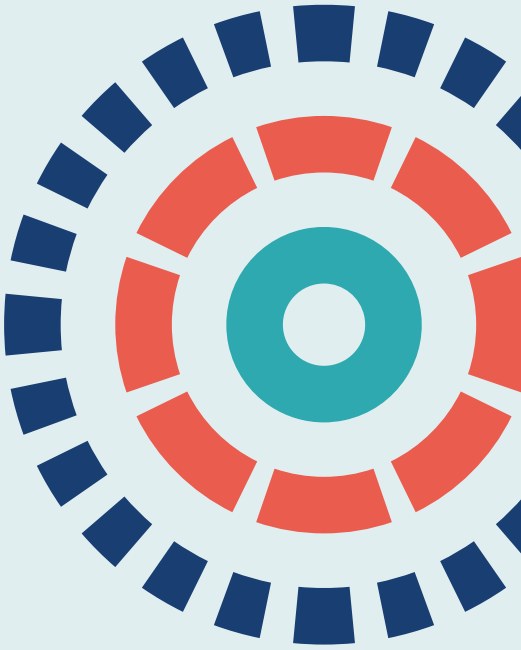

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Lansoprazole for persistent throat symptoms in secondary care: the TOPPITS RCT

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This report

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Abstract

Lansoprazole for persistent throat symptoms in secondary care: the TOPPITS RCT

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Background: Persistent throat symptoms are commonly attributed to 'laryngopharyngeal reflux'. Despite a limited evidence base, these symptoms are increasingly being treated in primary care with proton pump inhibitors.

Objective: To assess the value of proton pump inhibitor therapy in patients with persistent throat symptoms.

Design: This was a double-blind, placebo-controlled, randomised Phase III trial.

Setting: This was a multicentre UK trial in eight UK ear, nose and throat departments.

Participants: A total of 346 participants aged ≥ 18 years with persistent throat symptoms and a Reflux Symptom Index score of ≥ 10, exclusive of the dyspepsia item, were recruited.

Intervention: Random allocation (1 : 1 ratio) to either 30 mg of lansoprazole twice daily or matched placebo for 16 weeks.

Main outcome measure: Symptomatic response (i.e. total Reflux Symptom Index score after 16 weeks of therapy).

Results: A total of 1427 patients were screened and 346 were randomised. The mean age was 52 years (standard deviation 13.7 years, range 20–84 years); 150 (43%) participants were male and 196 (57%) were female; 184 (53%) participants had a mild Reflux Symptom Index minus the heartburn/dyspepsia item and 162 (47%) had a severe Reflux Symptom Index minus the heartburn/dyspepsia item. A total of 172 patients were randomised to lansoprazole and 174 were randomised to placebo.

Main outcomes: A total of 267 participants completed the primary end-point visit (lansoprazole, $n = 127$; placebo, $n = 140$), of whom 220 did so between 14 and 20 weeks post randomisation ('compliant' group); 102 received lansoprazole and 118 received placebo. The mean Reflux Symptom Index scores at baseline were similar [lansoprazole 22.0 (standard deviation 8.0), placebo 21.7 (standard deviation 7.1), overall 21.9 (standard deviation 7.5)]. The mean Reflux Symptom Index scores at 16 weeks reduced from baseline in both groups [overall 17.4 (standard deviation 9.9), lansoprazole 17.4 (standard deviation 9.9), placebo 15.6 (standard deviation 9.8)]. Lansoprazole participants had estimated Reflux Symptom Index scores at 16 weeks that were 1.9 points higher (worse) than those of placebo participants (95% confidence interval –0.3 to 4.2; $p_{adj} = 0.096$), adjusted for site and baseline severity.

Secondary outcomes: Ninety-five (43%) participants achieved a Reflux Symptom Index score in the normal range (< 12) at 16 weeks: 42 (41%) in the lansoprazole group and 53 (45%) in the placebo group. A total of 226 participants completed the end-of-trial follow-up visit (lansoprazole, $n = 109$; placebo, $n = 117$), of whom 181 were 'compliant'. The mean Reflux Symptom Index scores at 12 months reduced from baseline in both groups [lansoprazole 16.0 (standard deviation 10.8), placebo 13.6 (standard deviation 9.6), overall 14.7 (standard deviation 10.2)]. A total of 87 (48%) participants achieved a Reflux Symptom Index score in the normal range at 12 months: 33 (40%) in the lansoprazole group and 54 (55%) in the placebo group. Likewise, the Comprehensive Reflux Symptom Score and Laryngopharyngeal Reflux – Health Related Quality of Life total scores and subscales all showed very similar changes in the lansoprazole and placebo cohorts at both 16 weeks and 12 months.

Limitations: Drop-out rate and compliance are issues in pragmatic clinical trials. The Trial Of Proton Pump Inhibitors in Throat Symptoms (TOPPITS) aimed to detect clinically relevant difference with 90% power. The 346 randomised participants reduced to 283 at the primary end point; 267 completed the primary outcome measure, 220 within the protocol time scale. Despite this, the powers to detect the clinically relevant difference in Reflux Symptom Index score at 16 weeks were 82% (compliant comparison) and 89% (pragmatic comparison). The lack of difference between lansoprazole and placebo is generalisable across NHS clinics.

Conclusions: Participants on lansoprazole did not report significantly better outcomes than participants on placebo on any of the three patient-reported outcome tools (Reflux Symptom Index, Comprehensive Reflux Symptom Score and Laryngopharyngeal Reflux – Health Related Quality of Life). This multicentre, pragmatic, powered, definitive Phase III trial found no evidence of benefit for patients by treating persistent throat symptoms with lansoprazole.

Trial registration: Current Controlled Trials ISRCTN38578686 and EudraCT number 2013-004249-17.

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Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 Supplementary tables and figures

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta25030).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
AIC	Akaike information criterion
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CReSS	Comprehensive Reflux Symptom Score
DMC	Data Monitoring Committee
ENT	ear, nose and throat
EOR	extraesophageal reflux
GORD	gastroesophageal reflux disease
GP	general practitioner
HR	hazard ratio
IMP	investigational medicinal product
IQR	interquartile range
ISF	investigator site file
ITT	intention to treat
LPR	laryngopharyngeal reflux
LPR-HRQL	Laryngopharyngeal Reflux – Health Related Quality of Life
MII-pH	multichannel intraluminal impedance and pH
NCTU	Newcastle Clinical Trials Unit
OR	odds ratio
PIS	patient information sheet
PPI	proton pump inhibitor
RCT	randomised controlled trial
RFS	Reflux Finding Score
RSI	Reflux Symptom Index
RSI-HB	Reflux Symptom Index minus the heartburn/dyspepsia item
SAE	serious adverse event
SAUC	standardised area under the curve
SD	standard deviation
SMD	standardised mean difference
TOPPITS	Trial Of Proton Pump Inhibitors in Throat Symptoms
TSC	Trial Steering Committee
TUF	TOPPITS User Forum
UOS	upper oesophageal sphincter

Plain English summary

Background

One of the commonest reasons for patients attending hospital throat or voice clinics is persistent throat symptoms, which include a feeling of a lump in the throat, a cough or a hoarse voice. Over time, more of these patients are being treated with proton pump inhibitors to suppress stomach acid in the belief that stomach acid entering the throat causes the symptoms, but there is little evidence that these medications work.

Study aim

The aim of this study is to explore whether or not having a 16-week course of proton pump inhibitors has any impact on throat symptoms. We also tested the usefulness of three different questionnaires in measuring throat symptoms, explored side effects and whether or not patients adhere to treatment, and measured patients' quality of life.

Methods

Patients with persistent (lasting for more than 6 weeks) throat symptoms who agreed to participate were randomised to receive either the proton pump inhibitor lansoprazole or a placebo. Participants took lansoprazole or placebo for 16 weeks. Symptoms and quality of life were measured before patients were randomised and at 4 and 12 months after randomisation.

Results

The total number of participants was 346. The mean Reflux Symptom Index outcome score (higher scores meaning worse symptoms) was 22 before the 4-month course of capsules, 16 after 4 months and 15 after 12 months. Participant-reported throat symptoms and quality of life in all participants improved over the 12 months of the study. There was no difference in the symptom improvement experienced by proton pump inhibitor and placebo participants.

Conclusions

This study shows that proton pump inhibitors do not benefit patients with persistent throat symptoms. Future research should focus on other available therapies.

Scientific summary

Background

Persistent throat symptoms, such as globus pharyngeus, catarrh, throat clearing and recurrent hoarseness, are among the commonest reasons for attendance at secondary care throat or voice clinics. There is a growing trend to treat throat symptom patients with proton pump inhibitors to suppress stomach acid, in the belief that acid refluxing into the throat leads to the symptoms. However, most controlled studies fail to demonstrate a significant benefit of proton pump inhibitors over placebo. In addition, patient views on proton pump inhibitor use vary widely.

Objectives

Primary objective

To compare the symptomatic response in patients with persistent throat symptoms at the end of 16 weeks' therapy with lansoprazole versus placebo.

Secondary objectives

- To explore recruitment feasibility using an internal pilot.
- To compare the symptom response at 12 months with that at 16 weeks.
- To assess potential outcome predictors, namely the Reflux Symptom Index, the Comprehensive Reflux Symptom Score, the Reflux Finding Score laryngoscopic evaluation, age, sex, smoking and body mass index.
- To assess side effects, treatment compliance and use of self-pay medications.
- To compare changes in disease-specific quality of life as assessed by the Laryngopharyngeal Reflux – Health Related Quality of Life.

Methods

Setting and conduct

This multicentre trial was conducted at eight UK NHS sites, recruiting participants from 28 April 2014 to 28 February 2017. The trial received a favourable ethics opinion from the National Research Ethics Service Committee North East – Tyne and Wear South (reference: 13/NE/0336) on 2 December 2013 and a Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency on 12 February 2014. A trial-specific website (www.TOPPITS.co.uk) was designed.

Trial design

This was a multicentre, Phase III, randomised, double-blind, placebo-controlled trial, with an internal feasibility pilot, carried out in secondary care. Patients with persistent throat symptoms were identified and recruited from NHS ear, nose and throat clinics. This was a pragmatic trial designed to mirror current NHS clinical practice. Participants were randomised in a double-blind fashion between two treatment groups in a 1 : 1 ratio, stratified by centre and baseline severity [on the basis of the Reflux Symptom Index score omitting item 9 ('Heart burn, chest pain, indigestion, or stomach acid coming up'), hereinafter referred to as Reflux Symptom Index minus the heartburn/dyspepsia item (range 0–40)]. The 'mild' cohort had Reflux Symptom Index minus the heartburn/dyspepsia item scores of 10–20 (inclusive) and the 'severe' cohort had scores of > 20.

Inclusion criteria

- Referred with a history of throat symptoms (globus pharyngeus, hoarseness, throat clearing, throat discomfort, choking spasms, excess mucus/postnasal drip, otherwise unexplained night-time cough or choking) that had been persistent for at least 6 weeks.
- Score of ≥ 10 on the non-heartburn items of the Reflux Symptom Index.

Exclusion criteria

- Reflux Symptom Index minus the heartburn/dyspepsia item score of < 10.
- Unwilling to undergo flexible endoscopy.
- Aged < 18 years.
- Endoscopic evidence of specific laryngopharyngeal pathology that would ordinarily be treated by surgical intervention or be investigated by specific investigations.
- Performing voice users.
- Pregnancy.
- Currently on acid suppressants, acid neutralisers and alginates and unwilling to discontinue use for (1) a 4-week pre-study washout period in the case of proton pump inhibitor usage or (2) a 24-hour period for alginate or acid neutraliser.

Randomisation

A blocked allocation (permuted random blocks of variable length) system was used to allocate participants in a 1 : 1 ratio, stratified by centre and baseline severity (Reflux Symptom Index minus the heartburn/dyspepsia item score: group 1, ≤ 20; group 2, > 20).

Interventions

The active intervention was a 16-week course of a 30-mg twice-daily dose of the proton pump inhibitor lansoprazole. The control group received a 16-week course of twice-daily matched placebo.

Outcomes

Primary outcome

The primary outcome measure was the symptomatic response measured using the Reflux Symptom Index in patients with persistent throat symptoms at the end of 16 weeks' therapy with lansoprazole versus placebo. The Reflux Symptom Index score is calculated from a nine-item, self-administered questionnaire scored on a Likert scale with each item score ranging from 0 to 5, giving a total score range of 0–45. A higher score indicates more severe symptoms.

Secondary outcome measures

- Reflux Symptom Index changes at 12 months after randomisation.
- Reflux Symptom Index minus the heartburn/dyspepsia item.
- Comprehensive Reflux Symptom Score total and subscales (oesophageal, upper airway and pharyngeal).
- Quality of life measured using the Laryngopharyngeal Reflux – Health Related Quality of Life total score and subscales.
- Laryngeal mucosal changes recorded by Reflux Finding Score total (range 0–29), scored by an independent observer.
- The ability of the Reflux Finding Score and patient characteristics (age, sex, smoking status and body mass index) to predict any observed responses.
- Side effects, adverse events and serious adverse events.
- Use of over-the-counter medication.
- Participant-reported satisfaction with the trial using a five-point overall satisfaction scale.
- Participant accuracy in determining which treatment they had received.

Sample size

A mean difference of 3 points in the Reflux Symptom Index score at 16 weeks was agreed to be a clinically relevant target. A mean difference of 3.1 points with an assumed standard deviation of 7.7 equates to a standardised mean effect size of 0.4 (upper bound of small effect, lower bound of medium effect). A total of 332 participants (166 in each group of the study) were required, to provide 266 participants (133 in each group) completing the trial intervention, to detect a standardised mean effect size of 0.4 with 90% power and a 5% significance level allowing for 20% loss to follow-up. There were no planned formal interim analyses or stopping rules.

Statistical methods

Descriptive statistics were used to summarise patient characteristics, treatment compliance, Reflux Symptom Index and other secondary measures. For the primary outcome measure, an unadjusted univariate analysis of the 16-week Reflux Symptom Index was carried out. The primary analysis was a multivariable analysis using the analysis of covariance and multilevel mixed-effect linear regression to compare the Reflux Symptom Index at 16 weeks while adjusting for potential confounders, specifically stratification factors at randomisation.

The primary hypothesis tested was H_0: the mean Reflux Symptom Index at 16 weeks in the lansoprazole group is equal to the mean Reflux Symptom Index at 16 weeks in the placebo group after adjustment for baseline stratification factors. Secondary analyses of the primary outcome measure considered adjustment for important clinical and demographic baseline factors, specifically sex, age, body mass index, smoking status, alcohol consumption, baseline laryngeal appearance scores by the Reflux Finding Score, Comprehensive Reflux Symptom Score total and subscales and categories of symptoms. Three models were derived for each outcome:

- model 1 – adjusted for stratification factors at randomisation [recruiting centre (as a random effect) and baseline severity as defined by the binary Reflux Symptom Index minus the heartburn/dyspepsia item cut-off value of 20 (as a fixed effect)]
- model 2 – adjusted for baseline severity with Reflux Symptom Index minus the heartburn/dyspepsia item utilised better as a continuous measure
- model 3 – adjusted for baseline severity (Reflux Symptom Index minus the heartburn/dyspepsia item as a continuous measure) and other important clinical and demographic baseline factors, specifically age, sex, smoking status and body mass index.

Continuous covariates were investigated for non-linear relationships with outcomes using first-order fractional polynomial transformations, which were retained if they substantially improved the model fit based on the Akaike information criterion. The optimal model was derived using a forward selection method with comparison of –2log-likelihood for variable inclusion. Analyses were conducted at a two-sided 5% level of significance throughout. The impact of removing any covariates from the final model was assessed in order to derive the most parsimonious model.

The analysis of secondary outcomes followed a broadly similar strategy for questionnaire scores. Safety data were not subject to statistical comparison. Analyses were carried out on a complete-case basis. Missing data were described. The use of multiple imputation techniques was considered for the primary outcome and covariate data if data were missing for participants completing the study to a sufficient extent (> 10%) and deemed missing at random. No formal interim analyses were planned. A statistical analysis plan was in place prior to any comparative analyses and was approved by the external oversight committees. Primary statistical analyses were based on a compliant intention-to-treat group of participants who attended their 16-week follow-up visit between 14 and 20 weeks, with sensitivity analyses on a pragmatic intention-to-treat group including all 16-week follow-up assessments. Data were analysed using the statistical software package Stata® version 14 (StataCorp LP, College Station, TX, USA).

Results

A total of 346 participants, out of 1427 initially screened for eligibility, were recruited and randomised; 172 were randomised to the lansoprazole group and 174 were randomised to the placebo group. Of those randomised to lansoprazole, 101 were female (59%) and 71 were male (41%), with a mean age of 53.5 (standard deviation 13.3) years. In the placebo group, there were 95 (55%) females and 79 (45%) males, with a mean age of 50.8 (standard deviation 13.9) years. The mean overall body mass index was 28.1 kg/m^2 (standard deviation 5.6 kg/m^2, range 11.3–56.9 kg/m^2). A total of 184 (53%) participants in both groups had mild Reflux Symptom Index minus the heartburn/dyspepsia item scores at baseline, and 162 (47%) reported severe scores. Overall, there were 125 participant withdrawals and losses to follow-up. A total of 267 (77%) participants completed the primary outcome measure at 16 weeks as the 'pragmatic intention-to-treat group' (127 in the lansoprazole group and 140 in the placebo group) according to the sample size; 220 participants completed the primary outcome measure within the 14- to 20-week window as the 'compliant intention-to-treat group' (102 in the lansoprazole group and 118 in the placebo group).

Primary outcome measure

For the primary compliant intention-to-treat group, the mean Reflux Symptom Index in the lansoprazole group at baseline was 22.0 (95% confidence interval 20.4 to 23.6), reducing to 17.4 (95% confidence interval 15.5 to 19.4) after 16 weeks of treatment. The mean Reflux Symptom Index in the placebo group at baseline was 21.7 (95% confidence interval 20.5 to 23.0), reducing to 15.6 (95% confidence interval 13.8 to 17.3) after 16 weeks of treatment. The lansoprazole group had a mean 16-week score that was 1.8 points higher than that in the placebo group (t-score = 1.402, $p = 0.162$).

There was no statistically significant difference between the randomised groups (lansoprazole vs. placebo) when adjusted for site and baseline binary Reflux Symptom Index minus the heartburn/dyspepsia item ($p = 0.096$). The estimated difference between randomised groups when accounting for site and baseline severity indicated that participants receiving lansoprazole had Reflux Symptom Index scores at 16 weeks that were 1.9 points higher (worse) than those of the placebo group (95% confidence interval –0.3 to 4.2; $p = 0.096$). Participants in the severe symptom stratum at baseline had Reflux Symptom Index scores at 16 weeks that were 8 points higher (worse) than the mild stratum. Results were similar in the sensitivity analysis conducted in the pragmatic intention-to-treat group.

Reflux Symptom Index score omitting item 9

A secondary analysis of the primary outcome based on the Reflux Symptom Index minus the heartburn/dyspepsia item score showed that the lansoprazole group had a mean 16-week score that was 2.4 points higher than that of the placebo group: 16.3 (95% confidence interval 14.5 to 18.1) versus 13.9 (95% confidence interval 12.2 to 15.5), respectively ($t = 1.945$, $p = 0.053$). When adjusted for site and continuous baseline severity Reflux Symptom Index minus the heartburn/dyspepsia item, the placebo group again showed a greater reduction in symptoms, estimating that lansoprazole participants had Reflux Symptom Index minus the heartburn/dyspepsia item scores at 16 weeks that were 2.0 points higher (worse) than placebo participants (95% confidence interval 0.0 to 4.0; $p = 0.049$).

Secondary outcome measures

Reflux Symptom Index changes at 12 months after randomisation

The mean Reflux Symptom Index in the lansoprazole group at 12 months was 16.0 (95% confidence interval 13.6 to 18.4); in the placebo group, it was 13.6 (95% confidence interval 11.7 to 15.5). There was no statistically significant difference between lansoprazole and placebo when adjusted for site and baseline continuous Reflux Symptom Index minus the heartburn/dyspepsia item. The estimated difference between the groups is that lansoprazole participants have Reflux Symptom Index scores at 12 months 1.7 points higher (worse) than placebo (95% confidence interval –0.7 to 4.1; $p = 0.157$). Results were similar in the sensitivity analysis conducted in the pragmatic intention-to-treat group.

Comprehensive Reflux Symptom Score total and subscales (oesophageal, upper airway and pharyngeal)

The total Comprehensive Reflux Symptom Score was 50.3 (95% confidence interval 44.9 to 55.7) at baseline in the lansoprazole group, reducing to 38.9 (95% confidence interval 33.4 to 44.3) at 16 weeks and 36.6 (95% confidence interval 29.8 to 43.5) at 12 months. In the placebo group, the total Comprehensive Reflux Symptom Score was 51.1 (95% confidence interval 46.4 to 55.8) at baseline, 34.7 (95% confidence interval 29.6 to 39.9) at 16 weeks and 31.8 (95% confidence interval 26.6 to 36.9) at 12 months.

The relationship between the Reflux Symptom Index at baseline and total Comprehensive Reflux Symptom Score at baseline for the compliant intention-to-treat group demonstrates a linear relationship, suggesting that an increased Comprehensive Reflux Symptom Score is associated with an increased Reflux Symptom Index score. Baseline Comprehensive Reflux Symptom Score total and subscales appear to be significant predictors of the primary outcome (Reflux Symptom Index at 16 weeks). The Comprehensive Reflux Symptom Score upper airway covariate explains more variability in the Reflux Symptom Index score at 16 weeks than the total Comprehensive Reflux Symptom Score does but, nevertheless, performs less well than Reflux Symptom Index minus the heartburn/dyspepsia item.

Quality of life: change in Laryngopharyngeal Reflux – Health Related Quality of Life total score and subscales at 16 weeks and 12 months

The overall Laryngopharyngeal Reflux – Health Related Quality of Life mean score (adjusted scale 0–100) was 28.9 (95% confidence interval 24.5 to 33.3) at baseline in the lansoprazole group, reducing to 20.5 (95% confidence interval 16.1 to 25.0) at 16 weeks and 18.8 (95% confidence interval 13.7 to 23.8) at 12 months. In the placebo group, the total Laryngopharyngeal Reflux – Health Related Quality of Life mean score was 26.5 (95% confidence interval 22.5 to 30.5) at baseline, 17.1 (95% confidence interval 13.3 to 21.0) at 16 weeks and 13.9 (95% confidence interval 10.0 to 17.8) at 12 months.

Laryngeal mucosal changes recorded by Reflux Finding Score total (range 0–29), scored by an independent observer

Reflux Finding Scores were available for 256 participants included in the trial. Within the compliant intention-to-treat group, 80% of participants in the lansoprazole group and 72% of participants in the placebo group had Reflux Finding Scores at baseline. The mean Reflux Finding Scores were 9.7 (standard deviation 4.1) in the lansoprazole group and 9.2 (standard deviation 3.8) in the placebo group. The baseline Reflux Finding Score was not significantly related to the Reflux Symptom Index score at 16 weeks.

The ability of Reflux Finding Score and patient characteristics (age, sex, smoking status and body mass index) to predict any observed responses

None of the patient baseline characteristics or the baseline Reflux Finding Score was found to be univariate predictors of Reflux Symptom Index at 16 weeks (see *Appendix 8*, *Tables 11* and *57*, for baseline Reflux Finding Scores).

Side effects, adverse events and serious adverse events

There were 112 reported adverse events in 74 unique participants. Six were classed as 'probably related' to the lansoprazole treatment (one severe event and five moderate events). There were no such events in the placebo group.

Participant-reported satisfaction with the trial using a five-point overall satisfaction scale

At 12 months' follow-up, 213 out of 346 (62%) participants answered the satisfaction question, of whom 115 (54%) were very satisfied, 59 (28%) were satisfied, 29 (14%) were neither satisfied nor dissatisfied, five (2%) were dissatisfied and five (2%) were very dissatisfied.

Participant accuracy in determining which treatment they had received

Forty-two per cent of the lansoprazole group and 56% of the placebo group correctly identified the treatment they had received at the end of the study period.

Conclusions

Twice-daily lansoprazole was not shown to offer any symptomatic benefit over matched placebo to patients with chronic throat symptoms. The severity of presenting symptoms dictated the level of symptoms following treatment. Therefore, the evidence from this trial does not support the common practice of prescribing proton pump inhibitors to this patient population.

Trial registration

This trial is registered as ISRCTN38578686 and EudraCT number 2013-004249-17.

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Chapter 1 Introduction

Background

TOPPITS addresses the problem of adults with persistent throat symptoms, such as globus pharyngeus (hereafter referred to as 'globus'), catarrh, throat discomfort, clearing, recurring dysphonia or excess mucus. In one UK survey,[2] 6% of the middle-aged female population reported a persistent feeling of something in the throat (globus) in the previous 3 months. Globus is also reported to account for up to 4% of ear, nose and throat (ENT) referrals to secondary care.[3] Throat clearing is the commonest single symptom in any voice clinic. Equally familiar are intermittent hoarse voice and postnasal drip.[4] It is claimed that 55% of patients referred to a voice clinic have symptoms of extraesophageal reflux (EOR), and an English study of primary care attenders indicated that 25% had recent experience of persistent upper respiratory symptoms.[5] In the general population, the lifetime incidence of milder variants of globus is > 40%.[6] There were 1,142,404 first ENT consultations in England in 2010–11.[7] A conservative estimate is that 5% of these patients were referred for very common throat symptoms, such as throat clearing, fluctuating voice change, catarrh and chronic throat discomfort, which equates to over 57,000 NHS patients referred to secondary care that year in England alone.[7] Some patients experience anxiety as they fear that they may have throat cancer. Even if they have no features and no risk factors for cancer, they may be referred in for urgent ENT clinic assessment, a process that prolongs the anxiety and, at times, the symptoms. In the absence of good-quality treatment algorithms, patients also undergo invasive and costly assessments, such as rigid endoscopic examination of the upper aerodigestive tract under general anaesthesia, which typically reveals no significant abnormality, and empiric trials of acid suppression, typically with proton pump inhibitors (PPIs).

Rationale

Upper airway symptoms are known to have a strong placebo response.[8] Early evidence from animal experiments gave rise to the term 'acid laryngitis' 40 years ago.[9] Intracellular reactivation of acidified pepsin may explain pepsin activity at weakly acid pH levels.[10,11] Despite a growing trend to treat throat symptoms empirically with PPIs, controlled studies fail to demonstrate a significant benefit of PPI over placebo.[12–14] An evidence-based medicine EOR conference concluded that work assessing PPIs in throat symptoms had variable study design and quality, small numbers and heavy selection bias, with inconsistent treatment regimes, and that the small proportion of controlled studies demonstrating overall benefit of PPI over placebo[15] may reflect the prompt response of heartburn to antacid treatment.[16,17] There was little evidence on other pharmaceuticals, such as H_2 antagonists.[18,19] In the patient and public involvement background work for this proposal, individual interviews were conducted with several patients, encompassing both young professionals and the retired. All fully supported the research proposal. It was also clear, even from a small sample, that patient views on PPIs vary widely, but all had been treated at some point with PPIs, sometimes on more than one occasion.

Over half of UK otolaryngologists prescribe PPIs for persistent throat symptoms in the absence of structural pathology.[20] Our early systematic review[12] of studies that used PPIs as an empiric treatment modality for suspected laryngopharyngeal reflux (LPR) identified 14 uncontrolled studies, one unblinded, non-randomised

study with a control group of healthy volunteers and six double-blind, placebo-controlled randomised trials from 1994 to 2004. A lack of common outcome measures, selection bias and inadequate blinding of the results were among the typical limitations. Although uncontrolled series reported positive results, randomised controlled trials (RCTs) demonstrated no statistically significant differences for changes in severity or frequency of throat symptoms between PPIs and placebo. It appeared that empiric treatment of suspected LPR with PPIs, by far the most common ENT practice in the UK, is based on poor levels of evidence from uncontrolled studies. A later meta-analysis[21] included further studies, notably that by Vaezi *et al.*,[22] and concluded that PPI therapy 'may offer a modest but non-significant clinical benefit' over placebo. The authors also concluded that validated diagnostic guidelines may facilitate the recognition of likely responders. The 2007 meta-analysis[13] included five RCTs, only two of which had more than 22 participants, and only one randomised over 100 participants. The conclusion was that there was no overall benefit of therapy and that further work was needed to identify likely responders.[13] Finally, the most recent meta-analysis included seven placebo-controlled trials totalling 396 participants with varying doses over 4 to 16 weeks, and again showed that PPI therapy lacked evidence of efficacy in those suspected to have LPR. Rather, high placebo response levels suggested a more complex and multifactorial pathophysiology.[23] Like previous authors, the reviewers concluded that further studies are needed to characterise subgroups of patients with reflux-associated laryngeal symptoms who might benefit from treatment with PPI.

The perception in primary care is that PPIs are a reasonable 'empirical' treatment strategy for this group of patients. Almost since their introduction in the late 1990s, PPIs have constituted the largest part of the NHS community drugs bill: £238M in 1999 (5.6%).[24] PPIs are highly efficient in reducing gastric acid secretion. The annual NHS expenditure on PPIs is > £300M (generic omeprazole, lansoprazole and pantoprazole are the NHS Quality, Innovation, Productivity and Prevention-endorsed low-cost PPIs). The practice of giving 'all comers' with upper respiratory symptoms anti-reflux therapy misses the opportunity to explore other potentially beneficial approaches, such as speech therapy or management of fatigue.[25]

Measuring treatment responses in throat symptoms

The most frequently used primary outcome measure in the assessment of persistent, hard-to-explain throat symptoms is the Reflux Symptom Index (RSI). This nine-item, self-administered questionnaire is scored on a Likert scale with a total score of 0–45.[26] A higher score indicates more severe symptoms. The nine-item RSI total score allows comparison with previous studies as it offers 10 years of comparative data in the literature. The RSI remains the 'area standard' and, despite well-rehearsed limitations, remained our chosen primary outcome measure. Some reported studies have a baseline RSI only just above the normal level and others have a considerably higher baseline RSI. An observational study included 455 participants in South Korea, in whom the mean RSI score fell from 15 at baseline to 5.6 after 12 weeks of the PPI rabeprazole.[27] Baseline RSI scores in a much smaller but comparative study of 62 participants treated with esomeprazole were considerably higher (> 20).[28] On the other hand, a rabeprazole RCT,[15] like the Korean descriptive study, had baseline RSI scores around 14, closer to those of Lee *et al.*[27] Despite these differences in baseline severity, both of these more recent trials showed a benefit from a 3-month trial of acid suppression, but Lam *et al.*[15] continued follow-up for a further 6 weeks, when the effect disappeared, whereas Reichel *et al.*'s[28] final measurement point was the end of therapy.

The RSI has a number of limitations, which we have addressed in derivation of our own participant-reported outcome measure: the Comprehensive Reflux Symptom Score (CReSS).[29] The CReSS is a 34-item questionnaire of oesophageal and extraesophageal symptoms, which has been tested on groups of 'throat' patients, healthy controls and those attending for an upper gastrointestinal endoscopy. It has three statistically robust symptom factors: (1) gastrointestinal; (2) an upper airway factor relating to cough, breathing, mucus and hoarseness; and (3) an obstruction/choking globus factor. The continuing use of the RSI alongside other variables by ourselves and others has at least allowed the summation of studies in some of the prior attempted evidence synthesis exercises. One factor to be borne in mind in the application of any throat

symptom questionnaire, however, is the baseline incidence of throat symptoms in the community. The upper limit of normal in the RSI is said to be 12 in the general population. The first UK study to assess RSI scores in general practice attenders identified 252 participants with a score of > 10.[5] However, only 29% had a zero rating on the integral heartburn/dyspepsia item (which accounts for up to 5 of the 45 points), which is as one would expect given that about 30% of the population have some symptoms of lower gastroesophageal reflux.

When this gastroesophageal item was excluded from the RSI analysis, 8% of general practice attenders had a RSI of > 10 owing to the remaining extraesophageal items. A more recent UK report of the population distribution of RSI values sampled 2000 adults who were also questioned on their health and lifestyle.[30] The mean RSI score was 8.3; 30% of participants had a RSI score of > 10, of whom 25% had a zero score on the gastroesophageal reflux disease (GORD) item, thus giving a 7.5% overall prevalence of suspected LPR, similar to that observed in general practice attenders.[5] Over the past 5 years, we have continued to refine our improved participant report tool, the CReSS.[29] We have demonstrated wide separation of 103 volunteers, with a mean score of < 7, from 177 throat participants, with a mean score of 31 [95% confidence interval (CI) 28 to 35]. Factor analysis in a total of 422 participants shows the CReSS to have three subscales. The greater level of detail of the CReSS and the likely better discrimination of normal from abnormal scores at baseline make it an invaluable secondary outcome variable. Such an approach addresses the research need identified in prior review work, namely that of better characterising the subgroup of suspected LPR patients who may benefit from acid suppression therapy.

Varying average baseline Reflux Symptom Index scores in different reported series

- A small trial (of fewer than 50 participants) showed some benefit from acid suppression in postnasal drip, but only in individual symptom items, and the method of recruitment was not a pragmatic reflection of patients in normal day-to-day practice.[4]
- A large observational study of 455 participants in South Korea, most with globus sensation, throat clearing and dysphonia, was undertaken.[27] In this cohort, the mean RSI score fell from 15 at baseline to 5.6 after 12 weeks of the PPI rabeprazole.[27] In 75% of this cohort, there was a reduction of > 50% in RSI, but the proportions in the abnormal range pre and post therapy are not clear. In comparison, Reichel *et al.*[28] recruited 62 participants to an esomeprazole study randomised against placebo; the baseline mean RSI levels in the two groups (23 and 21, respectively) were considerably higher than those in the Korean descriptive series,[27] as were those for the cohort described in an early report by the authors of the RSI, whose mean participant baseline RSI score was also 20.[26]
- In a RCT of 82 participants randomised to placebo versus rabeprazole,[15] mean baseline RSI scores were closer to those of Lee *et al.*[27] (around 14). Understandably, therefore, as there is a baseline incidence of throat symptoms in the general population, this study appears to show a floor effect with a much smaller decrement in RSI total scores than was observed in the Reichel *et al.*[28] cohort, who had 'further to fall'.

In other words, some reported studies have a baseline RSI score only just above the normal level and others have a baseline RSI score that is considerably higher. Despite these differences in baseline severity, both of these most recent trials[15,28] showed a benefit from a 3-month trial of acid suppression. Lam *et al.*[15] continued follow-up for a further 6 weeks, when the effect disappeared, whereas the Reichel *et al.*[28] final measurement point was the end of therapy. The RSI remains the 'area standard' and, although others have attempted to introduce other questionnaires, their uptake has been patchy and many studies have reverted to single-item visual analogue scales. As discussed previously, the RSI has been applied in numerous prior studies and, despite well-rehearsed limitations,[29] remains our chosen primary outcome.

The nine-item RSI total score allows comparison with previous studies as it offers 10 years of comparative data in the literature.

Description of the Comprehensive Reflux Symptom Score questionnaire

The CReSS[29,31] is a 34-item questionnaire of oesophageal and extraesophageal symptoms that has been tested on groups of 'throat' patients, healthy controls and those attending for an upper gastrointestinal endoscopy. It has three subscales [oesophageal (17 items), upper airway (nine items) and pharyngeal (five items)] on a large-scale factor analysis:

- The total score has 34 items, each scored from 0 to 5, so the range is 0–170. Higher values indicate worse symptoms.
- The oesophageal subscale has 17 items – heartburn, flatulence, regurgitation, acid/sour taste in mouth, gurgling, nausea, vomiting, bloating, belching, pressure in the chest, low appetite, feeling full too early in a meal, indigestion, stomach acid, back pain, headache and bad breath (each item is scored from 0 to 5, so the total range for the subscale is 0–85).
- The upper airway subscale has nine items – throat clearing, excess mucus, mucous drip, coughing when upright, coughing after eating, coughing when lying down, wheezing, difficulty breathing and hoarseness (each item is scored from 0 to 5, so the total range for the subscale is 0–45).
- The pharyngeal subscale has five items – lump in the throat, swallowing food, swallowing liquid, throat pain and feeling of things stuck in throat (total score out of 0–25).

Quality-of-life impact of throat symptoms: the Laryngopharyngeal Reflux Health Related Quality of Life questionnaire

Patient-reported generic health-related quality-of-life scores are abnormal in patients with throat symptoms,[32] who show abnormalities of health-related quality of life in social functioning, pain and general health perception,[33] but there is a perceived need for a disease-specific instrument to assess the impact of reflux on health-related quality of life.[34] This need led to the development of the Laryngopharyngeal Reflux – Health Related Quality of Life (LPR-HRQL),[35] which has been validated in a Swedish population.[36] Its 43 items are grouped into four domains and an overall impact category (which includes general questions on relationships, sleep and lifestyle). The LPR-HRQL has been used in at least one prior RCT[22] and shown to respond to change, and is a secondary outcome measure of TOPPITS.

The questionnaire contains questions about LPR (acid reflux into the upper throat and how it affects the patient).

Most questions are scored from 0 to 6, describing how often the patient experiences that symptom. The code for the scores is as follows:

0 = none of the time (never in the past month)
1 = rarely (once in the past month)
2 = a little of the time (2–3 days in the past month)
3 = some of the time (about once a week)
4 = a lot of the time (about 2–3 days a week)
5 = most of the time (4–5 days a week)
6 = nearly all of the time or always (6–7 days a week).

After a set of questions that relate to a particular symptom, there is a question rated on a scale from 1 to 10 known as a 'thermometer', which asks the patient to summarise the overall impact of those symptoms on their life, in which 1 represents 'no effect' and 10 represents 'an enormous effect' on their quality of life.

Finally, at the end of the questionnaire, there are a number of questions that use the 1–10 scale. These seek to quantify how much the symptoms effect energy levels, productivity at work, social relationships, marital relationships, sexual relationships, sleeping, ability to lie comfortably in bed, the way they feel about themselves, lifestyle (such as exercising, eating and drinking) and ability to do the things they enjoy.

A summary of how these component questions are combined to assess quality of life is given in the following section.

Laryngopharyngeal Reflux – Health Related Quality of Life questionnaire components

The total for each domain is scored by taking the total score, subtracting the mean and dividing by the standard deviation – to give the *z*-score for each domain. All 'thermometer' scales can be reported alone or alongside the relevant scale.

Voice

The voice scale consists of the first 12 questions in the LPR-HRQL questionnaire. They are all scored from 0 to 6 on a Likert scale. Note that the second question (I feel satisfied with the way my voice sounds) must be reversed before adding up the total voice score.

If any patient is missing fewer than six items, impute the mean item scores based on the sample being analysed, then compute the voice scale for that patient. If any patient is missing six or more items (out of the 12), they should be treated as missing. The voice scale is calculated by adding the 12 items together, resulting in a score between 0 and 72. The 13th item in the 'Voice' section is the voice thermometer.

Coughing

The cough scale consist of questions 14–19 in the LPR-HRQL questionnaire. They are all scored from 0 to 6 on a Likert scale. If any patient is missing fewer than three items, impute the mean item scores based on the sample being analysed, then compute the cough scale for that patient. If any patient is missing three or more items (out of the six), they should be treated as missing. The cough scale is calculated by adding the six items together, resulting in a score between 0 and 36. The 20th item is the cough thermometer.

Clear throat

The clear throat scale consist of questions 21–26 in the LPR-HRQL questionnaire. They are all scored from 0 to 6 on a Likert scale. If any patient is missing fewer than three items, impute the mean item scores based on the sample being analysed, then compute the clear throat scale for that patient. If any patient is missing three or more items (out of the six), they should be treated as missing. The clear throat scale is calculated by adding the six items together, resulting in a score between 0 and 36. The 27th item is the clear throat thermometer.

General

The general scale consist of questions 28–32 in the LPR-HRQL questionnaire. They are all scored from 0 to 6 on a Likert scale. If any patient is missing fewer than three items, impute the mean item scores based on the sample being analysed, then compute the general scale for that patient. If any patient is missing three or more items (out of the six), they should be treated as missing. The general scale is calculated by adding the six items together, resulting in a score between 0 and 30. The 33rd item is the general thermometer.

Overall score

The overall score is calculated by adding the four thermometer scores (questions 13, 20, 27 and 33) AND the domain scores (questions 34–43). They are all scored from 1 to 10 on a Likert scale. The overall score is calculated by adding the 14 items together, resulting in a score between 14 and 140. To ease interpretation, this is rescaled to a score out of 100 by subtracting 14 and dividing by 126.

Trial objectives

TOPPITS aimed to quantify, and to characterise, the effect of PPI therapy compared with placebo. Our comprehensive package of patient-centred outcomes allows us to assess which specific throat symptoms

respond, to assess whether or not any patient characteristics can predict any measured treatment response, to derive improved estimates of impact on quality of life and to define the proportion of likely non-responders for whom alternative therapeutic approaches may be more appropriate. Definitions in the RSI literature to characterise responders include 50% reduction and final score within the normal range. Here we use a normal-range end point for response.

Primary objective

To compare the symptomatic response as measured by the RSI in patients with persistent throat symptoms at the end of 16 weeks' treatment with lansoprazole versus placebo.

Secondary objectives

- To explore recruitment feasibility using an internal pilot.
- To evaluate the symptom response at 12 months in comparison with that at 16 weeks.
- To determine the utility of the RSI questionnaire,[26] the CReSS questionnaire[31] items and subscales and endolaryngeal examination findings as scored by the Reflux Finding Score (RFS)[37] as well as the value of patient demographics including age, sex, smoking status and body mass index (BMI)[38,39] as potential baseline determinants of treatment response.
- To assess side effects, treatment compliance and use of self-pay medications.
- To compare changes in LPR-HRQL (i.e. disease-specific quality of life).

Treatment choice in TOPPITS

Proton pump inhibitors suppress gastric acid secretion by specific inhibition of the H^+/K^+-ATPase enzyme pump at the secretory surface of the gastric parietal cell. There is now a wide range of available PPIs. The best-value PPIs, and the most prescribed in the UK, are omeprazole and lansoprazole. The class of drugs is generally well tolerated. The frequency of adverse effects associated with PPIs (5%) is similar to that of placebo. The commonest complaints are headache, diarrhoea, abdominal pain and nausea. Except for diarrhoea, whose incidence is < 5%, the adverse effects of PPIs seem to be independent of age, dosage or duration of treatment. The diarrhoea seems to be due to altered gut microbiome secondary to the loss of acid secretion.

The clinical side effects of PPI use include rebound hypersecretion after cessation of PPI therapy, making it hard to wean some patients off of PPIs, and, of course, reinforcing the notion that they were necessary in the first place.[40,41] Rarer side effects include pneumonia,[42] *Clostridium difficile*, infections, acute renal inflammation[43] and fractures of hip, wrist and spine.[44]

If a PPI is considered appropriate, there is no evidence that any one PPI is more effective than another, when used at therapeutically equivalent doses, but newer agents are considerably more costly:

- We used lansoprazole in TOPPITS as it is among those frequently recommended by commissioning groups[45] and formularies; the choice is justified through its inclusion in National Institute for Health and Care Excellence guidance.[46]
- In TOPPITS, as is typical of LPR studies, we used twice-daily treatment to minimise the risk of 'breakthrough' gastroesophageal refluxes occurring at night.[47]
- Lansoprazole has a lower unit cost than omeprazole – NHS prescribing data (January to March 2010) indicate that omeprazole is the most commonly prescribed PPI (4.9 million items, unit cost £4.90, total cost £24.2M); lansoprazole totalled 3.8 million items, at a somewhat lower unit cost of £3.00 (total cost £11.4M).[48]

Chapter 2 Methods

Setting and conduct

This multicentre RCT was conducted at eight UK NHS sites, recruiting patients from 28 April 2014 to 28 February 2017. The final study visit was on 23 March 2018. The trial was conducted in accordance with the principles of International Conference on Harmonisation good clinical practice, received a favourable ethics opinion from the National Research Ethics Service Committee North East – Tyne and Wear South (reference 13/NE/0336) on 2 December 2013 and clinical trial authorisation from the Medicines and Healthcare products Regulatory Agency on 12 February 2014. The trial was managed by the Newcastle Clinical Trials Unit (NCTU) with a Trial Management Group, together with an independent Trial Steering Committee (TSC) and Data Monitoring Committee (DMC). Site monitoring was undertaken by staff at NCTU and the trial was audited by the sponsor, The Newcastle upon Tyne Hospitals NHS Foundation Trust. The clinical trial protocol was published in 2016.[1] A statistical analysis plan was in place prior to any comparative analyses.[49]

Patient and public involvement

Several patients contributed to the design of the study and the development of the second-stage application. To canvass the views of a range of patients with different experiences of chronic throat symptoms and treatments, the patient contributors were young professionals and retired patients. These patients were identified from clinics in Sunderland by James O'Hara. Individual consultations with four patients with LPR were conducted by James O'Hara. Two of these four patients agreed to join the TSC.

There was full patient support for the research proposal; the length of time taken to treat this problem and the lack of knowledge of throat symptoms on the part of clinicians is a source of frustration. When asked about the collection of follow-up data, there was a preference for this to be conducted face to face. When discussing outcome measures, patients felt that the CReSS had greater symptom coverage than the RSI, which the team believed justified its inclusion as a secondary outcome measure. Other changes as a result of patient and public involvement are listed below:

- Duration of therapy. This was originally planned to be 2 months; however, our patient panel felt that this was too short and that a longer period (16 weeks) would provide a more definitive result.
- Number of follow-up visits. The patient and public involvement group had a preference for more-frequent follow-up visits but these were reduced to two in line with the Health Technology Assessment panel feedback.
- Data collection – remote versus face to face. The patient and public involvement group believed that, rather than complete questionnaires in their homes, people would prefer – and would be willing – to attend a clinic to complete the questionnaires.
- Outcome questionnaires. Some members of the patient and public involvement group felt that there was some ambiguity in the wording of the questionnaires. This was improved as far as possible, bearing in mind that the RSI in particular needed to be comparable to previously published studies.

Planned patient and public involvement for the duration of the trial

The plan at the application stage for patient and public involvement throughout the trial was to build on the individual consultations conducted and convene a trial user forum to obtain a group perspective. Once funding was confirmed, those involved in the consultations would be invited to join the TOPPITS User Forum (TUF). It was considered that the forum would yield better outputs if it were user led. We hoped for a group of six individuals, aimed to encourage a cross-section of views and experience and hoped to recruit representation from the voluntary sector (e.g. the British Voice Association and the British Laryngological Association).

This forum would be facilitated by the local network patient and public involvement lead. Although the frequency of meetings would ultimately be decided by the forum members, it was initially thought that they should meet prior to the TSC meetings. This would enable a member of the forum to attend the TSC, to represent the group and raise any issues or queries. The intention was that the TUF would assist the trial team to:

- develop the recruitment strategy
- inform the adequacy and accessibility of patient information
- encourage the TSC to stay focused on the needs of patients
- disseminate the findings – users may be co-authors and participate in presentations
- link to the voluntary sector (as described previously).

In return, the TUF would be offered:

- a group and personal role specification, so that we could go through the implications of joining with patients
- a meeting venue with project secretary support, ideally in a community setting, approximately three times per annum
- meeting support from the project secretary
- examples of user group formats from similar groups
- encouragement to develop its own pages on the trial website (www.TOPPITS.co.uk) and a link from this website to the INVOLVE website (www.invo.org.uk/)
- a discussion of learning and development requirements with the trial team, and regular feedback.

Attempt to implement the TOPPITS User Forum

At the project launch in April 2015, the TUF was discussed in order to seek the views of attendees on recruiting patients. The two patients who had taken part in the initial consultations during the development of the trial and funding application – who had also joined the TSC – were no longer able to be involved. James O'Hara, one of three head and neck otolaryngologists in the Sunderland site, was leading on patient and public liaison and it was agreed that another member of the team (JL) would provide support with patient and public involvement. The following steps were suggested to identify and recruit TUF members:

1. Sunderland and Newcastle site staff to approach pilot trial patients at their final follow-up appointment to ask if they would be willing to join the TUF.
2. Provide patient and public involvement information (overview and specification) and ask if Jan Lecouturier can contact them by telephone to discuss further.
3. If they are happy to be contacted further, site staff to pass name and telephone number to Jan Lecouturier.
4. Jan Lecouturier to contact them after 1 week to discuss.
5. Discuss terms of reference, availability and preferences for meeting.
6. Set up first meeting.

The first steps were for Jan Lecouturier to develop materials for the TUF and amend the patient and public involvement specification and send it on to site staff. Local site staff (Sunderland and Newcastle) agreed to identify and approach patients to ask if they would be willing to join the TUF. The relevant materials were sent to the Sunderland research nurses in the first instance. By early August 2015, it transpired that only two patients had completed follow-up and neither had expressed an interest in the TUF. It was decided to ask Newcastle research nurses to approach patients, again those attending for their final follow-up appointment. The Newcastle site team asked for packs to send out to patients (at that stage, there were six patients who had completed the trial). Only one patient had expressed an interest in joining the TUF by October 2015. This patient was contacted to thank them and to indicate that the team would be in touch further when more members had been recruited to the TUF.

The problem in recruiting patients to the TUF was escalated to the Newcastle research team lead for otolaryngology. In January 2016, the research team lead – who thought that the problem with recruiting to TUF was due to the small number of patients who had completed the trial – agreed to send the materials to any patients remaining who had completed the trial. Unfortunately, this strategy attracted no further interest in joining the TUF.

Our initial outline design included a qualitative study comprising in-depth face-to-face interviews with 15 patients to explore compliance, use of other medication and symptoms experienced during the trial. These discussions might have additionally fostered higher levels of patient engagement with interviewees who might then have joined our TUF. However, that component of the study was not funded and this inference is only speculative.

Trial design

This was a multicentre, Phase III, randomised, double-blind, placebo-controlled trial, with an internal feasibility pilot, carried out in secondary care. Patients with persistent throat symptoms were identified and recruited from NHS ENT clinics. This was a pragmatic trial designed to mirror current NHS clinical practice, and so patients were not subjected to the gamut of aerodigestive tract investigations that characterise many studies but do not routinely inform the patient pathway outside a research context. Patients were randomised in a double-blind fashion between two treatment groups in a 1 : 1 ratio, stratified by centre and baseline severity [on the basis of the RSI score omitting item 9: 'Heart burn, chest pain, indigestion, or stomach acid coming up' – hereinafter referred to as RSI-HB (Reflux Symptom Index minus the heartburn/dyspepsia item) (range 0–40)]. The 'mild' cohort had RSI-HB scores of 10–20 (inclusive) and the 'severe' cohort had scores of > 20. The heartburn/dyspepsia item was omitted to focus on throat symptoms rather than gastrointestinal symptom burden, although the total RSI was used as the primary outcome. Following successful demonstration of recruitment in three sites in the internal pilot, the main component of the trial recruitment was conducted over a total of 30 months (inclusive of the pilot phase).

Patients

Patients were adults who had been newly referred to secondary care otolaryngology clinics with persistent (> 6 weeks) unexplained throat symptoms, principally dysphonia, throat pain, globus sensation (feeling of something stuck in the throat), throat clearing, postnasal drip or mucus excess, and also night-time unexplained cough or choking. The clinics were in the following trial site hospitals:

- Newcastle upon Tyne – Freeman Hospital (The Newcastle upon Tyne Hospitals NHS Foundation Trust)
- Sunderland – Sunderland Royal Hospital (City Hospitals Sunderland NHS Foundation Trust)
- Nottingham – Queen's Medical Centre (Nottingham University Hospitals NHS Trust)
- Brighton – Royal Sussex County Hospital (Brighton and Sussex University Hospitals NHS Trust)
- Glasgow – Glasgow Royal Infirmary (NHS Greater Glasgow and Clyde)

- Manchester – Manchester Royal Infirmary (Manchester University NHS Foundation Trust)
- Birmingham – Queen Elizabeth Hospital (University Hospitals Birmingham NHS Foundation Trust)
- Stockport – Stepping Hill Hospital (Stockport NHS Foundation Trust).

Inclusion criteria

- Referred with a persistent primary throat symptom: globus, hoarseness, throat clearing, throat discomfort, choking spasms, excess mucus/postnasal drip, otherwise unexplained night-time cough or choking of ≥ 6 weeks' duration.
- Those with a score of ≥ 10 on the non-heartburn items of the RSI.
- Capacity to provide fully informed consent to participate in the study.

Exclusion criteria

- Patients whose RSI-HB score was < 10.
- Those unable to complete the TOPPITS questionnaires.
- Patients aged < 18 years.
- Patients who were unwilling to undergo flexible endoscopy to establish the findings below.
- Observed endoscopic laryngopharyngeal pathology that would typically require specific surgical intervention or investigations (e.g. suspected neoplasia/dysplasia, prominent Reinke's oedema or unilateral vocal fold polyp, vocal cord palsy or chronic inflammatory diseases).
- Confirmed or suspected current or prior malignancy of the head and neck or oesophagus.
- Performing voice users: singers, actors, media workers.
- Pregnant or lactating woman. Woman of childbearing potential must be using adequate contraception.
- Currently on acid suppressants, acid neutralisers and alginates and unwilling to discontinue these for (1) a 4-week pre-study washout period in the case of PPI usage or (2) a 24-hour period for alginate or acid neutraliser. For those discontinuing PPI, ad hoc alginate use was allowed until the final 24–48 hours of the washout period prior to reassessment to confirm ongoing eligibility.
- Prior adverse reaction to PPIs.
- Severe hepatic dysfunction.
- Patients taking warfarin, phenytoin, digoxin, ciclosporin, methotrexate, erlotinib, lapatinib, tacrolimus, sucralfate, citalopram, escitalopram, fluvoxamine, St John's wort, clozapine, ulipristal acetate, cilostazol or systemic antifungals (itraconazole, ketoconazole, posaconazole or voriconazole).
- Human immunodeficiency virus-positive patients/patients taking antiviral medications (atazanavir, nelfinavir, raltegravir, saquinavir or tipranavir).
- Use of other investigational study drugs within the preceding 30 days.

Patients meeting the eligibility criteria were provided with a patient information sheet (PIS) and were given time to consider participation and the opportunity to ask questions before agreeing to take part. Consent was obtained by a member of the site trial team, delegated with that task on the delegation log and reasons for non-participation were recorded on a screening log at each trial site.

Some patients were identified from routine ENT, voice or 2-week wait cancer clinics. Any patient scoring ≥ 10 on the RSI-HB, where this was in routine clinical use, and who was potentially interested in participating in TOPPITS was given a PIS. The potential participant was then invited to attend a dedicated TOPPITS clinic after a cooling-off interval of ≥ 48 hours. Some potential participants were also identified through primary care referral letters. The principal investigators at each site were responsible for posting an invitation letter and PIS detailing the study along with a clinic appointment card.

A screening log was completed for all potential participants who were screened, including the reason for ineligibility and/or refusal to participate.

Recruitment

Screening

At the dedicated TOPPITS trial clinic, any outstanding queries were answered and there was an opportunity to review the randomisation video, if this had not already been accessed online from the TOPPITS website (www.TOPPITS.co.uk), with time to discuss the study further in this clinic. At the first trial clinic appointment, a more detailed confirmatory eligibility screen was completed by the investigator to document patients' fulfilment of the eligibility criteria for all patients considered for the study and subsequently included or excluded. Owing to the small patient population, the PIS, consent form and questionnaires for the study were available in the English language only.

Patients taking acid suppressants, acid neutralizers or alginates prior to involvement in/being approached to take part in TOPPITS were required to undergo a 4-week washout period of PPIs, or 24 hours for alginates or acid neutralisers, before randomisation and commencement of TOPPITS trial medication (see *Appendix 2*, *Tables 36* and *37*). Written consent was obtained prior to this washout period. The eligibility of any patient undergoing a 4-week washout period was reconfirmed before prescribing trial medication.

Consent

Informed consent discussions were undertaken by appropriate site staff (as per the delegation log) involved in the study, including medical staff and research nurses, with the opportunity for patients to ask any questions. Those wishing to take part gave informed consent by signing and dating the study consent form, which was witnessed and dated by a member of the research team with documented, delegated responsibility to do so. Occasionally, a patient wishing to have further time to consider the trial also attended a subsequent clinic. The original signed consent form was retained in the investigator site file (ISF) with a copy in the clinical notes, and a copy was provided to the patient. Each patient specifically consented to their general practitioner (GP) being informed of their participation in the study. The right to refuse to participate without giving reasons was respected.

Randomisation

A blocked allocation (permuted random blocks of variable length) system was used to allocate patients in a 1 : 1 ratio stratified by centre and baseline severity (two groups, on the basis of the RSI-HB score: group 1, ≤ 20; group 2, > 20). The overall RSI-HB range was 10–38.

Allocation concealment mechanism

The treatment allocation was kept blind from the patients and investigators. Randomisation was conducted via the NCTU secure web-based randomisation service by a computer-generated allocation list utilising random permuted blocks to ensure concealment of allocation. The blinded randomisation system generated a unique treatment number for each patient that linked to a corresponding allocated trial drug (blinded) in accordance with block size and strata. The treatment number was clearly documented by the investigator on the trial prescription to ensure that the pharmacist dispensed the correct medication.

Implementation

The random computer-generated allocation sequence was produced by a statistician not furthermore involved with the trial in order to ensure concealment of allocation. Randomisation was administered centrally via the NCTU using a secure web-based system. The principal investigator or delegated personnel named on the delegation log obtained a unique trial number via this system, which was available 24 hours a day. Details of a nominated NCTU contact for randomisation was provided to sites.

Patients were enrolled at trial sites by staff members who were delegated the task by inclusion on the delegation log. These were generally the principal investigators (clinicians) and research nurses.

Medication

The trial medication was manufactured by Piramal Pharma Solutions (Morpeth, UK); its provision was administered by MODEPHARMA Limited (Beckenham, UK). Three campaigns of trial medication, blinded and randomised at the point of manufacture, were used in the trial. Management and handling comprised:

- ensuring that sites had enough kits to ensure continuous provision to patients over three campaigns and 33 months
- co-ordination of requirements at sites with drug expiry dates
- liaison with site pharmacy staff to ensure accurate drug accountability record keeping
- organisation of the management of returns and their subsequent destruction at sites
- organisation of the destruction of the remaining kits at the end of the trial
- in-person monitoring of site pharmacies
- documentation of all stages of provision, dispensing, return and destruction of trial medication, at sites and centrally.

Blinding

Both the patients and the investigators/assessors were blinded to assignment to either the lansoprazole group or the placebo group (double-blind). A set of sealed code-break envelopes was kept either in the pharmacy or in the ISF at participating hospitals; these envelopes were opened only in an emergency, with authorisation from the chief investigator. When the code was broken, details including the patient number, who broke the code, why and when were recorded and maintained in the ISF. Code breaks were not routinely carried out for patients who completed study treatment. There were no code breaks throughout the duration of the trial.

At the second, end-of-therapy, visit, the integrity of the blind was assessed by a questionnaire item asking the patient if they thought that they had been taking lansoprazole or placebo or if they did not know.

The blind was maintained until all trial data were collected and the database was locked. Patients were offered the opportunity at their final visit to be informed of their allocated group, once data analysis was complete.

The active intervention was a 16-week course of a 30-mg twice-daily dose of the PPI lansoprazole. The control group received a 16-week course of twice-daily matched placebo. Patients received the intervention in capsule form and swallowed the capsules in the morning and in the evening. The allocation was blind to patients and research team staff and this was maintained throughout the trial.

Outcomes

The primary outcome measure was the raw total RSI score at 16 weeks after randomisation, which was collected at the first follow-up ENT outpatient visit. The RSI score is calculated from a nine-item, self-administered questionnaire scored on a Likert scale, with each item score ranging from 0 to 5, giving a total score range of 0–45. A higher score indicates more severe symptoms. Any missing component deems the total score missing. The nine-item RSI total score allows comparison with previous studies as it offers 10 years' worth of comparative data in the literature. The RSI remains the 'area standard' and, despite well-rehearsed limitations, remained our chosen primary outcome. The treatment period of 16 weeks was selected on the basis of evidence that after 8 weeks there was very little further symptomatic improvement (as measured by RSI) in a validation sample of 40 patients.[50] A period of 8 weeks might, therefore, have seemed justified. However, owing to the fairly small and highly selected sample (all pH-metry positive) of this early report, we opted for a 16-week period in our

definitive, larger study, with a view to maximising the impact and uptake of the TOPPITS findings. In other words, we chose this longer period so that we would not be open to criticism for having discontinued therapy too early.

Secondary outcome measures

- RSI changes at 12 months after randomisation.
- RSI score omitting item 9 (heartburn, chest pain, indigestion or stomach acid coming up), as the inclusion of dyspepsia symptoms has the potential to skew the results in favour of PPIs in past small trials.
- CReSS total subscales: oesophageal (14 items), upper airway (eight items) and pharyngeal (seven items).
- Quality of life: change in LPR-HRQL total score and subscales at 16 weeks and 12 months.
- Laryngeal mucosal changes recorded by RFS (total range 0–29), scored by an independent observer, outside any of the recruiting sites, who was blind to treatment group.
- The ability of RFS and patient characteristics (age, sex, smoking status and BMI) to predict any observed responses.
- Side effects, adverse events (AEs) and serious adverse events (SAEs).
- Use of over-the-counter medication.
- Patient-reported satisfaction with the trial using a five-point overall satisfaction scale. This asked if the patient was very dissatisfied, dissatisfied, neither dissatisfied nor satisfied, satisfied or very satisfied. Additional comments were invited.
- Patient accuracy in determining which treatment they had received.

Laryngoscopy

Laryngoscopy assessment of the larynx and pharynx was undertaken at baseline by the recruiting clinician using a laryngoscope. The appearances contributed to the eligibility criteria. An image was captured to allow the independent clinician to score the appearances using the RFS reported for the analysis at the end of the trial. The scoring scheme for the RFS assessment (as originally published by Belafsky *et al.*[37]) is given in *Appendix 3*, *Table 40*. The images were anonymised, and stored and transferred securely. When possible, all imaging was captured using a video endoscope (digital) instrument rather than the poorer-definition fibrescope. The RFS is not credited with much validity by scientific scrutiny in the diagnosis of LPR.[17,51–53] However, the findings are important because non-specific laryngeal redness is often used by less experienced practitioners and, at times, speech therapists to presume a diagnosis of reflux. Hence, commentary on the significance of the images and their scores is of interest and impact. Scores can range from 0 to 26, with higher scores indicating more intense and/or widespread laryngeal inflammation.

Sample size

The primary outcome measure was the change in the RSI score between baseline and the 16-week assessment. A mean difference of 3 points in RSI score at 16 weeks was felt to be a clinically relevant target based on clinical and co-applicant experience and prior LPR therapy studies. A mean difference of 3.1 points, with an assumed SD of 7.7[54] equates to a standardised mean effect size of 0.4. Furthermore, a 0.4 effect size is of smaller magnitude than the effect of phonomicrosurgery or speech therapy.[55] A total of 332 patients (166 in each group of the study) were required, to provide 266 patients (133 in each group) completing the trial intervention, to detect a standardised mean effect size of 0.4 with 90% power and 5% significance level allowing for 20% loss to follow-up. A 20% loss to follow-up rate was believed to be a realistic estimate. NHS experience of the investigators in TOPPITS suggested that this was overly optimistic for a trial of this kind.

There were no planned formal interim analyses or stopping rules.

Statistical methods

Descriptive statistics are used to summarise patient characteristics, treatment compliance, RSI and other secondary measures at randomisation and 16 weeks. The descriptive analysis is based on presenting:

- Underlying distribution of RSI reported graphically (histograms with normal curve overlaid).
- RSI scores at baseline and 16 weeks summarised by randomised treatment group, and overall, using descriptive statistics. Means, SDs, medians, interquartile ranges (IQRs) and ranges are reported, as the score was treated as a continuous measure but is integer in nature.
- RSI scores inside versus outside the published normal range. The percentage of patients in and out of normal range. The upper limit of normal in the RSI is said to be 12 in the general population.[26]

The primary outcome measure was RSI score after 16 weeks. An unadjusted univariate analysis of 16-week RSI is presented. The primary analysis is a multivariable analysis using analysis of covariance (ANCOVA) and multilevel mixed-effect linear regression to compare the RSI at 16 weeks while adjusting for potential confounders. Although ANCOVA is generally robust to departures from normality, transformation is investigated and, if applied, is retained in the analyses throughout. Primary analysis adjusts for effects of stratification factors at randomisation [centre, as a random effect in the regression modelling, and baseline severity (mild RSI-HB of ≤ 20, severe RSI-HB of > 20), as a fixed effect in the regression modelling].

Data were analysed using a statistical software package [Stata® version 14 (StataCorp LP, College Station, TX, USA)]. The primary hypothesis tested was H_0: the mean RSI at 16 weeks in the lansoprazole group is equal to the mean RSI at 16 weeks in the placebo group after adjustment for baseline stratification factors. Secondary analyses of the primary outcome measure considered adjustment for important clinical and demographic baseline factors, specifically sex, age, BMI, smoking status, alcohol consumption, baseline laryngeal appearance scores using the RFS, CReSS total and subscales and categories of symptoms. Three models were derived:

- Model 1 – adjusted for stratification factors used at randomisation [recruiting centre (as a random effect) and baseline severity, as defined by the binary RSI-HB cut-off value of 20 (as a fixed effect)].
- Model 2 – adjusted for baseline severity with RSI-HB as a continuous measure.
- Model 3 – adjusted for baseline severity (RSI-HB as a continuous measure) and other important clinical and demographic baseline factors, specifically age, sex, smoking status and BMI.

Continuous covariates were investigated for non-linear relationships with outcome using first-order fractional polynomial transformations, which were used if they substantially improved model fit based on the Akaike information criterion (AIC). The optimal model was derived using a forward selection method with comparison of –2log-likelihood for variable inclusion. Analyses were conducted at a two-sided 5% level of significance throughout. The impact of removing any covariates from the final model was assessed in order to derive the most parsimonious model.

The analysis of secondary outcomes followed a broadly similar strategy for the questionnaire scores. Safety data were not subject to statistical comparison. Analyses were carried out on a complete-case basis. Missing data were described. The use of multiple imputation techniques was considered for the primary outcome and covariate data, should data be missing for patients completing the study to a sufficient extent (approximately > 10%) and deemed missing at random.

No formal interim analyses were planned. A statistical analysis plan was in place prior to any comparative analyses.

Definition of 'compliant intention-to-treat group'

Primary statistical analyses were based on a compliant intention-to-treat (ITT) group. The DMC recommended that a distribution approach should be employed to determine a clinically relevant compliance window to maximise inclusion of patients and exclude only significant outliers. Thus, the compliant ITT group was defined, prior to comparative analyses and documented in the statistical analysis plan, as those with all ineligible and protocol violator patients included in the analysis in their randomised treatment group and attending their 16-week follow-up visit between 14 and 20 weeks. The distribution of time from randomisation to completion of the follow-up visits is reported graphically in *Figure 1* (see also *Appendix 1*, *Table 29*).

Sensitivity analyses are based on a pragmatic ITT group, with all ineligible and protocol violator patients included in the analysis on an ITT basis with patients kept in their randomised treatment group. This includes outcome measures completed at any time point.

On this basis, the power achieved was as follows:

- compliant ITT group – 82% power based on a minimum of 102 (lansoprazole) and 118 (placebo) participants
- pragmatic ITT group – 89% power based on a minimum of 127 (lansoprazole) and 140 (placebo) participants.

The per-treatment analysis of safety data reports the AEs that are related to the treatment. All randomised patients who start treatment were included in the analysis according to the treatment they received.

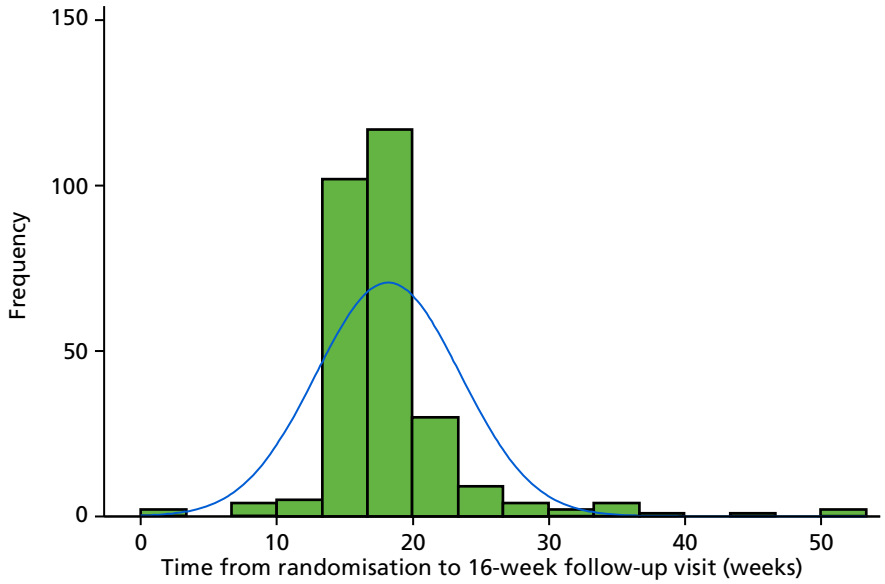

FIGURE 1 Histogram of time between randomisation and the 16-week follow-up visit in 283 patients.

Data management

A study-specific database was designed, built and tested using Elsevier's MACRO Electronic Data Capture (InferMed, London, UK) electronic data collection system. MACRO uses a secure web-based interface for data entry; no data are stored on computers at the site. Data for individual patients were entered by each principal investigator, or his/her delegated nominee, into the electronic case report forms. Each MACRO user is assigned role-based permissions specific to their site and role. MACRO has an inbuilt back-up facility, through Elsevier's hosting partner Rackspace's (Rackspace Ltd, Hayes, UK) secure premises in London, which is managed and supported by the Rackspace team.

Data entry and quality were monitored regularly by the Trial Management Group and sites were encouraged to enter all data as soon as possible. Frequent checks were made for missing and contradictory data, as well as ensuring that the data entered into the randomisation system matched those in MACRO. Data queries were raised with the sites on an ongoing basis, as necessary.

Chapter 3 Results

Recruitment to the trial is reported in a Consolidated Standards of Reporting Trials (CONSORT) flow diagram (*Figure 2*).

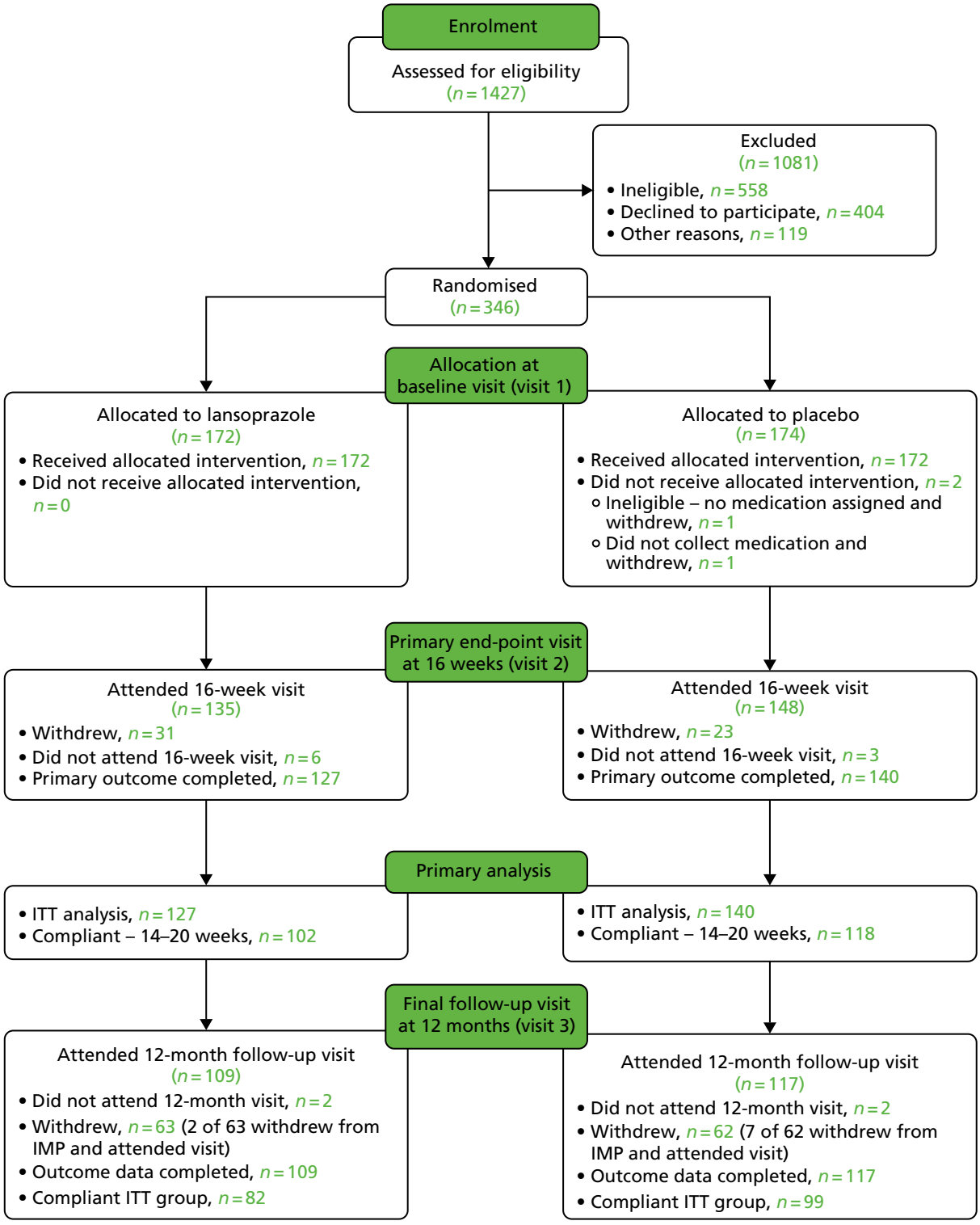

FIGURE 2 The CONSORT flow diagram. IMP, investigational medicinal product.

Screening and recruitment

Screening and recruitment activity are summarised in *Appendix 1*, *Tables 27* and *28*.

The trial opened to recruitment on 28 April 2014, but owing to slower-than-expected recruitment a no-cost extension was obtained; hence, the trial closed to recruitment on 28 February 2017. The original target recruitment figure was 332; this was revised following DMC recommendation on 29 January 2016 to allow recruitment to continue to 28 February 2017, at which point the number recruited was 346. This ensured that the numbers of participants reaching the 4- and 12-month trial visits were sufficient to satisfy the trial protocol (version 5.0, January 2017).

Recruitment overview

- Trial status: closed to recruitment (28 February 2017).
- Grant awarded: 27 June 2013.
- Ethics approval awarded: 2 December 2013.
- Number of sites: eight.
- Date first site opened: 28 April 2014 (site initiation date).
- Date first patient randomised: 27 May 2014.
- Date of data locks: 3 May 2018.
- Total number of patients randomised before recruitment closed: 346.
- Date last patient randomised: 24 February 2017.
- Last follow-up: 23 March 2018.

Randomisation

A blocked allocation (permuted random blocks of variable length) system was used to allocate patients in a 1 : 1 ratio, stratified by centre and baseline severity (RSI-HB mild, ≤ 20; RSI-HB severe, > 20).

Balance was confirmed by stratification factors. See *Appendix 1*, *Table 30*, for stratification by baseline severity in terms of RSI-HB and stratification by site in *Report Supplementary Material 1*, *Table 1*. *Appendix 1*, *Table 31*, gives details of patients who were mis-stratified.

Four ineligible patients were reported (see *Appendix 1*, *Table 32*).

Withdrawals

There were 125 patients who were reported as withdrawals (including losses to follow-up) with specified dates. Two patients did not complete the trial but did not have a withdrawal date and two patients did not have trial completion status confirmed (i.e. no date for completion of or withdrawal from the trial). A summary of the timing of withdrawals from the trial, with respect to the primary end-point visit, is given in *Appendix 1*, *Table 33*. Descriptive statistics for time to withdrawal from randomisation are given in *Appendix 1*, *Table 34*.

Baseline data

Demographic baseline characteristics (*Table 1*) show the two treatment groups to be balanced. The age and sex statistics are consistent with the population of participants with chronic throat symptoms.

Scrutiny of *Table 2* confirms that the compliant ITT group is a representative subsample of the total trial population.

TABLE 1 Baseline demographic characteristics and stratification variables, by treatment group (all randomised patients and the pragmatic ITT group) (primary outcome provided at any time)

	All trial patients ($N = 346$)			Pragmatic ITT group ($N = 267$)		
	Treatment group			Treatment group		
Variable	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Sex, *n* (%)						
Male	71 (41)	79 (45)	150 (43)	49 (39)	65 (46)	114 (43)
Female	101 (59)	95 (55)	196 (57)	78 (61)	75 (54)	153 (57)
Age (years)						
Mean (SD)	53.5 (13.3)	50.8 (13.9)	52.2 (13.7)	54.8 (12.8)	52.3 (13.7)	53.5 (13.3)
Range	21–84	20–80	20–84	23–84	21–80	21–84
Weight (kg)						
n	169	170	339	125	140	265
Mean (SD)	79.4 (18.2)	79.3 (16.8)	79.4 (17.5)	78.0 (18.5)	79.3 (16.1)	78.7 (17.3)
Range	43.8–142.0	42.5–140.3	42.5–142.0	43.8–142.0	48.0–140.3	43.8–142.0
Height (m)						
n	170	171	341	126	140	266
Mean (SD)	1.68 (0.12)	1.68 (0.10)	1.68 (0.11)	1.67 (0.1)	1.68 (0.1)	1.67 (0.1)
Range	1.43–2.50	1.45–1.92	1.43–2.50	1.43–2.50	1.45–1.91	1.43–2.50
BMI (kg/m^2)						
n	169	170	339	125	140	265
Mean (SD)	28.2 (5.9)	28.1 (5.3)	28.1 (5.6)	28.1 (6.3)	28.1 (5.3)	28.1 (5.8)
Range	11.3–56.9	18.3–49.1	11.3–56.9	11.3–56.9	18.3–49.1	11.3–56.9
Smoking (pack-years)						
n	168	171	339	124	140	264
Median (IQR)	0 (0–5)	0 (0–0.5)	0 (0–3)	0 (0–3)	0 (0–0.75)	0 (0–2.5)
Mean (SD)	4.7 (9.7)	3.9 (10.4)	4.3 (10.0)	4.1 (8.7)	4.2 (11.1)	4.2 (10.0)
Range	0–51	0–76	0–76	0–51	0–76	0–76
Alcohol consumption (units per week)						
n	169	167	336	125	138	263
Median (IQR)	4 (0–10)	3 (0–10)	4 (0–10)	4 (0–10)	3 (0–10)	3 (0–10)
Mean (SD)	8.7 (12.2)	6.6 (9.0)	7.7 (10.8)	8.3 (11.2)	6.8 (9.4)	7.5 (10.3)
Range	0–80	0–60	0–80	0–50	0–60	0–60
Baseline RSI-HB severity						
n	171	171	342	127	140	267
Mean (SD)	20.0 (6.8)	20.1 (6.5)	20.1 (6.6)	20.0 (6.9)	20.0 (6.5)	20.0 (6.7)
Range	10–38	10–38	10–38	10–38	10–38	10–38

continued

TABLE 1 Baseline demographic characteristics and stratification variables, by treatment group (all randomised patients and the pragmatic ITT group) (primary outcome provided at any time) (*continued*)

	All trial patients ($N = 346$)			Pragmatic ITT group ($N = 267$)		
	Treatment group			Treatment group		
Variable	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Site, *n* (%)						
Birmingham	5 (3)	5 (3)	10 (3)	5 (4)	4 (3)	9 (3)
Brighton	5 (3)	4 (2)	9 (3)	5 (4)	2 (1)	7 (3)
Glasgow	18 (10)	21 (12)	39 (11)	7 (6)	18 (13)	25 (9)
Manchester	15 (9)	12 (7)	27 (8)	14 (11)	9 (6)	23 (9)
Newcastle	66 (38)	67 (39)	133 (38)	46 (36)	51 (36)	97 (36)
Nottingham	34 (20)	36 (21)	70 (20)	31 (24)	33 (24)	64 (24)
Stockport	5 (3)	6 (3)	11 (3)	5 (4)	6 (4)	11 (4)
Sunderland	24 (14)	23 (13)	47 (14)	14 (11)	17 (12)	31 (12)

Green shading denotes stratification variables.
Two patients were randomised but never received medication and did not return baseline data (participant identifiers: 2106 and 1062).

TABLE 2 Baseline demographic characteristics, by treatment group (compliant ITT group)

	Treatment group		
Variable	Lansoprazole ($N = 102$)	Placebo ($N = 118$)	Total ($N = 220$)
Sex, *n* (%)			
Male	38 (37)	56 (47)	94 (43)
Female	64 (63)	62 (53)	126 (57)
Age (years)			
Mean (SD)	55.3 (12.8)	53.8 (13.4)	54.5 (13.1)
Range	23–84	21–80	21–84
Weight (kg)			
Mean (SD)	78.9 (19.6)	80.1 (16.2)	79.5 (17.8)
Range	43.8–142.0	50.6–140.3	43.8–142.0
Height (m)			
Mean (SD)	1.67 (0.13)	1.68 (0.10)	1.67 (0.12)
Range	1.43–2.50	1.45–1.91	1.43–2.50
BMI (kg/m^2)			
Mean (SD)	28.5 (6.7)	28.4 (5.4)	28.5 (6.1)
Range	11.3–56.9	18.3–49.1	11.3–56.9
Smoking (pack-years)			
n	101	118	219
Median (IQR)	0 (0–3)	0 (0–0)	0 (0–1)
Mean (SD)	4.3 (9.0)	4.3 (11.8)	4.3 (10.6)
Range	0–51	0–76	0–76

TABLE 2 Baseline demographic characteristics, by treatment group (compliant ITT group) (*continued*)

Variable	Treatment group		
	Lansoprazole (*N* = 102)	Placebo (*N* = 118)	Total (*N* = 220)
Alcohol consumption (units per week)			
Median (IQR)	4 (0–10)	3 (0–10)	4 (0–10)
Mean (SD)	8.0 (10.5)	7.1 (9.7)	7.5 (10.0)
Range	0–45	0–60	0–60
Baseline RSI-HB severity			
Mean (SD)	20.3 (7.4)	19.8 (6.6)	20.0 (7.0)
Range	10–38	10–38	10–38
Site, *n* (%)			
Birmingham	5 (5)	4 (3)	9 (4)
Brighton	3 (3)	2 (2)	5 (2)
Glasgow	5 (5)	14 (12)	19 (9)
Manchester	9 (9)	6 (5)	15 (7)
Newcastle	30 (29)	39 (33)	69 (31)
Nottingham	31 (30)	32 (27)	63 (29)
Stockport	5 (5)	4 (3)	9 (4)
Sunderland	14 (14)	17 (14)	31 (14)

Green shading denotes stratification variables.

Data quality

Data were received for analysis from:

- MACRO – the trial data
- the NCTU randomisation service – randomisation data including details of stratification (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA)
- RFS assessment – from an independent reviewer, validated by NCTU (using Microsoft Excel) (see *Appendix 3*, *Table 41*, for the RFS scoring scheme).

Data sets were merged according to the unique identifier allocated at randomisation.

Questionnaires and forms returned, by visit

Data were collected using case report forms. Case report forms were completed and collated in the following order:

1. registration and randomisation form – completed prior to treatment allocation (baseline and demographic data for potential covariates collected)
2. questionnaires completed at baseline visit – RSI (primary), CReSS (secondary), LPR-HRQL (secondary)
3. AEs and concomitant medication use recorded at baseline visit
4. trial questionnaires again completed at visit 2 (16-week follow-up) as at the baseline visit
5. returned medication – capsule count carried out at visit 2
6. electronic case report form completed at visit 2 showing which treatment (trial drug or placebo) the patient believed they were randomised to
7. AEs and concomitant medication use recorded at visit 2
8. questionnaires completed at visit 3 as at the baseline and 16-week follow-up visits
9. AEs and concomitant medication use recorded at visit 3.

The three trial questionnaires (RSI, CReSS and LPR-HRQL) were completed at all three visits:

- visit 1 – baseline visit (data locked: 3 May 2018)
- visit 2 – primary end-point, 16-week follow-up visit (data locked: 3 May 2018)
- visit 3 – 12-month follow-up visit (data locked: 3 May 2018).

Laryngoscopy assessment

The RFS data were included in the analysis to explore whether or not laryngeal appearance predicts outcome (i.e. response to lansoprazole). The image assessments were carried out (by PC) in four blocks: in December 2015, December 2016, June 2017 and December 2017.

Treatment received

The analysis set is the per-treatment analysis group defined in the statistical methods. Inclusion in the per-treatment set was based on capsule return at the 16-week primary end point. In total, 265 out of 346 participants (77%) had information on returned medication (including returned empty packaging for those who took the full course). Three patients did not take any trial medication and were removed from the per-treatment analysis group.

In total, 262 out of 346 trial participants (76%) are assumed to have taken at least one capsule of their trial medication and are included in the per-treatment analysis group [126 out of 172 (73%) in the lansoprazole group; 136 out of 174 (78%) in the placebo group]. Further details of dose taken are given in *Appendix 2*, *Table 38*.

Protocol treatment schedule

Treatment was with either a 30-mg (twice-daily) dose of the PPI lansoprazole or placebo for 16 weeks. The kits contained 17 weeks' supply so each patient received 238 capsules of either lansoprazole or placebo. The treatment was double blind; both patients and clinicians were blind to treatment.

Trial medication was prescribed by a clinician, and dispensed to the patient or clinical staff in accordance with local pharmacy policy.

Patients who were still in possession of any medication returned all leftover trial supplies in their original packaging (even if empty) to the clinician or pharmacist at the 16-week follow-up visit (primary end point).

Medication received

At 16 weeks ($\pm$ 2 weeks in protocol) following recruitment, the primary end-point clinic (visit 2) took place at the TOPPITS clinic. A patient who completed the course of medication in exactly 16 weeks would have taken $16 \times 7 \times 2 = 224$ doses of lansoprazole or placebo. The dose supplied at randomisation comprised 238 capsules, enough for 17 weeks, with two capsules per day as per the protocol. Forty-two per cent of participants reported taking the full dose, balanced across randomised groups, and 70% patients reported taking $\geq$ 90% of the dose, balanced across groups. The median percentage protocol dose is 99% (IQR 86–100%).

Appendix 2 contains further details of doses taken.

Proton pump use and concomitant medication

Recent PPI usage at randomisation was collected at baseline and is presented in *Appendix 2*.

A total of 377 concomitant medication uses were reported during the trial among the per-treatment analysis group, in 143 unique patients (*Table 3*).

TABLE 3 Concomitant medication reported at baseline and follow-up visits (per-treatment group)

	Visit								
	1 (baseline)			2 (primary end point: 16 weeks)			3 (12-month follow-up)		
	Treatment group			Treatment group			Treatment group		
Participant concomitant medication use	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Total number of participants reporting medications	108	73	181	38	40	78	57	56	113
Number of unique participants reporting medications	41	33	74	26	25	51	32	34	66

Awareness of treatment group by patients

Each patient was asked which drug they believed that they had been taking at the 16-week follow-up visit. Fourteen per cent were not able to identify (or attempt to identify) which treatment they had been randomised to and answered 'Don't know' (*Table 4*).

Three assessments were missing: one for a participant randomised to lansoprazole and two for participants randomised to placebo.

Outcomes and estimation of treatment effects

Primary outcome measure

Compliance was assessed in relation to the time frame of 14–20 weeks post randomisation. The distribution of time from randomisation to the primary end-point 16-week follow-up visits (visit 2) is reported graphically in *Figure 3*. The graph shows how much time has elapsed since randomisation to the 16-week follow-up visit for all patients who attended the visit ($n = 283$). The dashed lines show patients included in the compliant ITT group ($n = 220$). Further information on compliance is given in *Appendix 1*, *Tables 29* and *35*. See *Appendix 2*, *Tables 39* and *40*, for details of individual RSI items.

TABLE 4 Patient assessment of drug taken

	Actual randomised treatment, *n* (%)		
Participant opinion of drug taken	Lansoprazole (*N* = 126)	Placebo (*N* = 136)	Total (*N* = 262), *n* (%)
Lansoprazole	**53 (42)**	43 (32)	96 (37)
Placebo	51 (40)	**76 (56)**	127 (48)
Don't know	21 (17)	15 (11)	36 (14)
Total number assessed	125 (99)	134 (99)	259 (99)

Bold denotes correct opinion.

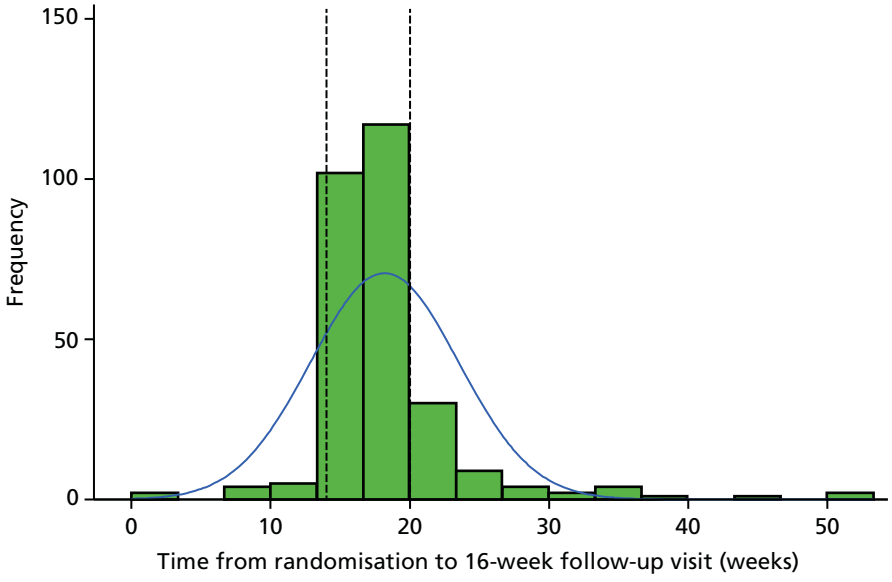

FIGURE 3 Histogram of time between randomisation and the primary end-point 16-week follow-up visit (overall). The dashed lines show patients included in the compliant ITT group ($n = 220$).

Baseline itemised severity scores: Reflux Symptom Index in all patients and the compliant group

The item descriptive statistics for RSI are listed in *Appendix 3*, *Table 39*. The top five RSI items, for both the trial population and the compliant group, in ranked mean endorsement severity were:

1. lump in the throat
2. throat clearing
3. excess mucus
4. troublesome cough
5. hoarseness.

Reflux Symptom Index score at baseline for the compliant analysis group (n = 220)

The means (SDs) are reported with medians, IQRs and ranges as the (total) RSI score is treated as a continuous measure but is integer in nature (*Table 5*).

The summary statistics show that the randomised groups are similar at baseline.

The underlying distribution of the RSI at baseline visits is reported graphically in *Figure 4* in the form of a histogram with both groups combined ($n = 220$) and normal curve overlaid.

TABLE 5 Primary outcome measure: RSI at baseline (visit 1) (compliant ITT group)

	Treatment group		
Baseline RSI	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	20.5 (15–28)	21.5 (16–27)	21 (15.5–27)
Mean (SD)	22.0 (8.0)	21.7 (7.1)	21.9 (7.5)
95% CI of mean	20.4 to 23.6	20.5 to 23.0	20.9 to 22.9
Range	10–41	10–43	10–43

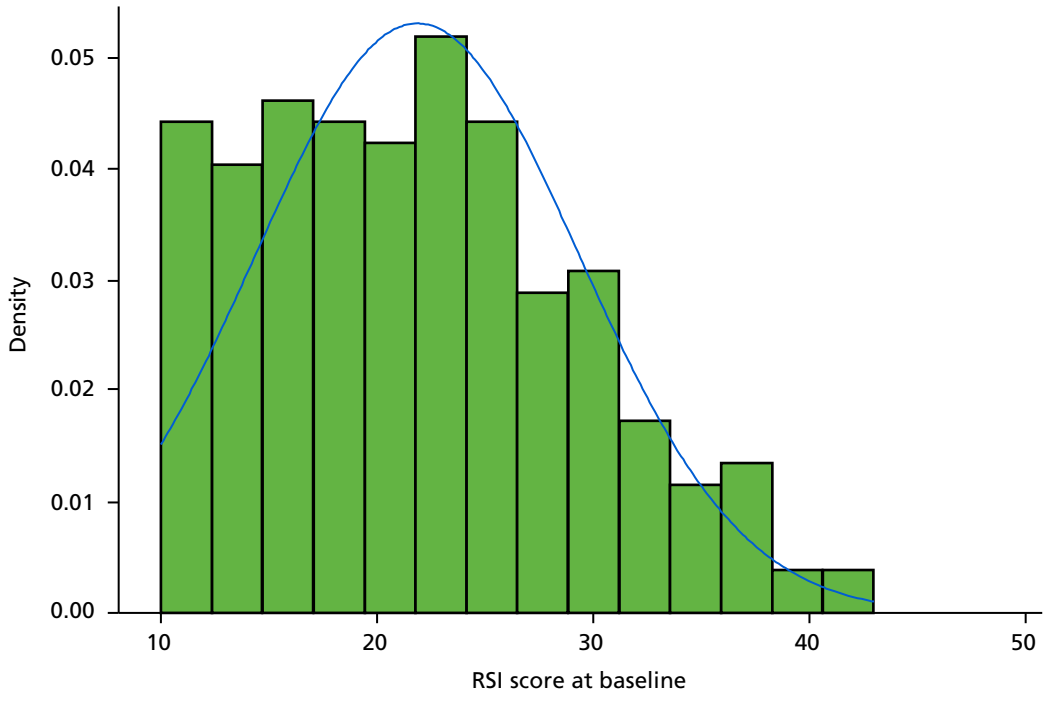

FIGURE 4 Underlying distribution of RSI at baseline (compliant ITT group).

Reflux Symptom Index score at 16 weeks (primary end point) for the compliant analysis group

Figure 5 and *Table 6* show the underlying distribution and summary statistics of the RSI score at the primary end point of 16 weeks for the 220 patients in the compliant ITT group.

A higher RSI score indicates more severe symptoms. RSI reduced overall from a median score of 21 at baseline to a median score of 15 at 16 weeks. RSI reduced overall from a mean score of 21.9 (SD 7.5) at baseline to a mean score of 16.4 (SD 9.9) at 16 weeks. The reduction in RSI is observed in both randomised treatment groups. The lansoprazole group has a mean 16-week score 1.8 points higher than that of the placebo group [17.4 (95% CI 15.5 to 19.4) vs. 15.6 (95% CI 13.8 to 17.3)], with overlapping CIs, indicating no statistical difference between the groups.

The primary outcome data for the compliant ITT group are presented graphically in *Figure 6*.

Univariate analysis of unadjusted primary outcome measure for the compliant analysis group

The underlying distribution of the primary outcome measure (see *Figure 5*) appears sufficiently normally distributed (overall mean = 16.4, median = 15) for parametric analysis of the primary outcome. The primary hypothesis to be tested is H_0: the mean RSI scores at the primary end point (16-week visit) are equal for both groups (lansoprazole vs. placebo). A two-sided significance level of $p < 0.05$ is used throughout.

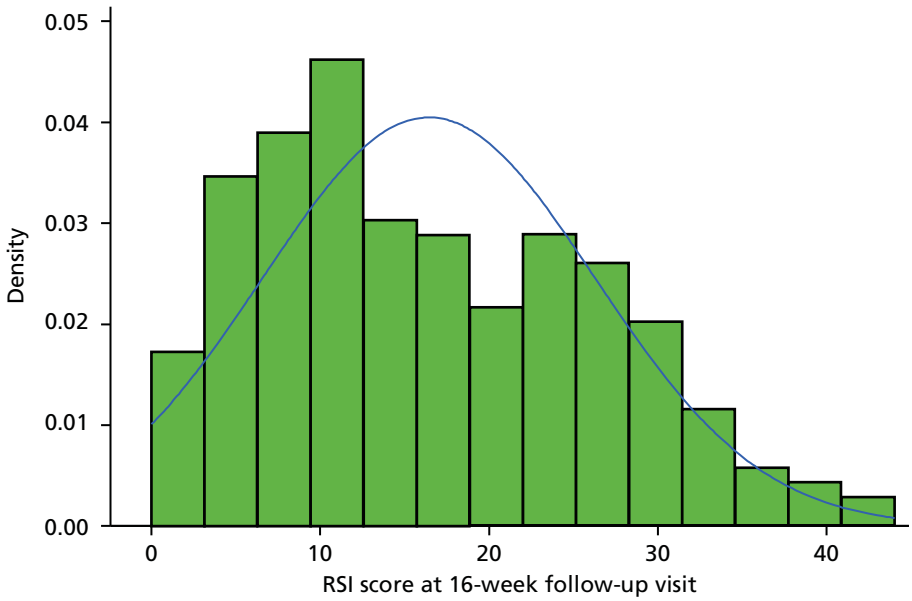

FIGURE 5 Underlying distribution of RSI at the primary end-point visit (compliant ITT group).

TABLE 6 Primary outcome measure: total RSI at the 16-week follow-up (visit 2) (compliant ITT group)

	Treatment group		
RSI at 16 weeks	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	16 (9–26)	14 (7–23)	15 (9–24.5)
Mean (SD)	17.4 (9.9)	15.6 (9.8)	16.4 (9.9)
95% CI of mean	15.5 to 19.4	13.8 to 17.3	15.1 to 17.7
Range	0–41	0–44	0–44

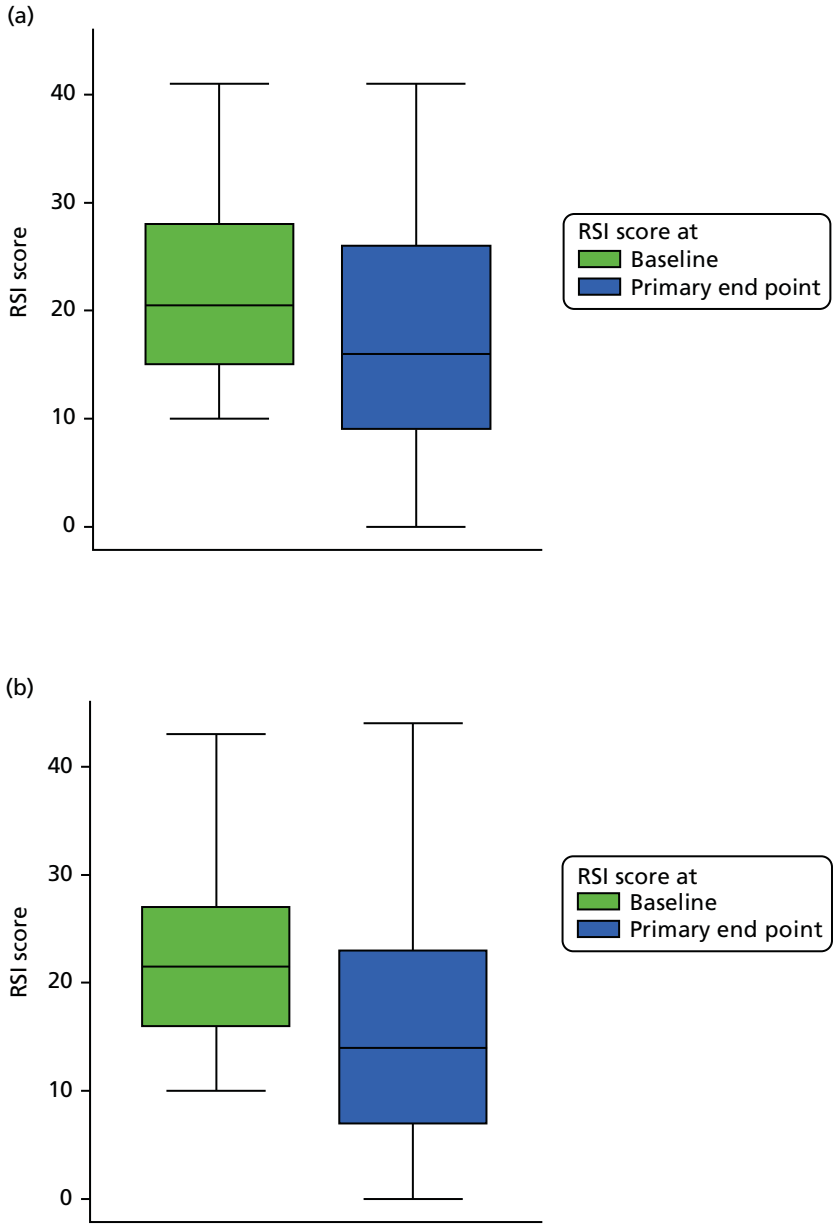

FIGURE 6 Box plots showing medians, IQRs and overall ranges of RSI score at baseline and primary end-point visit (compliant ITT group). (a) Lansoprazole group ($n = 102$); and (b) placebo group ($n = 118$).

The null hypothesis is no difference between means for PPI (17.4, 95% CI 15.5 to 19.4) versus placebo (15.6, 95% CI 13.8 to 17.3). The test statistic was $t = 1.402$ and the two-sided p-value was 0.162, leading to the conclusion that there was no statistically significant difference in the RSI score at 16 weeks between lansoprazole and placebo.

Table 7 and *Figure 7* show the change in RSI score (change RSI = 16-week RSI – baseline RSI) to the primary end-of-treatment end point.

The overall mean reduction in RSI score from baseline to 16 weeks is 5.4, which is observed across both randomised groups: lansoprazole group, 4.6-point reduction; placebo group, 6.2-point reduction (with overlapping CIs indicating no statistical difference between the groups). The lansoprazole group had a mean reduction of 1.6 points less than the mean reduction observed in the placebo group.

TABLE 7 Change in RSI (0 to 16 weeks) (compliant ITT group)

Change in RSI scores (baseline to 16 weeks)	Treatment group		
	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	–4 (–10 to 1)	–5 (–13 to 1)	–5 (–11 to 1)
Mean (SD)	–4.6 (8.0)	–6.2 (9.0)	–5.4 (8.6)
95% CI of mean	–6.2 to –3.0	–7.8 to –4.5	–6.6 to –4.3
Range	–31 to 19	–29 to 11	–31 to 19

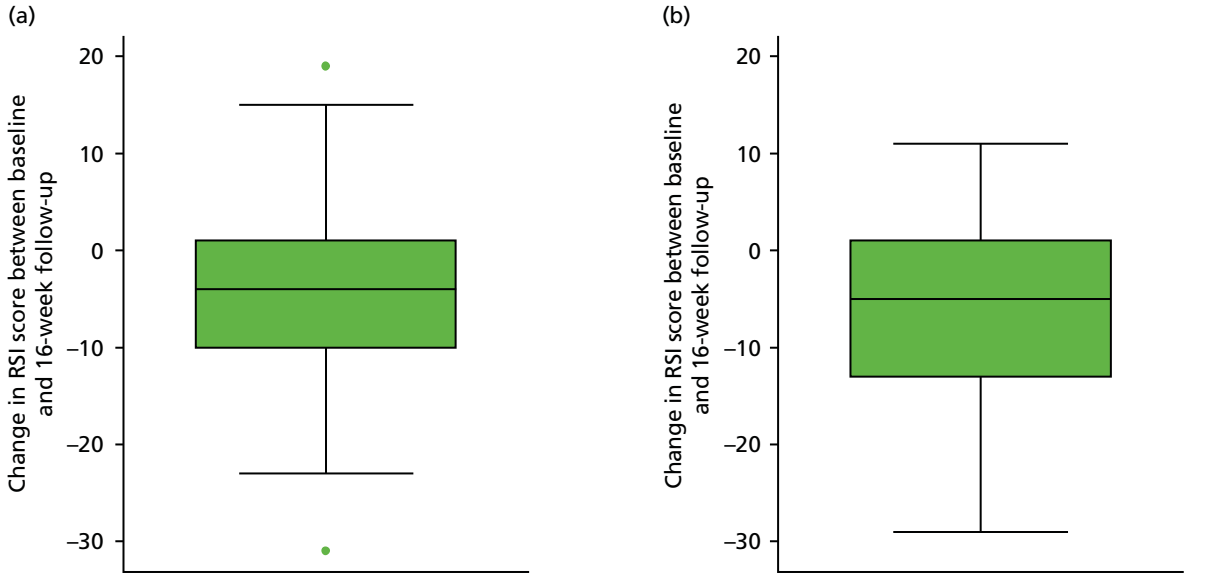

FIGURE 7 Box plots showing medians, IQRs and overall ranges for change in RSI score from baseline to the 16-week follow-up (compliant ITT group). (a) Lansoprazole group ($n = 102$); and (b) placebo group ($n = 118$).

Comparison of Reflux Symptom Index scores at baseline and 16 weeks with the published upper limit of normal range, for the compliant intention-to-treat analysis group

The upper limit of normal in the total nine-item RSI is said to be < 12 in the asymptomatic population.[26] Overall, 10% of patients are within normal range at baseline, balanced across randomised groups (this figure reflects the inclusion severity criterion, i.e. the eight-item version RSI excluding the dyspepsia item 9, 'RSI-HB'). At 16 weeks, 43% (95% CI 37% to 50%) of participants were within the normal range, balanced across randomised groups: 41% (95% CI 31% to 51%) for the lansoprazole group versus 45% (95% CI 36% to 54%) for the placebo group. The overlapping CIs indicate no statistical difference between the groups.

Multivariable analysis of primary outcome for the compliant intention-to-treat analysis group

The primary outcome measure was RSI score after 16 weeks and was initially analysed using ANCOVA methods in order to compare the 16-week RSI scores between the treatment groups while adjusting for potential confounders, as specified in the protocol (*Table 8*). Although ANCOVA was generally robust to departures from normality, normality was assumed (see *Figure 5*).

There did not appear to be a statistically significant difference in RSI at 16 weeks between randomised treatment groups ($p = 0.106$). In ANCOVA, site is not a reliable estimate as the algorithm deals with the location numerals as if they were quantitative data. Site is more properly modelled as a random effect in a multilevel model.

TABLE 8 Primary outcome measure as response, with adjustment for site and baseline severity (compliant ITT group)

Source	Partial SS	df	Mean square	F-ratio	*p*-value
Model	5502.119	9	611.347	8.14	< 0.001
Arm	198.180	1	198.180	2.64	0.106
Site	1822.126	7	260.304	3.47	0.002
Baseline severity	3429.688	1	3429.688	45.68	< 0.001
Residual	15,765.859	210	75.076		
Total	21,267.977	219	97.114		

df, degrees of freedom; SS, sum of squares.
Adjusted $R^2 = 0.227$ ($n = 220$).

Statistical modelling of the primary outcome

A multilevel mixed-effect linear regression was used to model the primary outcome measure – 16-week RSI – on a complete-case basis. Three models were developed as specified in *Statistical methods* (see *Table 12* for a summary of the model results for both the compliant and the pragmatic ITT populations).

Model 1

Model 1 adjusted for stratification factors used at randomisation as covariates in the analysis: (1) recruiting centre (as a random effect) and (2) binary baseline severity as defined by the binary RSI-HB cut-off value of 20 (as a fixed effect) (*Table 9*).

Modelling site as a random effect demonstrates no impact of site on RSI score at 16 weeks, as anticipated, and demonstrates the advantage of modelling these data more appropriately.

TABLE 9 Results of multilevel mixed-effect linear regression (model 1), adjusted for stratification factors used at randomisation (site and baseline severity) (compliant ITT group) ($n = 220$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	1.929	1.160	1.66	0.096	–0.345 to 4.203
Site (reference = Birmingham)						
Brighton	Random	–6.010	4.727	–1.27	0.204	–15.275 to 3.254
Glasgow		–0.973	3.478	–0.28	0.780	–7.789 to 5.843
Manchester		5.123	3.576	1.43	0.152	–1.886 to 12.131
Newcastle		–1.871	3.047	–0.61	0.539	–7.843 to 4.101
Nottingham		–5.937	3.028	–1.96	0.050	–11.871 to –0.003
Stockport		–3.701	4.025	–0.92	0.358	–11.590 to 4.188
Sunderland		–3.385	3.216	–1.05	0.293	–9.689 to 2.919
RSI-HB baseline severity: severe (reference = mild)	Fixed	8.173	1.181	6.92	< 0.001	5.858 to 10.489
Constant		14.349	3.044	4.71	< 0.001	8.383 to 20.315

SE, standard error.
Log-likelihood = –782.084; Wald chi-squared test = 76.78; *p*-value > χ^2 < 0.001.

Binary RSI-HB at baseline is confirmed as being statistically significantly, related to 16-week RSI and justified as a stratification factor in the trial design. Patients in the severe severity stratum at baseline are estimated to have a RSI score that is 8 points higher (worse) at 16 weeks.

There is no statistically significant difference between randomised groups [lansoprazole compared with placebo ($p = 0.096$)] when adjusted for site and baseline binary RSI-HB. The difference between randomised groups, when accounting for site and baseline severity, indicates that lansoprazole patients are estimated to have RSI scores at 16 weeks that are 1.9 points higher (worse) than the scores of placebo patients (95% CI –0.3 to 4.2; $p = 0.096$).

Random errors are assumed to produce residuals that are normally distributed, as is the case for model 1, in which the residuals fall in a symmetrical pattern and have a constant spread throughout the range (*Figures 8* and *9*).

Further information on model 1 at 12 months, for the compliant ITT group, is given in *Appendix 7*, *Table 53*, and similarly for model 2 in *Appendix 7*, *Table 54*.

Model 2

Model 2 adjusted for the stratification factor recruiting centre (as a random effect) at randomisation and baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect).

The continuous covariate (RSI-HB) was explored to assess whether or not transformation of RSI-HB was a better fit to the relationship with outcome than an untransformed continuous measure based on a reduction in AIC. There was no reduction in AIC, so to build the most parsimonious, clinically interpretable model, RSI-HB was retained as an untransformed continuous covariate, under the assumption of linearity with outcome (*Table 10*).

The log-likelihood statistics show that continuous baseline severity substantially improves the model fit (reduction in –2log-likelihood) compared with model 1, which included severity as a binary stratification factor.

A 1-unit increase in baseline severity is associated with a 0.7-unit increase (95% CI 0.6 to 0.9) in 16-week RSI.

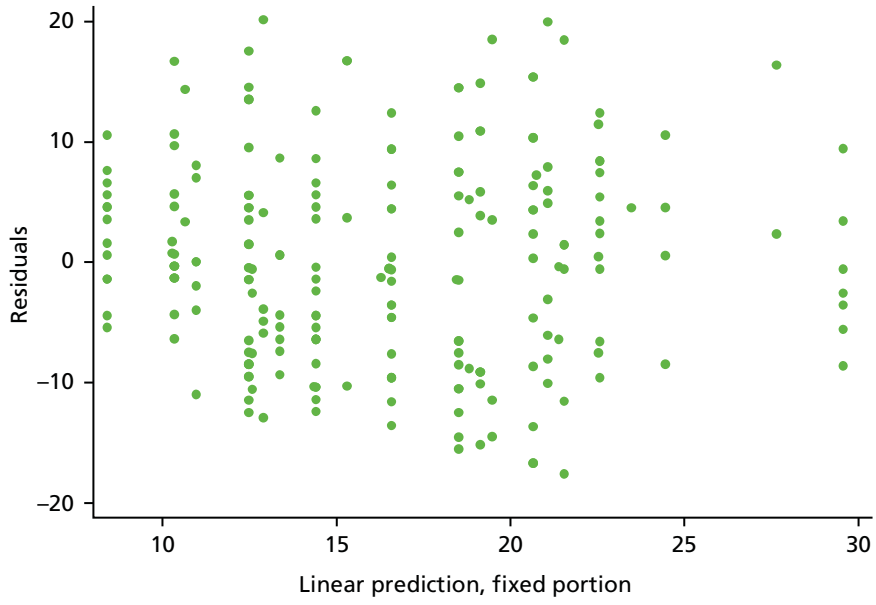

FIGURE 8 Scatterplot of residuals for model 1 (both groups combined, $n = 220$) (compliant ITT group).

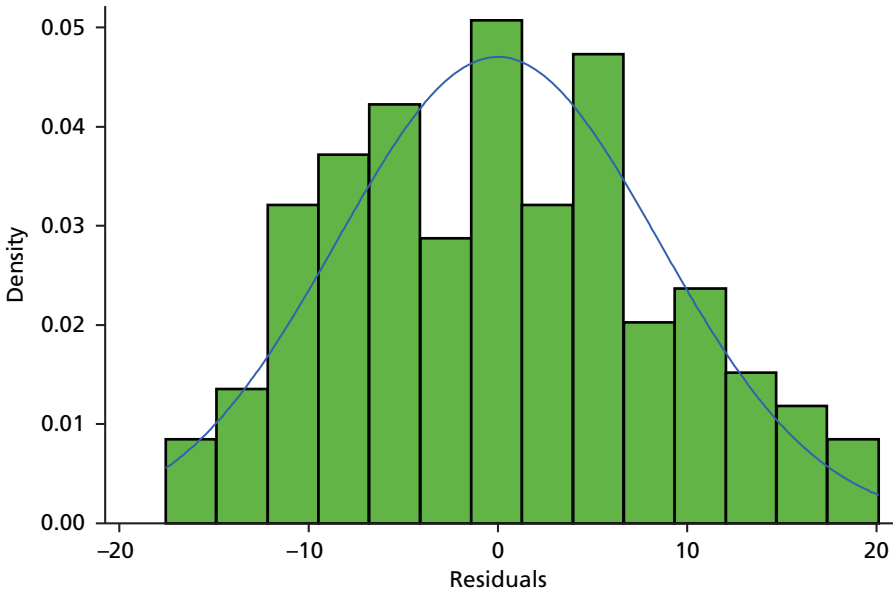

FIGURE 9 Histogram of residuals for model 1 (both groups combined, $n = 220$) (compliant ITT group).

TABLE 10 Results of multilevel mixed-effect linear regression (model 2), adjusted for the stratification factor site used at randomisation and continuous baseline severity (compliant ITT group) ($n = 220$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	1.410	1.091	1.29	0.196	–0.728 to 3.549
Site (reference = Birmingham)						
Brighton	Random	–1.300	4.493	–0.29	0.772	–10.106 to 7.506
Glasgow		–1.694	3.252	–0.52	0.602	–8.067 to 4.679
Manchester		3.003	3.359	0.89	0.371	–3.579 to 9.586
Newcastle		–2.785	2.840	–0.98	0.327	–8.351 to 2.781
Nottingham		–5.664	2.847	–1.99	0.047	–11.243 to –0.084
Stockport		–3.085	3.783	–0.82	0.415	–10.499 to 4.329
Sunderland		–2.759	3.027	–0.91	0.362	–8.693 to 3.174
RSI-HB continuous baseline severity	Fixed	0.721	0.079	9.10	< 0.001	0.566 to 0.877
Constant		4.320	3.274	1.32	0.187	–2.098 to 10.738

SE, standard error.
Log-likelihood = –768.621; Wald chi-squared test = 115.42; *p*-value > χ^2 < 0.001.

There is no statistically significant difference between randomised groups [lansoprazole compared with placebo ($p = 0.196$)] when adjusted for site and baseline continuous RSI-HB. The estimated difference between randomised groups, when accounting for site and baseline severity, indicates that patients receiving lansoprazole are estimated to have RSI scores at 16 weeks that are 1.4 points higher (worse) than the scores of placebo patients (95% CI –0.7 to 3.5; $p = 0.196$).

Residual plots demonstrate the underlying assumptions of the model to not be substantially violated (*Figures 10* and *11*).

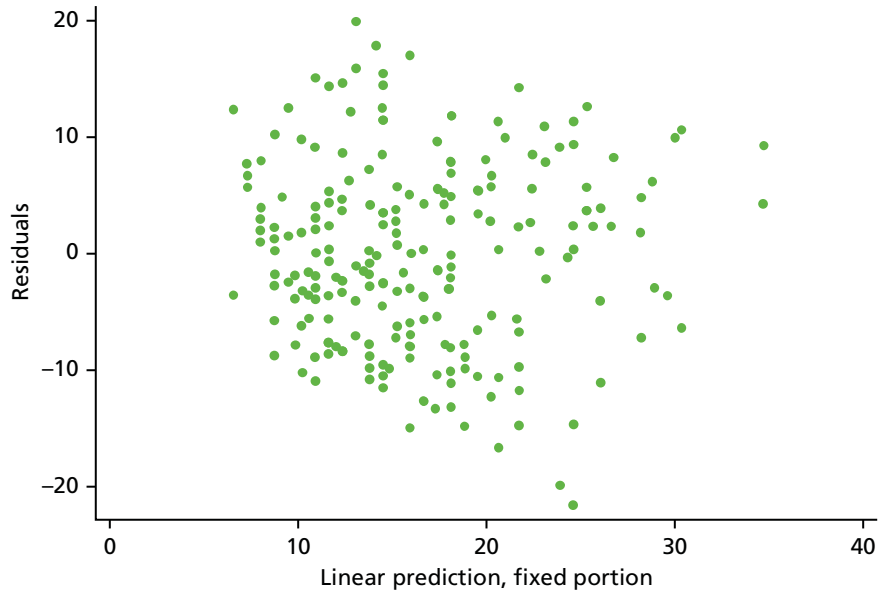

FIGURE 10 Scatterplot of residuals for model 2 (both groups combined, $n = 220$) (compliant ITT group).

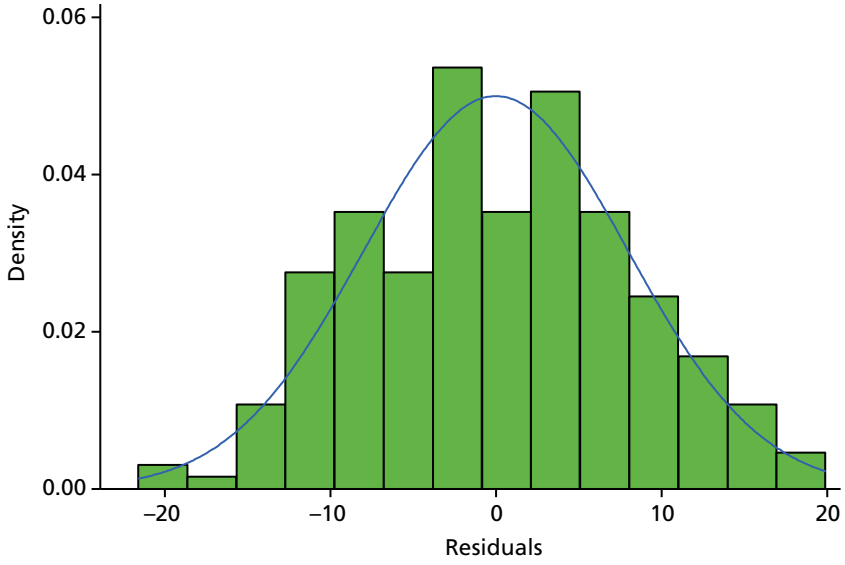

FIGURE 11 Histogram of residuals for model 2 (both groups combined, $n = 220$) (compliant ITT group).

Model 3

Model 3 adjusted for baseline severity (RSI-HB as a continuous measure) and the baseline factors age, sex, smoking status (binary), alcohol consumption (binary) and BMI. Non-linear continuous covariates were explored but continuous covariates were retained as untransformed (*Table 11*).

As none of the potential covariates appears to have a significant univariate relationship with the RSI score at the primary end point, model 2 remains optimum.

Sensitivity analysis of the primary outcome

A sensitivity analysis based on the pragmatic ITT group including all patients with the 16-week visit at any time was also carried out. This did not change the conclusions of the trial (*Table 12*).

TABLE 11 Univariate relationships including transformed continuous covariates

Covariate	*n*	AIC	Beta	SE	Test statistic	*p*-value
BMI						
Continuous	220	1634.002	0.017	0.110	0.15	0.878
Log-transformed		1634.017				
Complex transformation (BMI^{-2})		1633.240				
Age						
Continuous	220	1633.977	–0.011	0.051	–0.22	0.826
Log-transformed		1633.791				
Complex transformation (age^{-2})		1629.129				
Smoking (binary)	219	1626.368	1.547	1.520	1.02	0.310
Sex (binary – male/female)	220	1632.896	1.423	1.343	1.06	0.291
Alcohol consumption (binary)	217	1611.289	–1.761	1.483	–1.19	0.236

SE, standard error.

TABLE 12 Summary of model results for compliant and pragmatic ITT populations

	ITT population			
	Complaint ($n = 220$)		Pragmatic ($n = 267$)	
Model	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
1	1.9 (–0.35 to 4.20)	0.096	1.5 (–0.60 to 3.53)	0.165
2	1.4 (–0.73 to 3.55)	0.196	1.1 (–0.83 to 3.05)	0.264
3	Model 2 optimum	N/A	Model 2 optimum	N/A

N/A, not applicable.

Appendix 5 provides further details of the secondary analyses of the primary outcome measure (the pragmatic ITT group). *Appendix 5*, *Table 47*, gives summary statistics for the primary outcome measure: RSI for the pragmatic ITT population at baseline and primary end point. *Appendix 5*, *Table 48*, shows the ANCOVA results. *Appendix 5*, *Table 49*, shows results for model 1, primary outcome measure as response with adjustment for stratification and other baseline factors. In addition, during the DMC closed session held on 9 March 2018, the DMC discussed the different analysis groups. The chairperson felt that a sensitivity analysis looking at the per-protocol group would be useful to support the primary analysis. Details of this analysis are provided in *Appendix 5*. *Appendix 5*, *Table 50*, shows summary statistics at the primary end point.

Secondary analysis of the primary outcome measure using derived Reflux Symptom Index minus the heartburn/dyspepsia item

A secondary analysis of the primary outcome based on the reduced RSI score (derived from eight items excluding item 9, the dyspepsia and heartburn component – RSI-HB) was planned and undertaken. RSI-HB, scored out of 40, was calculated and analysed as was the primary outcome measure (complete nine-item RSI).

Means, SDs, medians, IQRs and ranges for RSI-HB are reported as the score is treated as a continuous measure but is integer in nature. The summary statistics show that the randomised groups are similar at baseline (*Table 13*).

A higher RSI score indicates more severe symptoms. RSI-HB reduced overall from a median of 19 at baseline to a median of 13 at 16 weeks. RSI-HB reduced overall from a mean score of 20.0 (SD 7.0) at baseline to a mean score of 15.0 (SD 9.2) at 16 weeks (*Table 14* and *Figure 12*). The reduction in RSI-HB is observed in both randomised treatment groups. The lansoprazole group has a mean 16-week score that is 2.4 points higher than the score for the placebo group [16.3 (95% CI 14.5 to 18.1) vs. 13.9 (95% CI 12.2 to 15.5), respectively], with overlapping CIs indicating no statistical difference between the groups. The null hypothesis was that there was no difference between the means. The test statistic was $t = 1.945$ and the two-sided p-value was 0.0530.

There is no statistically significant difference in the RSI-HB score at 16 weeks between the lansoprazole and placebo groups.

Change in Reflux Symptom Index minus the heartburn/dyspepsia item score from baseline to 16 weeks for the compliant intention-to-treat group

Table 15 and *Figure 13* show the change in RSI-HB score (change RSI-HB = 16 weeks' RSI-HB – baseline RSI-HB). The reduction in RSI-HB score from baseline to 16 weeks is similar between randomised groups.

The overall mean reduction in RSI-HB score from baseline to 16 weeks is 5.0 (95% CI –6.1 to –3.9), a reduction that is observed across both randomised groups [lansoprazole, 4.0-point reduction (95% CI –5.5 to –2.5); placebo, 5.9-point reduction (95% CI –7.4 to –4.4)], with overlapping CIs indicating no statistical difference between the groups. The lansoprazole group had a mean reduction that is 1.9 points less than the mean reduction observed in the placebo group (see *Figure 13*).

TABLE 13 The RSI-HB at baseline (visit 1) (compliant ITT group)

	Treatment group		
RSI-HB	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	19 (14–25)	19.5 (14–24)	19 (14–24.5)
Mean (SD)	20.3 (7.4)	19.8 (6.6)	20.0 (7.0)
95% CI of mean	18.8 to 21.7	18.6 to 21.0	19.1 to 20.9
Range	10–38	10–38	10–38

TABLE 14 The RSI-HB at the 16-week follow-up (visit 2) (compliant ITT group)

	Treatment group		
RSI-HB	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	14 (9–25)	12 (7–19)	13 (8–22)
Mean (SD)	16.3 (9.4)	13.9 (9.0)	15.0 (9.2)
95% CI of mean	14.5 to 18.1	12.2 to 15.5	13.8 to 16.2
Range	0–39	0–39	0–39

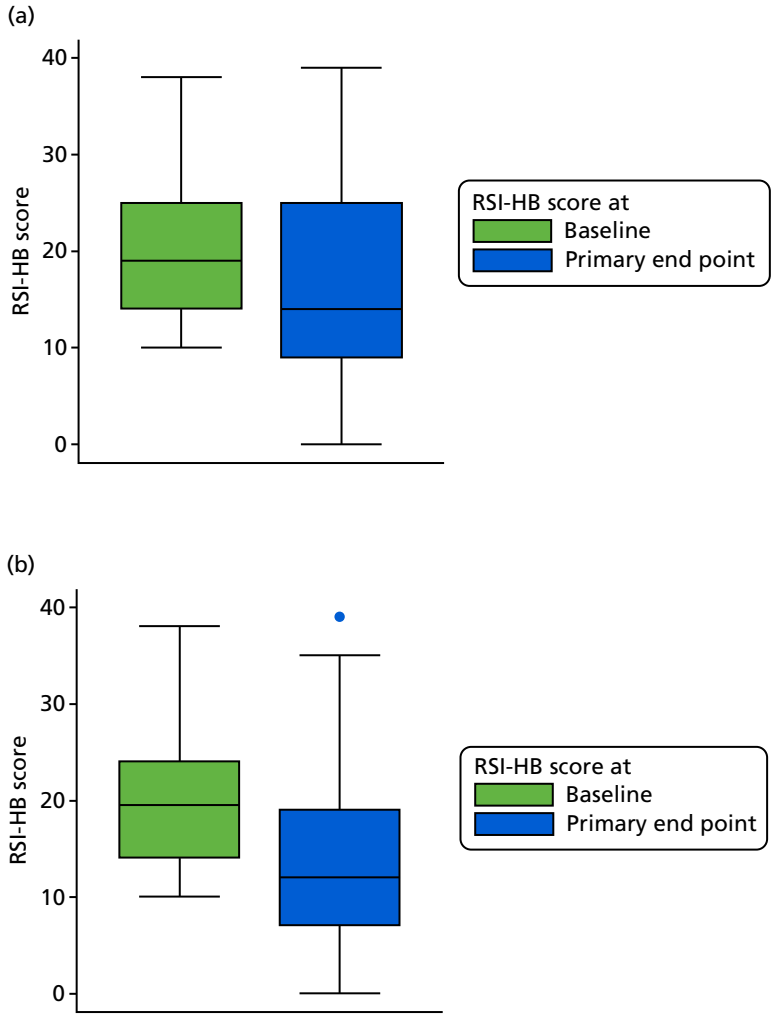

FIGURE 12 Box plots showing medians, IQRs and overall ranges of the RSI-HB score at baseline and 16-week follow-up (compliant ITT group). (a) Lansoprazole group ($n = 102$); and (b) placebo group ($n = 118$).

TABLE 15 Change in RSI-HB (compliant ITT group)

Change in RSI-HB scores (baseline to 16 weeks)	Treatment group		
	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Median (IQR)	–3 (–9 to 1)	–5.5 (–12 to 0)	–4.5 (–10 to 0.5)
Mean (SD)	–4.0 (7.6)	–5.9 (8.4)	–5.0 (8.1)
95% CI of mean	–5.5 to –2.5	–7.4 to –4.4	–6.1 to –3.9
Range	–31 to 17	–27 to 12	–31 to 17

Multivariate analysis and statistical modelling of the RSI-HB for the compliant group are given in *Appendix 4*. *Appendix 4*, *Table 42*, presents ANCOVA results, *Table 43* presents the results of model 1 (adjusted for stratification factors) and *Table 44* presents the results of model 2 (adjusted for stratification factor recruiting centre and for baseline severity in terms of RSI-HB as a continuous measure).

A sensitivity analysis based on the pragmatic ITT group including all patients with their 16-week primary end-point visit taking place at any time did not change the conclusions (see *Appendix 6*). *Appendix 6*,

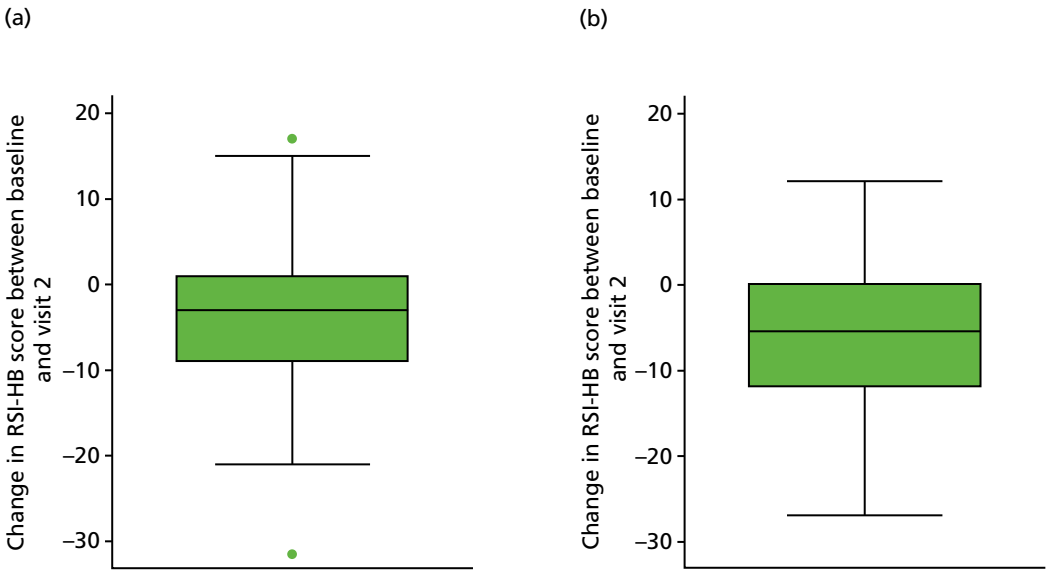

FIGURE 13 Box plots showing medians, IQRs and overall ranges of change in RSI-HB score from baseline to the 16-week follow-up (compliant ITT group). (a) Lansoprazole group ($n = 102$); and (b) placebo group ($n = 118$).

Table 51, shows summary statistics for RSI-HB for the pragmatic ITT group at baseline and the primary end point. In *Appendix 7*, *Table 53*, RSI-HB at baseline is confirmed as being statistically significantly related to 12-month RSI. Patients with greater severity at baseline are estimated to have RSI scores that are 8.2 points higher (worse) at 12 months.

Secondary outcome measures

Reflux Symptom Index at the 12-month follow-up for the compliant intention-to-treat group

The 12-month RSI scores were secondary outcome measures, both the complete nine-item RSI and the reduced eight-item RSI-HB. These 12-month scores were assessed descriptively in unadjusted models and in multivariable models adjusted by stratification factors (*Table 16*).

The longitudinal changes in total RSI are summarised in *Table 17* and *Figure 14*. Values show some further reduction in the post-treatment 8-month follow-up phase.

TABLE 16 Descriptive analysis of RSI scores at 12 months (compliant ITT group)

	RSI 12-month follow-up (visit 3)		
	Treatment group		
RSI at 12 months	Lansoprazole	Placebo	Total
n	82	99	181
Median (IQR)	15 (6–24)	12 (6–19)	13 (6–21)
Mean (SD)	16.0 (10.8)	13.6 (9.6)	14.7 (10.2)
95% CI of mean	13.6 to 18.4	11.7 to 15.5	13.2 to 16.2
Range	0–43	0–41	0–43

TABLE 17 Median, IQR and range at baseline, 16 weeks and 12 months and the associated median differences (compliant ITT group)

	Time point						Change			
	Baseline		16 weeks		12 months		Baseline to 16 weeks		Baseline to 12 months	
RSI score	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group
n	102	118	102	118	82	99	102	118	82	99
Median (IQR)	20.5 (15 to 28)	21.5 (16 to 27)	16 (9 to 26)	14 (7 to 23)	15 (6 to 24)	12 (6 to 19)	–4 (–10 to 1)	–5 (–13 to 1)	–6 (–13 to 0)	–8 (–14 to –3)
Range	10 to 41	10 to 43	0 to 41	0 to 44	0 to 43	0 to 41	–31 to 19	–29 to 11	–34 to 15	–27 to 22

Green shading denotes the descriptive statistics for the change from baseline to follow-up points.

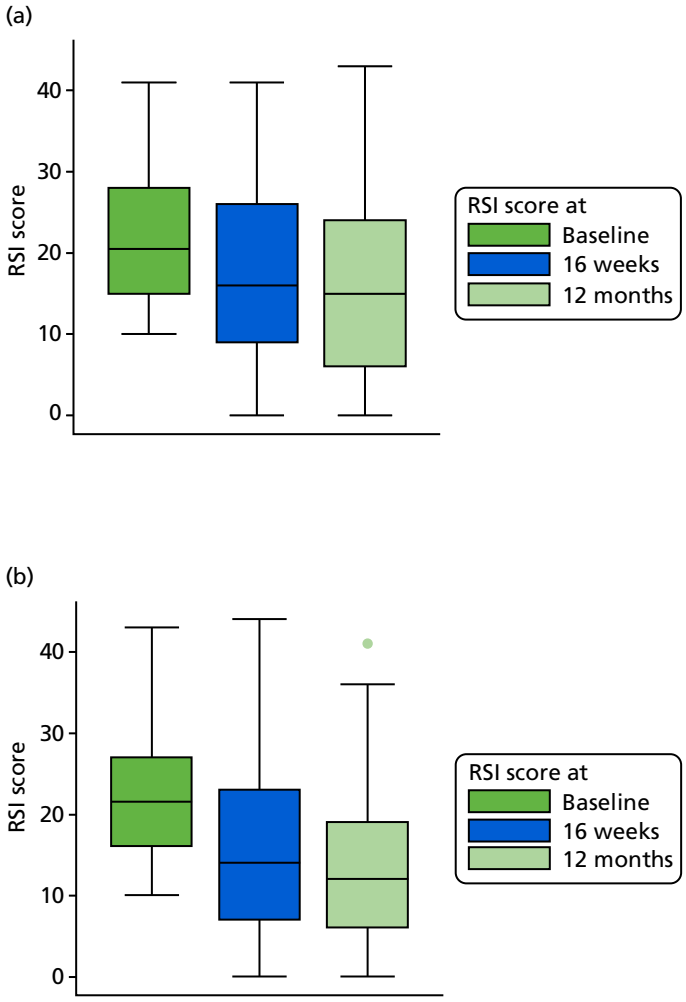

FIGURE 14 Box plots showing medians, IQRs and overall ranges of RSI score at baseline, 16 weeks and 12 months (compliant ITT group). (a) Lansoprazole group ($n = 82$); and (b) placebo group ($n = 99$).

Mean RSI reduces in both groups at 16 weeks and further reduces at 12 months.

Univariate analysis RSI scores were reported at 12 months for the compliant ITT group, in which the null hypothesis is of no difference between means. The test statistic was $t = 1.583$ and the two-sided p-value was 0.115, concluding that there is no statistically significant difference in the RSI score at 12 months between the lansoprazole and placebo groups.

Reflux Symptom Index scores at the 12-month follow-up within the published normal range (< 12) for the compliant intention-to-treat group

Overall, 10% of patients were within the normal range at baseline, balanced across randomised groups (the inclusion criterion being the eight-item version of the RSI excluding the dyspepsia item 9). At 16 weeks, 43% (95% CI 37% to 50%) of participants are within the normal range. There is a slight increase at 12 months to 48% (95% CI 41% to 55%) of participants being within the normal range, balanced across randomised groups: lansoprazole 40% (95% CI 29% to 51%) versus placebo 55% (95% CI 45% to 65%). The overlapping CIs indicate no statistical difference between the groups.

Multivariable analysis of Reflux Symptom Index at 12 months for the compliant intention-to-treat group

Note that ANCOVA for RSI at 12 months (see *Appendix 7*) showed no statistically significant difference in RSI at 12 months between randomised treatment groups ($p = 0.256$), but site and baseline severity remain significantly related to 12-month RSI. Age and sex also appear to be significantly related to 12-month RSI when all are included in the ANCOVA analysis. The statistical modelling of the 12-month RSI for the compliant ITT group is also included in *Appendix 7* and was conducted similarly to the prior modelling exercises.

The difference between randomised groups, when accounting for site and binary baseline severity, indicates that lansoprazole participants are estimated to have RSI scores at 12 months that are 2.5 points higher (worse) than those of placebo participants (95% CI –0.1 to 5.0; $p = 0.06$).

The underlying assumptions of the model were not substantially violated. As none of the potential covariates appears to have a significant univariate relationship with the 12-month RSI score, model 2 with continuous baseline severity (RSI-HB) and site remains the optimum. There was no statistically significant difference between the lansoprazole group and the placebo group when adjusted for site and baseline continuous RSI-HB. There is an estimated difference that lansoprazole participants have RSI scores at 12 months that are 1.7 points higher (worse) than those of placebo participants (95% CI –0.7 to 4.1 points; $p = 0.157$). Further information is given in *Appendix 7*, *Table 54*.

Reflux Finding Score for the compliant intention-to-treat group

The RFS was independently scored by a single expert rater (PC) who was blind to patient treatment group. Images were scored (*Table 18*) from 0 to 26 and assessed as a potential predictor of RSI at 16 weeks. There were a total of 256 RFSs for unique participants (see *Appendix 3*), of which 167 were for participants in the compliant ITT group.

Reflux Finding Score at baseline for the compliant intention-to-treat group

The means, SDs, medians, IQRs and ranges are reported as the score is treated as a continuous measure but is integer in nature (see *Table 18*).

A higher RFS indicates more severe laryngeal inflammation. Overall, RFS at baseline is, on average, 9.4 points (95% CI 8.8 to 10.0 points). The summary statistics show the number and value of RFSs to be similar in both treatment groups at baseline. Usable RFS assessments were available for 76% of participants in the compliant ITT analysis group.

TABLE 18 The RFS total scores at baseline (visit 1) (compliant ITT group)

	Treatment group		
RFSs of images	Lansoprazole ($N = 102$)	Placebo ($N = 118$)	Total ($N = 220$)
n (%) with RFSs	82 (80)	85 (72)	167 (76)
Median (IQR)	9 (7–12)	9 (7–11)	9 (7–12)
Mean (SD)	9.7 (4.1)	9.2 (3.8)	9.4 (3.9)
95% CI of mean	8.8 to 10.6	8.4 to 10.0	8.8 to 10.0
Range	0–20	0–18	0–20

The utility of the Reflux Finding Score as a response predictor for the compliant intention-to-treat group

The use of both first-order fractional polynomial transformations and a fourth model of primary outcome baseline RFS failed to find any significant relationship of baseline RFS with the RSI score at the primary end point (see *Appendix 8*).

Comprehensive Reflux Symptom Score

Comprehensive Reflux Symptom Score total and subscale scores baseline descriptive analysis: compliant intention-to-treat analysis group

The CReSS at baseline was assessed as a potential predictor of RSI at 16 weeks (*Table 19*). A higher CReSS indicates worse symptoms. There was a 98% completion rate for CReSS at baseline in the compliant ITT analysis set. The score is treated as a continuous measure but is integer in nature. The summary statistics and box plots for CReSS total (see *Appendix 9*, *Figure 17*) and subscale (see *Appendix 9*, *Figures 18–20*) scores, and information on missing data, are included in *Appendix 9*. Missing observations were few and so multiple imputation was not used.

Appendix 9 shows the similarity of 16-week and 12-month outcomes in total and subscale CReSSs between those treated with lansoprazole and those treated with placebo (see *Appendix 9*, *Tables 58–62*).

Baseline itemised severity score: Comprehensive Reflux Symptom Score

The item descriptive statistics for CReSS are listed in *Report Supplementary Material 1*, *Table 12*, for the whole trial population and in *Report Supplementary Material 1*, *Table 13*, for the compliant group.

The top five CReSS items, for both the trial population and the compliant group, in ranked mean endorsement severity were:

1. throat clearing
2. feeling things stuck in throat
3. lump in throat
4. excess mucus
5. hoarseness.

The relationship between the RSI at baseline and total CReSS at baseline for the compliant ITT group is shown in *Figure 15*, which demonstrates a linear relationship (i.e. an increased CReSS is associated with increased RSI score). (It should be remembered that the RSI symptom items were all purposively included in the CReSS and so the two are not independent of each other.)

Comprehensive Reflux Symptom Score subscale scores as covariates for Reflux Symptom Index at 16 weeks

The reduction in AIC through simple log or complex (fractional polynomial) transformations was not substantial (see *Appendix 9*, *Table 59*). In order to build the most parsimonious, clinically interpretable model, the CReSS total and subscale scores were retained as untransformed continuous covariates, under the assumption of linearity with outcome. The optimum predictive model based on CReSS incorporated the upper airway subscale, but this performed less well than inclusion of RSI-HB in the predictive model.

TABLE 19 The CReSS total and subscale scores at baseline (visit 1) (compliant ITT group)

	CReSS total (range: 0–170)			CReSS oesophageal subscale (range: 0–85)			CReSS upper airway subscale (range: 0–45)			CReSS pharyngeal subscale (range: 0–25)		
	Treatment group			Treatment group			Treatment group			Treatment group		
Descriptive statistic	Lansoprazole (*N* = 102)	Placebo (*N* = 118)	Total (*N* = 220)	Lansoprazole (*N* = 102)	Placebo (*N* = 118)	Total (*N* = 220)	Lansoprazole (*N* = 102)	Placebo (*N* = 118)	Total (*N* = 220)	Lansoprazole (*N* = 102)	Placebo (*N* = 118)	Total (*N* = 220)
n (% of compliant group)	100 (98)	115 (97)	215 (98)	101 (99)	115 (97)	216 (98)	101 (99)	116 (98)	217 (99)	102 (100)	116 (98)	218 (99)
Median (IQR)	47.5 (27.5–69)	50 (33–69)	49 (30–69)	20 (9–29)	19 (11–27)	19 (10–29)	16 (10–24)	17 (10–25.5)	17 (10–25)	9 (5–13)	9.5 (4.5–14)	9 (5–14)
Mean (SD)	50.3 (27.4)	51.1 (25.7)	50.7 (26.4)	20.7 (14.9)	21.2 (14.1)	21.0 (14.5)	17.3 (9.9)	17.9 (9.9)	17.6 (9.9)	9.4 (5.8)	9.4 (5.6)	9.4 (5.7)
95% CI of mean	44.9 to 55.7	46.4 to 55.8	47.2 to 54.3	17.8 to 23.7	18.6 to 23.8	19.0 to 22.9	15.4 to 19.3	16.1 to 19.7	16.3 to 19.0	8.2 to 10.5	8.4 to 10.4	8.6 to 10.2
Range	2–142	8–141	2–142	0–76	0–63	0–76	0–45	0–44	0–45	0–22	0–22	0–22

The summary statistics show the CReSS total and subscale scores are similar in both treatment groups at baseline.

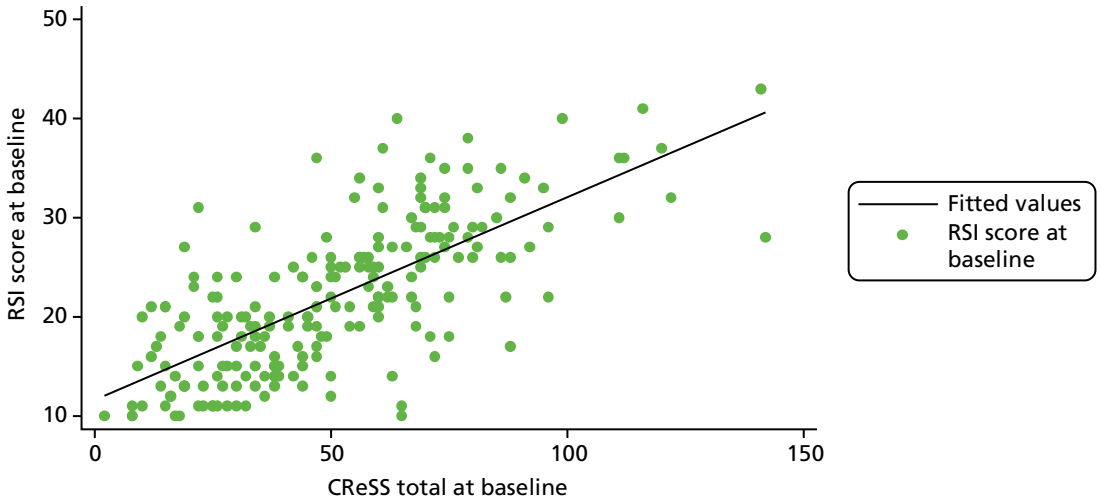

FIGURE 15 Scatterplot of the relationship between the total CReSS and RSI at baseline (compliant ITT group, $n = 215$).

Laryngopharyngeal Reflux – Health Related Quality of Life questionnaire

Patient quality of life was assessed using the LPR-HRQL. Higher scores indicate worse LPR quality of life. The total LPR-HRQL score and subscales at baseline and 16-week and 12-month follow-ups are presented for the compliant ITT population. Missing item rules dictate that three questionnaires with missing items can be imputed [two at baseline and one at the primary end point (16 weeks)].

Baseline Laryngopharyngeal Reflux – Health Related Quality of Life scores

Table 20 shows baseline scores (raw and standardised) for overall score and the voice, cough, clear throat and general subscales. Each remaining item not included in the subscales is reported separately.

Higher scores indicate worse LPR quality of life.

Raw scores appear skewed. Each subscale is reported as a standardised '*z*-score' calculated by subtracting the means and dividing by SD, which appear less skewed. Each subscale section also has an extra question labelled 'the thermometer', reported individually and with the appropriate subscale (see *Appendix 10*, *Tables 62* and *63*).

Laryngopharyngeal Reflux – Health Related Quality of Life at primary end point (16-week follow-up)

The results are shown in *Table 21*.

The raw scores again appear skewed, and the standardised scores less so. The 16-week scores (see *Table 21*) show a marked reduction from baseline across all domains and across both treatment groups. The equivalent thermometers are given in *Appendix 10*, *Table 65*.

The median overall LPR-HRQL scale at the 16-week primary end point reduced (improved) by around half, with almost identical reductions in the two treatment groups.

Laryngopharyngeal Reflux – Health Related Quality of Life at 12-month follow-up (visit 3)

Corresponding data provided at 12-month follow-up are shown in *Appendix 10*, *Table 64*, with thermometer scores in *Appendix 10*, *Table 65*.

TABLE 20 The LPR-HRQL baseline scores (compliant ITT group) ($n = 220$; lansoprazole = 102, placebo = 118). All subscales were complete except for those of two placebo participants. Overall complete: lansoprazole, $n = 99$; placebo, $n = 115$

	Scores					
	Raw			Standardised		
	Treatment group			Treatment group		
Scale and descriptive statistics	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Voice (raw range: 0–72)						
Median (IQR)	8 (6 to 22)	7.5 (6 to 15.5)	8 (6 to 19)	–0.46 (–0.59 to 0.45)	–0.40 (–0.52 to 0.19)	–0.44 (–0.59 to 0.38)
Mean (SD)	15.1 (15.4)	12.9 (13.4)	13.9 (14.4)	0 (1)	0 (1)	0 (1)
95% CI	12.1 to 18.1	10.5 to 15.4	12.0 to 15.9	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 67	0 to 62	0 to 67	–0.98 to 3.37	–0.96 to 3.65	–0.98 to 3.65
Cough (raw range: 0–36)						
Median (IQR)	6 (1 to 15)	5 (0 to 13)	5 (1 to 13)	–0.35 (–0.87 to 0.59)	–0.32 (–0.88 to 0.56)	–0.34 (–0.87 to 0.56)
Mean (SD)	9.3 (9.5)	7.9 (9.0)	8.6 (9.3)	0 (1)	0 (1)	0 (1)
95% CI	7.5 to 11.2	6.2 to 9.6	7.3 to 9.8	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 34	0 to 35	0 to 35	–0.98 to 2.58	–0.88 to 3.00	–0.98 to 3.00
Clear (raw range: 0–36)						
Median (IQR)	8 (3 to 14)	7 (2.5 to 13.5)	8 (3 to 14)	–0.16 (–0.81 to 0.63)	–0.23 (–0.83 to 0.65)	–0.16 (–0.81 to 0.63)
Mean (SD)	9.2 (7.6)	8.7 (7.4)	8.9 (7.5)	0 (1)	0 (1)	0 (1)
95% CI	7.7 to 10.7	7.3 to 10.0	7.9 to 9.9	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 35	0 to 33	0 to 35	–1.21 to 3.39	–1.17 to 3.27	–1.21 to 3.39
General (raw range: 0–30)						
Median (IQR)	5.5 (2 to 10)	5 (1 to 11)	5 (1 to 11)	–0.22 (–0.77 to 0.48)	–0.26 (–0.91 to 0.71)	–0.26 (–0.91 to 0.64)
Mean (SD)	6.9 (6.4)	6.6 (6.2)	6.8 (6.3)	0 (1)	0 (1)	0 (1)
95% CI	5.7 to 8.2	5.5 to 7.8	5.9 to 7.6	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 27	0 to 26	0 to 27	–1.08 to 3.14	–1.08 to 3.14	–1.08 to 3.14
Overall (raw rescaled range: 0–100)						
Median (IQR)	24 (10 to 45)	22 (8 to 41)	23 (9 to 42)	–0.23 (–0.84 to 0.74)	–0.20 (–0.86 to 0.68)	–0.20 (–0.84 to 0.70)
Mean (SD)	28.9 (22.2)	26.5 (21.7)	27.6 (21.9)	0 (1)	0 (1)	0 (1)
95% CI	24.5 to 33.3	22.5 to 30.5	24.7 to 30.6	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 95	0 to 87	0 to 95	–1.30 to 2.99	–1.22 to 2.80	–1.30 to 2.99

TABLE 21 The LPR-HRQL scores at the 16-week follow-up (compliant ITT group) ($n = 220$[a])

	Scores					
	Raw			Standardised		
	Treatment group			Treatment group		
Scale and descriptive statistics	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Voice (raw range: 0–72)						
Median (IQR)	7 (6 to 18)	6 (6 to 14)	6.3 (6 to 15)	–0.47 (–0.54 to 0.35)	–0.39 (–0.39 to 0.32)	–0.39 (–0.54 to 0.32)
Mean (SD)	13.3 (13.4)	10.4 (11.2)	11.7 (12.4)	0 (1)	0 (1)	0 (1)
95% CI	10.6 to 16.0	8.3 to 12.4	10.1 to 13.4	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 59	0 to 67	0 to 67	–0.99 to 3.40	–0.92 to 5.04	–0.99 to 5.04
Cough (raw range: 0–36)						
Median (IQR)	4 (0 to 12)	2 (0 to 7)	2 (0 to 10)	–0.39 (–0.85 to 0.54)	–0.41 (–0.69 to 0.28)	–0.41 (–0.69 to 0.42)
Mean (SD)	7.4 (8.6)	5.0 (7.2)	6.1 (8.0)	0 (1)	0 (1)	0 (1)
95% CI	5.7 to 9.1	3.6 to 6.3	5.0 to 7.1	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 31	0 to 34	0 to 34	–0.85 to 2.74)	–0.69 to 4.04	–0.85 to 4.04
Clear (raw range: 0–36)						
Median (IQR)	5 (1 to 11)	3 (0 to 10)	4 (0 to 11)	–0.31 (–0.84 to 0.49)	–0.36 (–0.80 to 0.66)	–0.31 (–0.80 to 0.52)
Mean (SD)	7.3 (7.6)	5.5 (6.8)	6.3 (7.2)	0 (1)	0 (1)	0 (1)
95% CI	5.8 to 8.8	4.2 to 6.7	5.4 to 7.3	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 30	0 to 34	0 to 34	–0.97 to 3.00	–0.80 to 4.18	–0.97 to 4.18
General (raw range: 0–30)						
Median (IQR)	2.5 (0 to 6)	2 (0 to 7)	2 (0 to 7)	–0.35 (–0.75 to 0.21)	–0.45 (–0.80 to 0.41)	–0.45 (–0.75 to 0.37)
Mean (SD)	4.7 (6.2)	4.6 (5.8)	4.6 (6.0)	0 (1)	0 (1)	0 (1)
95% CI	3.5 to 5.9	3.6 to 5.7	3.8 to 5.4	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 29	0 to 29	0 to 29	–0.75 to 3.92	–0.80 to 4.23	–0.80 to 4.23
Overall (raw rescaled range: 0–100)						
Median (IQR)	11 (3 to 33)	10 (2 to 25)	10 (2 to 27)	–0.42 (–0.79 to 0.57)	–0.36 (–0.71 to 0.36)	–0.42 (–0.74 to 0.47)
Mean (SD)	20.5 (22.4)	17.1 (20.9)	18.7 (21.6)	0 (1)	0 (1)	0 (1)
95% CI	16.1 to 25.0	13.3 to 21.0	15.8 to 21.6	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
Range	0 to 83	0 to 96	0 to 96	–0.92 to 2.80	–0.82 to 3.77	–0.92 to 3.77

a Either 217/220 patients or 219/220 patients contributed data to the table.

Plots of laryngopharyngeal reflux health-related quality of life

Plots of LPR-HRQL (subscales and corresponding thermometer scores) are shown in *Report Supplementary Material 1*, *Figures 1–8*. *Report Supplementary Material 1*, *Figures 9–18*, shows the LPR-HRQL domain score graphs at baseline, 16 weeks and 12 months.

Overall subscale values are shown in *Figure 16*.

The overall score is calculated by adding the thermometer scores [voice (question 13), coughing (question 20), clear throat (question 27) and general (question 33)] and the remaining domain scores (questions 34–43).

The mean voice, coughing, clear throat, general subscale scores and overall scores were relatively low at baseline and had reduced by 16 weeks in both groups, with further reduction at the 12-month visits. The same patterns are also reflected in the median thermometers, when a score of 3 or 4 indicates a small effect and scores of 2 and 1 indicate minimal to no effect on quality of life.

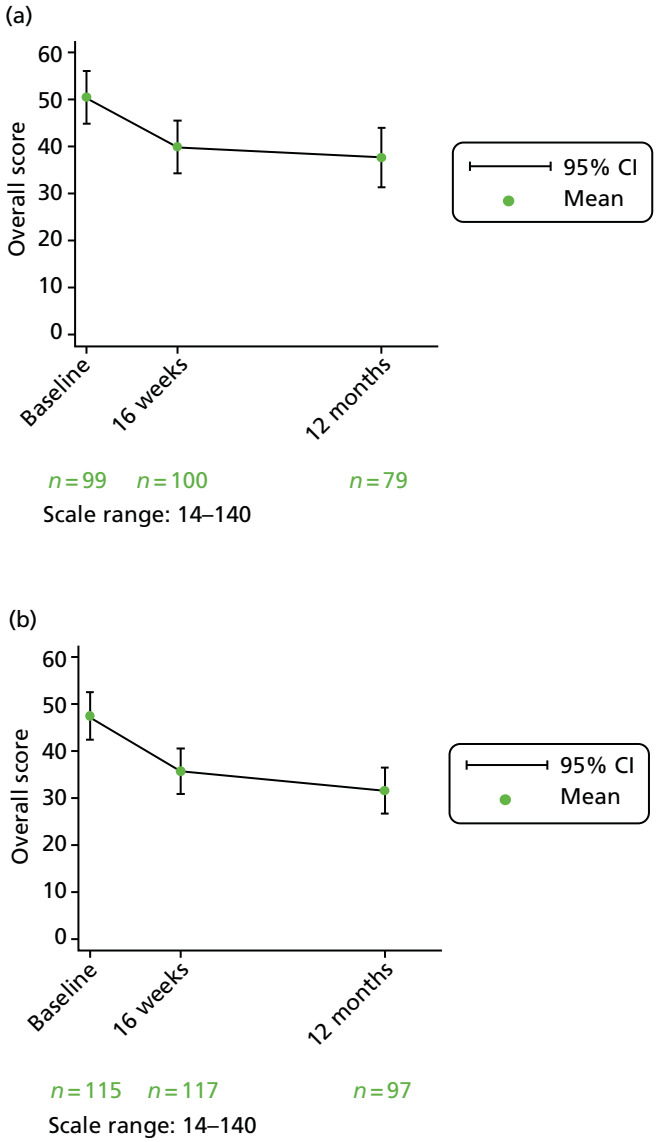

FIGURE 16 The LPR-HRQL overall subscale scores aggregated at visits, by treatment group. (a) Lansoprazole group; and (b) placebo group.

Each of the remaining domain scores used to calculate the overall score is also presented individually at baseline and 16-week and 12-month follow-up visits in *Report Supplementary Material 1*, *Figures 9–18*.

There is only a small effect on overall quality of life relating to individual domain scores.

The IQRs of the domain scores generally decrease from baseline levels by 16 weeks in both treatment groups.

None of the baseline median LPR-HRQL domain scores reflects a large impact of symptoms on the individual domains and the small reductions (improvements) by 16 weeks are similar across treatment groups.

Standardised area under the curve for overall Laryngopharyngeal Reflux – Health Related Quality of Life

A standardised area under the curve (SAUC) is calculated for each patient, defined as area under the curve as a proportion of time observed, and reported descriptively. A total of 213 out of the 220 participants in the compliant ITT group are included in SAUC analysis (for lansoprazole, 75 participants have LPR-HRQL scores at all three time points, 22 participants have LPR-HRQL scores at visits 1 and 2 and one participant has LPR-HRQL scores at visits 1 and 3; for placebo, 94 participants have LPR-HRQL scores at all three time points, 20 participants have LPR-HRQL scores at visits 1 and 2 and one participant has LPR-HRQL scores at visits 1 and 3). The distribution is skewed.

Median SAUC over 12 months is 32.6 (IQR 22.5–53.1) for lansoprazole and 29.9 (IQR 19.9–50.4) for placebo. In other words, patients reported approximately 30% of a maximum 100 LPR-HRQL score, similar across groups over 12 months' follow-up.

Repeated-measures mixed model

A repeated-measures mixed-effects multilevel model accounts for longitudinal data within patients over time (*Table 22*).

There is a significant decrease (improvement in quality of life) from baseline to the 16-week and 12-month follow-up visits. The lansoprazole group had an overall LPR-HRQL score that was, on average, 2.9 points higher (worse) than that for the placebo group (95% CI –4.3 to 10.1; $p = 0.427$), increasing from 16 weeks to 12 months.

TABLE 22 Mixed-effects multilevel regression ($n = 220$)

Model	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	2.903	3.656	0.79	0.427	–4.262 to 10.069
Time					
16 weeks	–11.719	2.069	–5.66	< 0.001	–15.775 to –7.664
12 months	–14.826	2.209	–6.71	< 0.001	–19.155 to –10.497
Interaction: group*time					
Lansoprazole*16 weeks	1.302	3.048	0.43	0.669	–4.673 to 7.276
Lansoprazole*12 months	2.111	3.290	0.64	0.521	–4.338 to 8.560
Constant	47.209	2.489	18.97	< 0.001	42.331 to 52.087

SE, standard error.
Group variable: study identifier, log-likelihood = –2734.185; Wald chi-squared test = 88.20; *p*-value > χ^2 < 0.001.

Summary of Reflux Symptom Index, total Comprehensive Reflux Symptom Score and Laryngopharyngeal Reflux – Health Related Quality of Life scores for the compliant group at all three time points

Table 23 provides a summary of total RSI, CReSS and LPR-HRQL scores at three time points.

Patient satisfaction with TOPPITS

At the 12-month follow-up (visit 3), 213 out of 346 (62%) participants answered the satisfaction question, of whom 115 (54%) were very satisfied, 59 (28%) were satisfied, 29 (14%) were neither satisfied nor dissatisfied, five (2%) were dissatisfied and five (2%) were very dissatisfied.

Safety

Information was gathered on AEs at all three TOPPITS clinic visits. We recorded any untoward medical occurrence in a patient to whom a medicinal product had been administered, including occurrences that were not necessarily caused by or related to that product. In the protocol,[1] it was stated that causality would be graded on a five-point scale [unrelated, unlikely, possible, probable and definitely related to the investigational medicinal product (IMP)]. MACRO was set up for data collection on a three-point scale (not related, possibly related and probably related). A file note was added to the trial master file detailing this change from the protocol.

Adverse event causality was reported on the three-point scale available from MACRO. The numbers of patients reporting any AE are reported, clarifying those deemed to be treatment related. SAEs and occurrence of suspected unexpected serious adverse reactions are also recorded by group. The clinical side effects of PPI use include gastrointestinal disturbance and rebound hypersecretion after cessation of PPI therapy. Rarer side effects include pneumonia, *C. difficile* infections, acute renal inflammation and fractures of the hip, wrist and spine.

TABLE 23 Summary of total RSI/CReSS/LPR-HRQL (overall) scores at three time points (compliant group, $n = 220$)

	Scores, mean (95% CI)		
	Treatment group		
Questionnaire	Lansoprazole ($n = 102$)	Placebo ($n = 118$)	Total ($N = 220$)
Baseline			
RSI	22.0 (20.4 to 23.6)	21.7 (20.5 to 23.0)	21.9 (20.9 to 22.9)
CReSS total	50.3 (44.9 to 55.7)	51.1 (46.4 to 55.8)	50.7 (47.2 to 54.3)
LPR-HRQL	28.9 (24.5 to 33.3)	26.5 (22.5 to 30.5)	27.6 (24.7 to 30.6)
16 weeks			
RSI	17.4 (15.5 to 19.4)	15.6 (13.8 to 17.3)	16.4 (15.1 to 17.7)
CReSS total	38.9 (33.4 to 44.3)	34.7 (29.6 to 39.9)	36.6 (32.9 to 40.4)
LPR-HRQL	20.5 (16.1 to 25.0)	17.1 (13.3 to 21.0)	18.7 (15.8 to 21.6)
12 months			
RSI	16.0 (13.6 to 18.4)	13.6 (11.7 to 15.5)	14.7 (13.2 to 16.2)
CReSS total	36.6 (29.8 to 43.5)	31.8 (26.6 to 36.9)	33.9 (29.8 to 38.1)
LPR-HRQL	18.8 (13.7 to 23.8)	13.9 (10.0 to 17.8)	16.0 (13.0 to 19.2)

LPR-HRQL raw scores rescaled so that range is 0–100.

Adverse events for the per-treatment analysis group

There were 112 reported AEs in the per-treatment group (*Tables 24* and *25*) in 74 unique patients.

Further information from the database manager indicates that two of the three AEs with missing dates pre-date the start of the trial. One was marked 'not available' by the site in MACRO. More details are provided in *Report Supplementary Material 1*.

TABLE 24 Adverse events that occurred while the patient was taking allocated treatment (per-treatment group)

	AEs, *n* (%)		
	Treatment group		
Status	Lansoprazole (*N* = 60)	Placebo (*N* = 52)	Total (*N* = 112)
Patient taking treatment? Yes	42 (70)	38 (73)	80 (71)
Patient taking treatment when AE occurred? No	15 (25)	14 (27)	29 (26)
AE dates missing	3 (5)	0 (0)	3 (3)

TABLE 25 Reported AEs (per-treatment group) (three AEs with missing dates are excluded)

	AEs, *n* (%)					
	Treatment group					
	Lansoprazole		Placebo		Total	
Related to treatment?	During treatment	After treatment	During treatment	After treatment	During treatment	After treatment
Probably						
Severe	1 (2)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Moderate	5 (12)	0 (0)	0 (0)	0 (0)	5 (6)	0 (0)
Mild	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Possibly						
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Moderate	5 (12)	0 (0)	3 (8)	0 (0)	8 (10)	0 (0)
Mild	7 (17)	0 (0)	3 (8)	0 (0)	10 (13)	0 (0)
Not related						
Severe	1 (2)	0 (0)	2 (5)	0 (0)	3 (4)	0 (0)
Moderate	11 (26)	4 (27)	10 (26)	2 (14)	21 (26)	6 (21)
	1 (AE dates missing)				1 (AE dates missing)	
Mild	12 (29)	10 (67)	20 (53)	12 (86)	32 (40)	22 (76)
	2 (AE dates missing)				2 (AE dates missing)	
Not reported	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (3)
Total	42[a] (100)	15[a] (100)	38 (100)	14 (100)	80a (100)	29a (100)

a Totals and percentages omit the three AEs that cannot be categorised into during/after treatment owing to missing AE dates.

A check was carried out to see if any patients who attended the primary end-point visit but did not provide information on returned medication reported any AEs. These could still be attributed to the trial medication, but would not be included in the per-treatment group as no assumption on medication taken was made. There were two such events: one unrelated (dental abscess) and one possibly related to the medication (details: Patient 6009, randomised to lansoprazole, reported a mild AE – 'confusion, weakness on left leg, chest pain after swallowing the trial drug').

Report Supplementary Material 1 provides a line listing of the breakdown of AEs by treatment group, with categorisation in terms of relationship to medication, severity and whether or not the participants were taking the medication at the time when the AE occurred. Most of the AEs and adverse reactions were expected treatment-related toxicities.

Serious adverse events for the per-treatment analysis group

There were two SAEs, both unrelated to the trial medication. One was unintentional bleach ingestion on an overseas holiday due to an error made by a hotel staff member (PPI group) and the other was an exacerbation of pre-existing asthma (placebo group).

Chapter 4 Discussion

Terminology

Persistent throat symptoms include chronic throat clearing, hoarse voice (dysphonia), sensation of a lump in the throat (globus) and increased mucus sensation (catarrh). The symptoms most commonly experienced by the TOPPITS participants were, in order of frequency, as recorded by the RSI severity endorsement [see *Report Supplementary Material 1*, *Tables 16* (whole population) and *17* (compliant group)]:

1. lump in the throat
2. throat clearing
3. excess mucus
4. troublesome cough
5. hoarseness.

Similar frequencies were, not surprisingly, seen with CReSS:

1. throat clearing
2. feeling things stuck in throat
3. lump in throat
4. excess mucus
5. hoarseness.

Laryngopharyngeal reflux was promoted as an umbrella term in the mid-1990s and has since grown in popularity despite ongoing debate regarding pathophysiology, diagnosis and treatment. We aimed to quantify shifts in medical terminology for throat symptoms over time. Search terms included 'throat clearing', 'reflux laryngitis', 'acid laryngitis', 'globus pharyngeus', 'globus sensation', 'globus hystericus', 'catarrh' or 'laryngopharyngeal reflux' in the title or abstract. The total number of publications per decade was derived along with subtotals for clinical research and reviews. Catarrh ($n = 473$) and the various terms for globus ($n = 468$) featured prominently for the decades 1960s to 1980s, with fewer instances of acid/reflux laryngitis ($n = 96$). The 209 references to throat clearing date from 1980 (numerically the commonest symptom in most detailed surveys). There has been an exponential rise in LPR from the 1990s ($n = 810$), although fewer than one in five reports were classed as a 'clinical study'. The predilection for LPR is no doubt supported by the fact that > 50% of the US general population has heartburn.[56] The use of anticholinergic medications, especially in combination, increases the odds of experiencing globus by a factor of 3.52.[57] An investigation of the frequency of throat clearing and cough and how often each is associated with a positive symptom index for reflux found a low probability of objective association. This is even less likely if both symptoms are present or if patients report an 'excessive' cough.[58]

The premise for TOPPITS was that without a robust UK trial we saw nothing to question the increasing popularity of acid suppression medications as a prime therapy for upper respiratory symptoms. If all putative LPR patients referred to otolaryngologists were treated with PPIs, the costs are estimated at £4M per annum. Although the link between LPR and upper respiratory symptoms is little more than speculative or intuitive when close enquiry of the evidence base is made, the level of acceptance in primary care is also increasing. Many patients seen by non-TOPPITS otolaryngologists at participating centres might have considered TOPPITS had they not already had substantial trials of PPIs in primary care and thus never even reached the screening clinic.

There is no agreed, standard, core patient self-report outcome even for lower oesophageal reflux; the only COMET website reference to reflux is to a workshop that concluded that members strongly supported the development of validated patient-reported outcome instruments. This lack of a pre-eminent outcome tool led us to develop the CReSS.[59] The CReSS covers all oesophageal and extraesophageal reflux symptoms by incorporating all items from the original Gastrointestinal Symptom Assessment Score,[60] together with all components of the RSI. CReSS totals are independent of age, and all items were endorsed by ≥ 17% of throat symptom patients.[61]

The inexorable rise in popularity of LPR as the default term for persistent throat symptoms appears to have fuelled huge popularity for PPI therapy despite a lack of evidence. Attempts to reverse this trend, in view of recent adverse PPI publicity, will be supported by the overall negative finding of the TOPPITS data. Globus pharyngeus was described as a 'tainted term' in a recent opinion article due to its connotation of 'globus hystericus'.[62] The authors propose that a feeling of having a lump in the throat on dry swallow is a normal sensation, accentuated by circumstances. Their proposed contemporary term is 'troublesome Throat Awareness' (tTA). However, this idiosyncratic acronym, although functionally useful, will not readily supplant the classical term.

Recent reports on epidemiology of persistent throat symptoms

The 1982 ENT outpatient globus prevalence figure of 4.2%[3] has fallen little in the ensuing decades, being 3.8% in a recent report.[63] Despite its name, there is little evidence linking the symptom items of the RSI with any demonstrable oesophagopharyngeal reflux. Indeed, the very first attempt – almost 30 years ago – to treat a similar list of symptoms with H_2 antagonists yielded a negative result.[19] The RSI has nonetheless been used to assess 'LPR' in a number of recent studies. A population prevalence study approached 2000 UK-dwelling adults, who were sent the RSI and questions on their health and lifestyle. The mean RSI was 8.3; 30% had a RSI score of > 10, of whom 75% had symptoms of GORD. Patients with depression and irritable bowel syndrome were more likely to have higher RSI scores. In other words, in this population survey, correlates of the RSI questionnaire score appear to be gastroesophageal reflux, depression and irritable bowel syndrome.[30] In the general Greek population, the prevalence of 'LPR' was 18.8%, similar in both sexes ($p > 0.05$), with a peak age of 50–64 years and with a positive association with tobacco smoking and alcohol consumption.[64] A total of 3006 individuals surveyed in Guangdong Province, China,[65] completed questionnaires about their physical and psychological characteristics and globus symptomatology, and our own, physician-generated Glasgow Edinburgh Throat Scale[66] with questionnaires on quality of sleep and life. In this survey, those with no history of GORD, dysphagia, odynophagia or alerting symptoms, such as weight loss and hoarseness, were diagnosed as having globus. The overall lifetime prevalence of globus so defined was 21.5%, with a peak age at disease onset of 35–54 years, commoner in urban dwellers and with no sex bias. Anxiety (40%), depression (31%) and sleep disorders (24%) in respondents with globus were significantly commoner than in those without globus.[65] A more informal enquiry made by our group many years ago in a high street survey of UK shoppers indicated a (within the last 3 months) female population prevalence of globus in 6% of those questioned.[2]

Perception of reflux causation of persistent throat symptoms in general practice

The risk of overattribution of throat symptoms to so-called LPR has been recognised in the specialist ENT literature for some time. A retrospective chart review analysis identified 105 patients in a private laryngology clinic setting with a previous diagnosis of LPR as the cause of hoarseness. After anti-reflux therapy, 82% had no improvement or felt worse, leading the authors to conclude that LPR was overdiagnosed, especially when no other explanation was readily apparent.[67] A similar reliance on a putative LPR diagnosis in the absence of clear evidence has filtered into the wider, non-ENT, medical community. A US web-based survey of 314 (13%) doctors (46% family practitioners) showed that 64% preferred to treat rather than immediately

refer a patient with chronic (> 6 weeks') unexplained hoarseness, most often with anti-reflux medication (86%), even in the absence of GORD symptoms and antihistamines (54%).[68] Pre-treatment appears to significantly delay diagnosis. A retrospective case review of 755 patients referred to a voice service in Kansas City[69] reported that 244 patients (32%) received a diagnosis before attending, this being LPR in over half, and, of those, > 65% had no GORD symptoms. Over 80% of diagnoses changed following attendance at the voice clinic and so those with prior treatment had a median duration of symptoms that was 6 weeks longer than those without ($p = 0.04$).[69]

Similar trends seem to prevail in the UK. Although only 27% of TOPPITS recruits had taken PPIs in the preceding 12 months (see *Appendix 2*, *Table 36*), many others who had previously had this treatment were understandably reluctant either to discontinue it simply to enter a RCT of the same medication or to return to it when it had previously failed, and so the figure of 27% under-represents the general laryngology referral population usage of PPIs.

Misuse of PPIs is also documented internationally in a wider context. Only 34% of Swiss GPs are reported to attempt dose reduction in long-term users.[70] An Italian primary care study found that almost 15% of a sample of over 6300 patients were taking PPIs – over 30% potentially inappropriately.[71] A Canadian study of over 870 patients presenting to the emergency department of a teaching hospital also found PPI prescription to be inappropriate in > 30% of participants.[72] An observational study of the patients admitted to an acute hospital in Ireland in February 2018[73] identified that almost half of the sample of 1764 patients were regular PPI users. Almost 55% had no documented indication. Polypharmacy in the elderly gave particular cause for concern.[73] Pre-admission and discharge prescriptions were reviewed in a tertiary teaching hospital in Singapore to determine continuation of pre-admission and new PPI prescriptions at discharge.[74] Of 150 patients, 53% received prescriptions for PPIs, of whom > 80% had no valid reason.[74]

What does TOPPITS tell us about the impact of proton pump inhibitor treatment on throat symptoms?

The key messages from the trial are:

- There was no statistically significant difference between randomised groups, lansoprazole compared with placebo, when adjusted for site and baseline binary RSI-HB. This difference indicates that lansoprazole patients are estimated to have RSI scores at 16 weeks that are 1.9 points higher (worse) than placebo patients (95% CI –0.3 to 4.2; $p = 0.096$) (see *Table 9*).
- There is no statistically significant difference in the mean RSI score at 16 weeks between lansoprazole (17.4, 95% CI 15.5 to 19.4) and placebo (15.6, 95% CI 13.8 to 17.3) ($p = 0.162$). (See the *t*-test results in *Chapter 3*, *Univariate analysis of unadjusted primary outcome measure for the compliant analysis group*.)
- At 16 weeks, 43% of participants had RSI scores within the normal range, with no significant difference between the lansoprazole (41%) and placebo (45%) groups (see *Report Supplementary Material 1*, *Table 15*).
- Patient demographics[39,75] were explored as potential baseline determinants of treatment response but age, sex, smoking status, alcohol consumption and BMI did not improve the RSI 16-week prediction (model 3; see *Table 11*).
- At 12 months, there is a further minor drop in RSI scores (see *Table 17* and box plots in *Figure 14*).
- Baseline RFS does not predict PPI response (see *Appendix 8*, *Table 56*).

TOPPITS is a considerably larger trial than the majority of series included in recent meta-analyses. Pre TOPPITS, a trial in 146 selected patients, all with signs of posterior laryngitis,[22] showed no symptom benefit from PPI therapy over placebo, but did not report RSI scores. Lee *et al.*[76] noted less marked PPI responses in older patients (to a lower-dose PPI regimen than was used in TOPPITS). However, this may have reflected the fact that the oldest cohort had the highest baseline RSI levels and/or that the authors used a dichotomous definition of response (i.e. a 50% drop in RSI) rather than a continuous variable assessment. Baseline severity was a major determinant of end-point severity in TOPPITS.

Awareness of treatment group by patients

We were interested to explore patient perception of their treatment group as there was a concern that those with more severe heartburn might recognise a prompt heartburn response as implying that they were in the PPI group. However, the awareness (true-positive opinion) of group was broadly equal in the cohorts (see *Table 4*). Of the PPI cohort, 42% correctly called their allocation, compared with 56% of placebo participants.

The recent TOPPITS context

The premise for TOPPITS was that, without a robust UK trial, we saw nothing to stop the increasing 'belief' in LPR as a prime cause of upper respiratory symptoms, as the theory was supported by prominent laryngological enthusiasts, some respiratory medicine experts and, of course, the pharmaceutical industry. If all putative LPR patients referred to otolaryngologists were treated with PPI, we would calculate the costs to be approximately £4M per annum. Although the link between LPR and upper respiratory symptoms is little more than speculative or intuitive when close enquiry of the evidence base is made, the level of acceptance in primary care is also increasing. Many patients seen by non-TOPPITS otolaryngologists at participating centres might have considered TOPPITS had they not already had substantial trials of PPI in primary care and thus never even reached the screening clinic.

A 2016 review[52] of the evidence linking reflux and voice changes concluded that the association lacked supporting data from clinical trials. The authors describe using the Bradford Hill criteria to support their conclusion that 'the evidence toward causality between reflux and voice is insufficient'.[52] Tantalisingly, however, the authors conclude by saying that a relationship 'does exist which deserves careful consideration' – despite having concluded that:

> *To date, neither clinical trials nor comparative observational studies have been able to demonstrate a strong dose response between reflux and voice disorders, temporality (reflux precedes dysphonia), consistent treatment effects or strength of association between anti-reflux treatment and improved voice among patients with presumed LPR.*
>
> *Schneider* et al.[52]

Three meta-analyses have been reported since TOPPITS was designed. A 2014 meta-analysis of eight papers comprising 370 patients found no statistical difference in effect between PPIs and placebo.[77] Separate assessment of the impact on cough was also not statistically significant.[77] This result was in disagreement with two meta-analyses published in 2016.[78,79] Both of these reports include a subset of studies with RSI as primary outcome. Wei[78] examined pooled relative risks for the response rate and standardised mean differences (SMDs) for RSI and RFS. Of 13 RCTs, five reported RSI (total $n = 277$, ranging from only 37 to 82[15] participants per study). Pooled results are reported to demonstrate that the total RSI improved significantly more for PPI therapy than for placebo (SMD 3.65, 95% CI 1.56 to 5.75), although no significant difference was found in response rate (0.04, 95% CI –0.06 to 0.14) or RFS (SMD 0.91, 95% CI –0.53 to 2.35). Scrutiny of the tabulated and forest plot findings, however, indicates that, of the five trials in the RSI analysis, three favour PPI, but with highly significant heterogeneity (i.e. variability in results across studies), questioning the pooling of the data in the first place. The smallest mean difference in RSI was 0.26. The greatest SMD total RSI score (14.21 in 60 patients) is reported in Chinese with an English-language abstract. However, this was not a study comparing PPIs with placebo but of 'golden voice capsule' plus or minus PPI.[80] This study was omitted when Guo *et al.*[79] carried out a similar RSI meta-analysis on the remaining four studies (total $n = 217$). Despite dropping the outlying ineligible study, there remained highly significant heterogeneity ($p < 0.00001$), and the SMD had fallen to 1.65 (95% CI 0.15 to 3.14).

Reichel *et al.*[81] carried out a RCT of PPI in patients with throat symptoms, although the citation in Wei's[78] bibliography is of their publication of 49 patients on the lack of correlation between the symptom change

after PPI with measurable 24-hour pH monitoring change. The actual RCT carried out by this group had RSI as the principal outcome in 58 patients.[28] (Moreover, the reference numbering in the table of all 13 included studies is awry[78]). However, the representation of Reichel *et al.*'s[81] data in the appropriate paper is accurate. Reichel *et al.*[81] included only patients with a RFS of > 7 and their sample showed a RSI SMD of 3.85 at 3 months. The TOPPITS median RFS was 9 at baseline (IQR 7–12) (see *Table 18*) (i.e. a majority of patients would meet Reichel *et al.*'s[81] qualifying criterion). The end of treatment mean change from baseline in the total RSI was 14.3 in the esomeprazole group, which was statistically greater than in the placebo group (7.8, SMD 3.85).[28] The authors note the marked placebo response, which was indeed greater than that in either group of the much larger TOPPITS cohort at 4 months (mean change from baseline in all patients = 5.3).

Other authors have considered whether or not oropharyngeal pH monitoring (Restech, Respiratory Technology Corporation, Houston, TX, USA) may predict PPI response. RSI, laryngoscopy and 24-hour oropharyngeal pH monitoring were undertaken in 22 patients who were given a 3-month course of 40 mg of pantoprazole twice a day.[82] A symptom response was defined as a 5-point fall in the RSI score. Laryngoscopic findings did not correlate with response and only nine patients (40.9%) had abnormal pH-metry, all being responders. Four pH-metry negative patient were also responders. Thus, oropharyngeal pH monitoring showed a sensitivity of 69% and a specificity of 100%.[82] In another report of 24-hour multichannel intraluminal oesophageal impedance/pH-metry, GORD was confirmed in < 40% of patients previously labelled as having LPR, which the authors attribute to 'the low specificity of the laryngoscopic findings'.[83]

Optimal administration of PPI usually takes place 30 minutes before food; > 30% of patients are suboptimal users.[84] (Esomeprazole seems not to lose efficacy when administered after meals.[85]) Fifty-one patients with throat symptoms completed a face-to-face semistructured interview, a questionnaire and the RSI. Over 62% of participants described an incorrect routine in taking their PPI (taking it with other pills, taking it with food/drink and uncertainty about which pill is for reflux), although this did not have an impact on the RSI. RSI scores were moderately correlated with patient-reported reflux severity ($r = 0.62$, $p < 0.0001$, $R^2 = 0.34$). Even when PPI compliance was adequate, symptoms such as globus, mucus, voice dysfunction and dysphagia persisted. In addition to the dubious effect size of PPI therapy, there are now also increasing concerns about the safety of PPIs.

Proton pump inhibitor risk

The US veterans study[86] of the impact of PPI use on all-cause mortality in almost 350,000 individuals found that, over a median follow-up of 5.71 years, PPI use was associated with an increased risk of death compared with the use of H_2 antagonist blockers [hazard ratio (HR) 1.25]. The risk of death was increased when considering PPI use versus no PPI and no H_2 blockers (HR 1.23). Among new PPI users, there was a graded association between the duration of exposure and the risk of death. The authors concluded that limiting PPI use and duration to instances when it is medically indicated may be warranted.[86] A systematic review of PPIs and cardiovascular events analysed five studies that directly compared the effect of PPI use on mortality and/or cardiovascular morbidity (including 22,427 patients in mortality data sets and 354,446 patients in morbidity data sets). For patients taking PPIs, all-cause mortality [odds ratio (OR) 1.68] and rate of major cardiovascular events (OR 1.54) were significantly higher, indicating a significant increase in morbidity due to cardiovascular disease.[87] Long-term PPI use has also been linked to acute interstitial nephritis, fractures, and *C. difficile*-associated diarrhoea, suggesting a need for cautious prescribing and regular monitoring, especially in older adults.[88]

Gastric cancer risk with PPIs was assessed in over 63,000 individuals in Hong Kong who were given clarithromycin-based triple therapy for *Helicobacter pylori*.[89] During a median follow-up of 7.6 years, 153 people (0.24%) developed gastric cancer (HR 2.44); this was not observed with those taking H_2 antagonists (HR 0.72). The risk increased with duration of PPI use: the HR was 5.04 at 1 year and

8.34 after 3 years. The adjusted absolute risk difference for PPI use versus non-PPI use was a 4.29-fold excess of gastric cancer per 10,000 person-years.[89] Similar conclusions were reached in a contemporaneous meta-analysis of almost 1 million individuals in west China.[90]

Using data from Danish nationwide registries and Cox models regressing for both propensity scores and drug use, a Danish group[91] explored the current practice of using PPIs as an adjunctive therapy in cancer patients. Cancer-specific and non-cancer death among PPI users (two or fewer prescriptions within 6 months after diagnosis, $n = 36,066$) were compared with non-users (fewer than two prescriptions, $n = 311,853$) or users of histamine H_2-receptor antagonists ($n = 5152$). Adjusted HRs for cancer-specific mortality among postdiagnostic PPI users as compared with non-users or H_2-receptor antagonist users were 1.29 and 1.15, respectively, and the risk was greatest for ovarian cancer. Although the associations were stronger among new PPI users after cancer diagnosis, indicating potential confounding, and the impact of PPIs on mouse tumour models was variable, the authors raise concerns about PPI safety among cancer patients.[91]

Alginate/alkaline water

The alginate preparation Gaviscon Advance [Reckitt Benckiser Healthcare (UK) Ltd] was assessed alone versus co-prescription with a PPI in an open-label study of '100 consecutive LPR patients' with a RSI of > 10 attending a joint voice clinic.[92] All were treated with Gaviscon Advance four times daily. If patients had already been started on a PPI, this was optimised to a twice-daily dosing regimen. Follow-up RSI scores in 72 patients showed no significant RSI differences from the additional use of PPI.

At the cellular level, tissue-bound pepsin is fundamental to reflux pathophysiology. Human pepsin remains stable at a pH level of 7.4 and may be reactivated by hydrogen ions from any source. Most tap and bottled waters (typically with pH levels of 6.7–7.4) would not be expected to affect pepsin stability. Artesian well water containing natural bicarbonate (pH level of 8.8) irreversibly inactivated human pepsin (in vitro). In addition, it has good acid-buffering capacity. Thus, the consumption of alkaline water may have therapeutic benefits for reflux patients.[93] In vitro tests of the proprietary alginate Gaviscon Advance show that it can specifically remove both pepsin and bile acids, limit their diffusion and affect enzymatic activity of pepsin, hence the potential for oesophageal protection.[94] Gaviscon Advance, it should be noted, relies principally on its alginate raft and not on an acid-buffering capacity.

The Comprehensive Reflux Symptom Score

The advantages of CReSS include standardised, comprehensive capture of patient experience; discriminant validity of ENT and GORD patients from volunteers; and discrete oesophageal, pharyngeal and upper airway subscales.[31] The CReSS and RSI are correlated (see *Figure 15*) as they are not independent, the CReSS incorporating all RSI symptoms. However, the addition of the CReSS upper airway domain to RSI-HB improved the ability to predict RSI at 16 weeks (see *Appendix 9*, *Table 62*).

The Reflux Finding Score is unreliable

We felt that it was important to include a report on the endolaryngeal examination findings as scored by the RFS because of its common use in clinical practice. This is despite limited evidence to suggest that laryngeal mucosal changes – increased 'Reflux Finding' Scores – discriminate between 'normals' and general throat symptom patients.[95] Furthermore, the RFS has not been proven to be a valid tool to diagnose LPR.[17,51–53] In our study, the RFS was independently scored 0–26 and assessed as a potential response predictor (alongside patient characteristics of age, sex, smoking status and BMI), comparing it with the RSI at 16 weeks.
The number and value of RFSs were similar in both treatment groups at baseline. Adjusted for important baseline factors and RFS baseline assessment, the RFS was not suitable for first-order fractional polynomial

transformations and not considered for inclusion in the multivariable model. Thus, the total RFS was not subsequently considered as a predictive factor of treatment response. Several authors have suggested that one feature in the RFS – presence of pseudosulcus – is the best predictor of EOR,[96,97] but this level of individual items analysis was not possible. Pseudosulcus has been reported generally as a rare finding.[97] Others have found that RFS raters are influenced by patient symptoms and so the reliability and objectivity of the RFS is questionable.[98] The RFS is also insensitive to postfundoplication symptomatic benefit.[99]

In a selected series of 78 patients with chronic cough and/or suspected vocal cord dysfunction,[100] 87% had a RSI score of > 13 and 51% had a RFS of > 7. Salivary pepsin had a sensitivity of 78% and specificity of 53% for predicting a high RFS. There were significant correlations between the RSI and RFS ($r = 0.51$) and between the severity of laryngeal inflammation and the concentration of pepsin ($r = 0.28$). All cases investigated with pH-impedance study had objective evidence of proximal reflux.[100] However, these findings in selected patients do not mirror observations in the generality of those presenting to clinics with non-specific throat symptoms, who are the focus of TOPPITS.

Update on pH-metry and manometry in throat symptoms

Up to 50% of the patients suspected of reflux laryngitis syndrome fail to respond to acid suppression therapy. This has led to measurement of acid exposure times in an attempt to improve the specificity of the diagnosis. Using distal and cervical oesophageal pH-metry in 46 'LPR' patients and 58 healthy control patients, the percentage of time that the pH level is < 4 and the number of LPR episodes emerged as diagnostic LPR criteria.[101] Up to 50% of the patients suspected of reflux laryngitis syndrome fail to respond to acid suppression therapy. Laryngopharyngeal bolus exposure time during multichannel intraluminal impedance and pH (MII-pH) testing was the best response predictor in one study.[102] Of 109 patients evaluated by MII-pH, 47% were classed as 'positive' for evidence of significant LPR, with an average of 46 episodes of proximal reflux exposure (either acid or non-acid). RSI scores were significantly different between positive and negative studies, whereas RFSs were not.[103]

High-resolution manometry metrics in 24 globus patients were compared with 24 age-matched and sex-matched subjects with non-obstructive dysphagia and 21 healthy control patients.[104] In a multivariate model, receiver operating characteristic analysis identified a threshold of 0.4-mmHg upper oesophageal sphincter (UOS) residual pressure in globus patients (sensitivity 66.7%, specificity 71.5%, positive predictive value 55.2%, negative predictive value 80.0%).[104] Those globus patients who also have GORD may also have a longer UOS zone.[105] Repeated reactive dry swallowing and/or throat clearing might contribute to these observations, which may have a historical correlate in the so-called 'inferior constrictor strain swallow' described by Gray.[106]

There is recent interest in ambulatory 24-hour oropharyngeal aerosol acid exposure assessment, which was used in 101 patients with GORD symptoms and cough, hoarseness, asthma symptoms or globus sensation alongside concomitant oesophageal pH monitoring. Oesophageal 24-hour pH-metry was positive in 66 patients (65%), of whom 39% also had evidence of aerosol oropharyngeal acid. Only eight of those with normal oesophageal pH-metry had oropharyngeal acid exposure.[107] Our own prior work shows that aspiration of bile acids may induce airway fibrosis through the production of transforming growth factor beta 1 and fibroblast proliferation. Early intervention to attenuate these processes may reduce fibrogenesis in various airway diseases associated with GORD.[108]

Throat symptom patient-reported outcome tools

Three patient-reported outcome measures were utilised in TOPPITS. The RSI was considered the 'market-leader' in terms of popularity and its seemingly ubiquitous association with 'LPR'. There was concern from the research team that the ninth questionnaire item groups four traditional GORD symptoms (heartburn,

indigestion, chest pain and stomach acid coming up). It was hypothesised that this item could lead to overall PPI treatment response reporting given that these symptoms are commonly treated with PPIs, hence the rationale to refine the RSI into a score including and excluding this item for the purposes of baseline stratification. The CReSS questionnaire unbundles this item into distinct questions and has additional items cited as important by patients. The CReSS was included to assess whether or not the more comprehensive symptom profiling would allow greater sensitivity to change than the RSI does. In a study of the quality-of-life impact of throat symptoms in 80 patients, females experienced a greater impact on vitality and mental health than males did.[109] A South Korean study explored the added impact of throat symptoms (RSI) on quality of life in 300 GORD patients. Those with supra-oesophageal symptoms had lower quality-of-life scores proportional to the symptom severity.[110] The LPR-HRQL was included in recognition of the lack of quality-of-life measures or published outcomes in the field of chronic throat symptoms.

All three outcome measures show significant improvement in both the treatment group and the placebo group from baseline to 16 weeks and from baseline to 12 months. The ninth RSI item did not affect treatment reporting between the two groups, as was considered by the research team. The quality-of-life measure (LPR-HRQL) also demonstrated proportionate reductions at 16 weeks and 12 months. This again proves the significant throat symptom placebo effect (Reichel *et al.*[28]). Presumably, both the experience of being in a trial and the additional clinical team contact contributed to the pharmacological component of the placebo response. Evidence suggests that a substantial proportion of patients with unexplained throat symptoms are susceptible to additional, unrelated medically unexplained symptoms. This would accord with the magnitude of the placebo effect in TOPPITS.[23] A person's locus of control is either internal (believes to personally control his or her life) or external (believes to be controlled by others, by environmental factors that cannot be influenced or by chance). An external locus of control has been found to be related to higher placebo response.[111] Contrary to expectation, somatisation in a primary care study was found not to correlate with locus of control,[112] and this whole territory in throat symptoms warrants further investment. Although antidepressants modulate oesophageal sensation and reduce functional chest pain,[113] throat symptom patients regularly discontinue therapy.[114]

Psychological aspects

In a study of US Vietnam War veterans,[115] the prevalence of globus was 6.4%. Those men with globus had increased risks of being diagnosed with somatisation disorder, major depression, generalised anxiety disorder, post-traumatic stress disorder and drug abuse or dependence (OR 1.89), giving rise to the hypothesis that men may develop globus to 'represent' other, related and treatable psychopathology.[115] More widely, evidence suggests that a substantial proportion of patients with unexplained throat symptoms are susceptible to additional, unrelated medically unexplained symptoms. The propensity to multiple unexplained physical symptoms can be quantified by completion of a Review Of Symptoms or similar checklist.[116]

In a recent therapy trial, 148 refractory globus patients were randomised to receive 6 weeks of paroxetine, amitriptyline or lansoprazole. Response (> 50% reduction on the Glasgow Edinburgh Throat Scale) was achieved by 72% of paroxetine users, 46% of those on amitriptyline and only 14% of the lansoprazole group.[117] In our own early study, 24 globus patients were assessed for current and past psychiatric illness and then received amitriptyline or placebo using a double-blind design. Nine patients met the criteria for psychiatric disorder in the past; six had suffered from panic disorder. Two further patients had been troubled by classic panic attacks. Nine of the 12 patients treated with amitriptyline and two of the placebo group discontinued treatment. Thus, the association of pathological anxiety with globus was associated with a high incidence of tricyclic antidepressant treatment failure.[114] Antidepressants modulate oesophageal sensation and reduce functional chest pain[113] but more research is required on their potential in throat symptoms.

Psychophysiological mechanisms

Recent work from China[118,119] suggested that serotonin transporter gene (*SLC6A4*) polymorphism may be associated with both globus pharyngeus and its antidepressant action. Globus patients were randomised into paroxetine or amitriptyline groups for 6 weeks. Treatment response was defined as a > 50% reduction in the Glasgow Edinburgh Throat Scale scores. A significant association between the genotype and the response to antidepressant treatment was observed.[118,119] A recent study of UOS and oesophageal body sensitivity and compliance between globus patients and healthy control patients found that somatisation, panic disorder and post-traumatic stress severity were significantly associated with globus. UOS compliance and somatisation were also found to be independently associated with globus, implying that globus is a complex disorder of the brain–gut axis rather than a 'psychosomatic' disorder or a peripheral oesophageal disorder.[120] Transnasal oesophagoscopy, high-resolution manometry and 24-hour MII-pH monitoring were conducted on 30 globus referrals in Helsinki.[121] There was no evidence of acid or non-acid GORD or elevated UOS pressure.[121]

Potential methods to address the limitations encountered in TOPPITS patient and public involvement

The patient and public involvement strand of TOPPITS was drawn up with high hopes, and nurtured by the ongoing efforts of our qualitative researcher, Jan Lecouturier, yet proved relentlessly disappointing. The following proposals might have, on refection, mitigated the low patient and public involvement input:

- Enhanced budget to fund a team member to attend clinics alongside the research nurses to explore reasons for non-engagement.
- Much of the allocated patient and public involvement budget went towards developing the website.
- Enhanced sampling strategy seeking participation – targeting TOPPITS pilot study patients was not productive; we might have approached those who declined TOPPITS or patients with other throat problems.
- Enhanced buy-in from the site staff (i.e. research staff there lead on developing the materials?). Would this have raised the profile of the patient and public involvement and/or resulted in greater commitment?

Generalisability

TOPPITS deserves a high profile as the results are generalisable for the following reasons:

- It had a large sample compared with prior single trials and even the total numbers in several meta-analyses.
- It was multicentre, UK-wide and pragmatic.
- The spread of baseline RSI scores was similar to the range in other publications in the field.
- The sex balance and age profile were typical of reports of persistent throat symptoms in the West.
- Key patient symptoms (lump in the throat, throat clearing, excess mucus, troublesome cough, hoarseness, feeling things stuck in throat) incorporate the majority of those seen in NHS ENT clinics.
- The message for primary and secondary care resonates with other messages concerning overuse of PPIs when evidence is weak or lacking.[122]
- This is a topical subject as some of the epidemiological adverse data on long-term PPI use including impact on life expectancy are only now emerging.

Interpretation

Given the lack of any trend in treatment response in TOPPITS presented in this report, there is a limit to the conclusions that can be drawn regarding the utility and merit of the questionnaires employed. It could be argued that the inclusion of three patient-reported outcome measures was unnecessary and that the RSI alone would have sufficed, providing a rapid measure, with a published literature context, patients' acceptability and demonstrable sensitivity to change. However, the lack of any trend towards a treatment

effect in TOPPITS is the very reason why it is so important that TOPPITS presents the most comprehensive evidence base possible. The use of multiple tools also offers the opportunity for the research team to analyse patients' symptoms in further detail in the near future. Many patients present with throat symptoms. TOPPITS has clearly demonstrated that the common practice of treating patients with PPIs is ineffective. Optimum management should focus on patients' symptoms and concerns, and address how these should be managed. The TOPPITS patients provide a wealth of patient-reported symptom data that will facilitate future research and clinical pathways.

The study was not powered for subgroup analysis, and, as a clinical trial of an investigational medicinal product, this TOPPITS main report rightly limits itself to the analysis presented to the DMC and TSC in the agreed statistical analysis plan. However, group data sets may contain identifiable subgroups of individuals who potentially stand to gain more from a trial therapy. We propose to explore the data distribution in greater detail, looking for any potential clustering of symptoms, to see whether or not there may be merit in pursuing anti-reflux approaches (not necessarily PPIs for the safety reasons outlined previously) or indeed whether or not future efforts would be more logically applied to different aetiological theories and therapeutic pathways, including psychological treatments.

Potential bias

Did patients guess whether or not they were taking the active drug? Apparently not, as the correct identification rate was similar in both groups (see *Table 4*). We were fortunate that our mucosal rater (PC) was working in Australia at the time and so had no way of judging the future allocation of therapy for any individual. The outcomes were all patient self-reported. This may have had some minor impact on outcomes measurement overall but not in any systematic way so as to influence one therapy over another.

Bias is minimised through ITT analyses retaining ineligible and protocol-violator patients in the analysis according to their randomised treatment group. The trial assumed a level of drop-out owing to the primary outcome measure being patient reported, and the sample size was inflated accordingly to retain power. Observed drop-out was as anticipated and was not differential across treatment groups. It was demonstrated that the patient characteristics of the pragmatic and compliant ITT groups were representative of the trial population. Planned secondary sensitivity analyses, based on a pragmatic ITT group, confirmed the conclusions of the primary analyses, based on the compliant ITT group.

Chapter 5 Conclusions

Health-care implications

TOPPITS is a robust clinical trial that confirms the findings of other work (which found no evidence to support PPI treatment benefit in cohort studies of those with persistent throat symptoms). De-prescribing, defined as lowering dosage, switching to as-needed use or complete discontinuation, should be considered for many PPI users.[88] Current NHS guidance for the management of persistent throat symptoms is lacking. The TOPPITS outcome stands to contribute to future throat symptom guidance, particularly given the current popularity for primary PPI treatment. The TOPPITS results provide evidence that patients and clinicians need to consider in making shared decisions about PPI use for persistent throat symptoms.

This is important as the substantial gamut of adverse consequences of PPI treatment is only now becoming apparent. A reversal of the terminology trend towards LPR as the terminology of choice for persistent throat symptoms is also worthy of consideration.[122]

Pursuit of alternative treatments

Mucosal protection

Sucralfate offers a safe, locally active treatment by protective adherence to denuded mucosal surfaces and also has bile salt-binding properties, with GORD efficacy comparable to that of H_2-receptor blockade.[123] To date, no studies comparing sucralfate with PPIs have been reported in the medical literature.[124] It could be argued that this is of little relevance in throat symptoms as we have shown that PPIs are irrelevant in any case. However, mucosal protection agents might play a part in the control of sensory symptoms, possibly even in the absence of pathological levels of acid exposure.

Lifestyle modification

The most significant lifestyle modification for persistent throat symptoms is weight loss. Additional lifestyle interventions include upright head-of-bed elevation, avoiding meals close to bedtime and avoiding high-fat meals within 2–3 hours of reclining. These simple low-cost interventions have understandably had relatively little research investment. A systematic review of lifestyle interventions in GORD concluded that weight loss and tobacco smoking cessation should be recommended when relevant, and that avoiding late-evening meals and head-of-bed elevation were effective in nocturnal GORD.[125]

In a study of supra-oesophageal reflux prevalence, timing and response to head-of-bed elevation by 6 inches,[126] nasopharyngeal pH-metry detected acid in 113 (48%) participants, with over half being only in the supine position. Sequential overnight nasopharyngeal pH monitoring before and after head-of-bed elevation was obtained in only 13 of those with supine reflux. Ten subjects demonstrated significant improvement, with complete resolution in most.[126] However, some bed types, such as storage divans, do not lend themselves easily to elevation and so the use of a mattress-top wedge is becoming increasing popular in the commercial sector (e.g. https://putnams.co.uk/products/memory-foam-bed-wedge; accessed 30 October 2019). Such wedges allow the sufferer to elevate the chest on a gentle slope while not affecting the sleep position of any bed partner.

Other pathways/future work

Primary care offers unique insights into an individual's history of multiple prior somatisation episodes; however, the rarity of laryngoscopic facilities in primary care distorts the management pathway for persistent

throat symptoms. There is reassurance from adequate explanation of the vicious behavioural cycles that can perpetuate throat symptoms (dry swallow, throat clearing), together with an indication to patients of the common occurrence of their problems. All are preferable to universal PPI prescription for undiagnosed throat symptoms.

When there are atypical features, early referral for laryngopharyngoscopy may be unavoidable. Secondary care offers a more straightforward locus for research owing to the concentration of patients seen in every general ENT clinic. Psychological approaches may be offered by speech therapists or as primary therapy or pharmacological interventions in their own right. Cognitive–behavioural therapy could feasibly be part of a package for treating functional dysphonia,[25,127–129] but the efficacy of cognitive–behavioural therapy in dysphonia and globus remains to be addressed in a substantive trial. The placebo phenomenon[111] might also usefully be exploited by the use of traditional voice care measures: hydration, steam and honey. More work is needed on the role of antidepressants.[113,114,117,118,130] Speech therapy delivered by specialist practitioners can be a primary globus therapy,[131] but needs to be explored in a wider range of practitioners.

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Professor Janet A Wilson (https://orcid.org/0000-0002-6416-5870) was the chief investigator and designed and developed the trial protocol. She oversaw the running of the trial, the data analysis and the preparation of the final report and subsequent outputs.

Professor Deborah D Stocken (https://orcid.org/0000-0001-8031-1738) was the senior clinical trials statistician and contributed to the design, analysis, interpretation and reporting of the trial.

Miss Gillian C Watson (https://orcid.org/0000-0003-2466-0268) managed the trial on a day-to-day basis and contributed substantially to the preparation of the final report.

Mr Tony Fouweather (https://orcid.org/0000-0002-2292-0495) was the clinical trials statistician and contributed to the design and analysis of the trial and the presentation of data for this paper.

Mr Julian McGlashan (https://orcid.org/0000-0001-6716-6089) was the principal investigator at the Nottingham site and contributed to the trial design, interpretation and dissemination.

Mr Kenneth MacKenzie (https://orcid.org/0000-0002-2952-7717) was the principal investigator at the Glasgow site and contributed to the design, interpretation and dissemination of the trial.

Professor Paul Carding (https://orcid.org/0000-0002-4206-1827) provided the blinded assessment of baseline digital images and contributed to the design, interpretation and dissemination of the trial.

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Dr James O'Hara (https://orcid.org/0000-0002-4096-3296) assisted in the design and development of the protocol and was, for a time, the principal investigator at the Sunderland site.

Publications

Watson G, O'Hara J, Carding P, Lecouturier J, Stocken D, Fouweather T, Wilson J. TOPPITS: Trial of Proton Pump Inhibitors in Throat Symptoms. Study protocol for a randomised controlled trial. *Trials* 2016;**17**:175–83.

O'Hara J, Stocken DD, Watson GC, Fouweather T, McGlashan J, MacKenzie K, *et al.* Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial. *BMJ* 2021;**372**:m4903.

Data-sharing statement

Anonymised data from this study may be available to the scientific community subject to regulatory and ethics approval. Requests for data should be directed to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Watson G, O'Hara J, Carding P, Lecouturier J, Stocken D, Fouweather T, Wilson J. TOPPITS: Trial Of Proton Pump Inhibitors in Throat Symptoms. Study protocol for a randomised controlled trial. *Trials* 2016;**17**:175. https://doi.org/10.1186/s13063-016-1267-7
2. Deary IJ, Wilson JA, Kelly SW. Globus pharyngis, personality, and psychological distress in the general population. *Psychosomatics* 1995;**36**:570–7. https://doi.org/10.1016/S0033-3182(95)71614-0
3. Moloy PJ, Charter R. The globus symptom. Incidence, therapeutic response, and age and sex relationships. *Arch Otolaryngol* 1982;**108**:740–4. https://doi.org/10.1001/archotol.1982.00790590062017
4. Pawar S, Lim HJ, Gill M, Smith TL, Merati A, Toohill RJ, Loehrl TA. Treatment of postnasal drip with proton pump inhibitors: a prospective, randomized, placebo-controlled study. *Am J Rhinol* 2007;**21**:695–701. https://doi.org/10.2500/ajr.2007.21.3098
5. Lowden M, McGlashan JA, Steel A, Strugala V, Dettmar PW. Prevalence of symptoms suggestive of extra-oesophageal reflux in a general practice population in the UK. *Logoped Phoniatr Vocol* 2009;**34**:32–5. https://doi.org/10.1080/14015430902735847
6. Thompson WG, Heaton KW. Heartburn and globus in apparently healthy people. *Can Med Assoc J* 1982;**126**:46–8.
7. NHS Digital. *Hospital Outpatient Activity – 2010–11*. 2011. URL: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-outpatient-activity/hospital-outpatient-activity-2010-11 (accessed 22 November 2019).
8. Noordzij JP, Khidr A, Evans BA, Desper E, Mittal RK, Reibel JF, Levine PA. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope* 2001;**111**:2147–51. https://doi.org/10.1097/00005537-200112000-00013
9. Delahunty JE. Acid laryngitis. *J Laryngol Otol* 1972;**86**:335–42. https://doi.org/10.1017/S0022215100075356
10. Franchi A, Brogelli B, Massi D, Santucci M, De Campora E, Gallo O. Dilation of intercellular spaces is associated with laryngo-pharyngeal reflux: an ultrastructural morphometric analysis of laryngeal epithelium. *Eur Arch Otorhinolaryngol* 2007;**264**:907–11. https://doi.org/10.1007/s00405-007-0295-z
11. Johnston N. Review article: uptake of pepsin at pH 7 – in non-acid reflux – causes inflammatory, and perhaps even neoplastic, changes in the laryngopharynx. *Aliment Pharmacol Ther* 2011;**33**:13–20.
12. Karkos PD, Wilson JA. Empiric treatment of laryngopharyngeal reflux with proton pump inhibitors: a systematic review. *Laryngoscope* 2006;**116**:144–8. https://doi.org/10.1097/01.mlg.0000191463.67692.36
13. Gatta L, Vaira D, Sorrenti G, Zucchini S, Sama C, Vakil N. Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007;**25**:385–92. https://doi.org/10.1111/j.1365-2036.2006.03213.x
14. Sen P, Georgalas C, Bhattacharyya AK. A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux. *Clin Otolaryngol* 2006;**31**:20–4. https://doi.org/10.1111/j.1749-4486.2006.01134.x
15. Lam PK, Ng ML, Cheung TK, Wong BY, Tan VP, Fong DY, *et al.* Rabeprazole is effective in treating laryngopharyngeal reflux in a randomized placebo-controlled trial. *Clin Gastroenterol Hepatol* 2010;**8**:770–6. https://doi.org/10.1016/j.cgh.2010.03.009

16. Ah-See K, Wilson J. Extra-oesophageal reflux: state of the knowledge base. *Clin Otolaryngol* 2012;**37**:9–16. https://doi.org/10.1111/j.1749-4486.2012.02443.x

17. Powell J, Cocks HC. Mucosal changes in laryngopharyngeal reflux-prevalence, sensitivity, specificity and assessment. *Laryngoscope* 2013;**123**:985–91. https://doi.org/10.1002/lary.23693

18. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995;**104**:550–5. https://doi.org/10.1177/000348949510400709

19. Kibblewhite DJ, Morrison MD. A double-blind controlled study of the efficacy of cimetidine in the treatment of the cervical symptoms of gastroesophageal reflux. *J Otolaryngol* 1990;**19**:103–9.

20. Karkos PD, Benton J, Leong SC, Karkanevatos A, Badran K, Srinivasan VR, *et al.* Trends in laryngopharyngeal reflux: a British ENT survey. *Eur Arch Otorhinolaryngol* 2007;**264**:513–17. https://doi.org/10.1007/s00405-006-0222-8

21. Qadeer MA, Phillips CO, Lopez AR, Steward DL, Noordzij JP, Wo JM, *et al.* Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2006;**101**:2646–54. https://doi.org/10.1111/j.1572-0241.2006.00844.x

22. Vaezi MF, Richter JE, Stasney CR, Spiegel JR, Iannuzzi RA, Crawley JA, *et al.* Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;**116**:254–60. https://doi.org/10.1097/01.mlg.0000192173.00498.ba

23. Reimer C, Bytzer P. Management of laryngopharyngeal reflux with proton pump inhibitors. *Ther Clin Risk Manag* 2008;**4**:225–33. https://doi.org/10.2147/TCRM.S6862

24. Hungin AP, Rubin GP, O'Flanagan H. Long-term prescribing of proton pump inhibitors in general practice. *Br J Gen Pract* 1999;**49**:451–3.

25. O'Hara J, Miller T, Carding P, Wilson J, Deary V. Relationship between fatigue, perfectionism, and functional dysphonia. *Otolaryngol Head Neck Surg* 2011;**144**:921–6. https://doi.org/10.1177/0194599811401236

26. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;**16**:274–7. https://doi.org/10.1016/S0892-1997(02)00097-8

27. Lee YS, Choi SH, Son YI, Park YH, Kim SY, Nam SY. Prospective, observational study using rabeprazole in 455 patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol* 2011;**268**:863–9. https://doi.org/10.1007/s00405-010-1475-9

28. Reichel O, Dressel H, Wiederänders K, Issing WJ. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2008;**139**:414–20. https://doi.org/10.1016/j.otohns.2008.06.003

29. Papakonstantinou L, Leslie P, Gray J, Chadwick T, Hudson M, Wilson JA. Laryngopharyngeal reflux: a prospective analysis of a 34 item symptom questionnaire. *Clin Otolaryngol* 2009;**34**:455–9. https://doi.org/10.1111/j.1749-4486.2009.01998.x

30. Kamani T, Penney S, Mitra I, Pothula V. The prevalence of laryngopharyngeal reflux in the English population. *Eur Arch Otorhinolaryngol* 2012;**269**:2219–25. https://doi.org/10.1007/s00405-012-2028-1

31. Drinnan M, Powell J, Nikkar-Esfahani A, Heading RC, Doyle J, Griffin SM, *et al.* Gastroesophageal and extraesophageal reflux symptoms: similarities and differences. *Laryngoscope* 2015;**125**:424–30. https://doi.org/10.1002/lary.24950

32. Siupsinskiene N, Adamonis K, Toohill RJ. Quality of life in laryngopharyngeal reflux patients. *Laryngoscope* 2007;**117**:480–4. https://doi.org/10.1097/MLG.0b013e31802d83cf

33. Cheung TK, Lam PK, Wei WI, Wong WM, Ng ML, Gu Q, *et al.* Quality of life in patients with laryngopharyngeal reflux. *Digestion* 2009;**79**:52–7. https://doi.org/10.1159/000205267

34. Lenderking WR, Hillson E, Crawley JA, Moore D, Berzon R, Pashos CL. The clinical characteristics and impact of laryngopharyngeal reflux disease on health-related quality of life. *Value Health* 2003;**6**:560–5. https://doi.org/10.1046/j.1524-4733.2003.65243.x

35. Carrau RL, Khidr A, Gold KF, Crawley JA, Hillson EM, Koufman JA, Pashos CL. Validation of a quality-of-life instrument for laryngopharyngeal reflux. *Arch Otolaryngol Head Neck Surg* 2005;**131**:315–20. https://doi.org/10.1001/archotol.131.4.315

36. Andersson O, Ryden A, Ruth M, Ylitalo Moller R, Finizia C. Validation of the Swedish translation of LPR-HRQL. *Med Sci Monit* 2010;**16**:CR480–7.

37. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;**111**:1313–17. https://doi.org/10.1097/00005537-200108000-00001

38. Saruç M, Aksoy EA, Vardereli E, Karaslaan M, Ciçek B, Ince U, *et al.* Risk factors for laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2012;**269**:1189–94. https://doi.org/10.1007/s00405-011-1905-3

39. Gao L, Weck MN, Rothenbacher D, Brenner H. Body mass index, chronic atrophic gastritis and heartburn: a population-based study among 8936 older adults from Germany. *Aliment Pharmacol Ther* 2010;**32**:296–302. https://doi.org/10.1111/j.1365-2036.2010.04334.x

40. Madanick RD. Proton pump inhibitor side effects and drug interactions: much ado about nothing? *Cleve Clin J Med* 2011;**78**:39–49. https://doi.org/10.3949/ccjm.77a.10087

41. Reimer C, Søndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009;**137**:80–7, 87.e1. https://doi.org/10.1053/j.gastro.2009.03.058

42. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;**292**:1955–60. https://doi.org/10.1001/jama.292.16.1955

43. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol* 2009;**104**(Suppl. 2):27–32. https://doi.org/10.1038/ajg.2009.49

44. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, Chen Z. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med* 2010;**170**:765–71. https://doi.org/10.1001/archinternmed.2010.94

45. NHS. *Proton Pump Inhibitor (PPI) Guidance April 2017*. URL: www.gwh.nhs.uk/media/295818/ppi-guidance-apr-17-post-gwh-comments.pdf (accessed 22 November 2019).

46. National Institute for Health and Care Excellence (NICE). *Gastro-oesophageal Reflux Disease and Dyspepsia in Adults: Investigation and Management*. URL: www.nice.org.uk/guidance/cg184 (accessed 22 November 2019).

47. Weigt J, Kandulski A, Busch F, Malfertheiner P. Nocturnal gastric acid breakthrough is not associated with night-time gastroesophageal reflux in GERD patients. *Dig Dis* 2009;**27**:68–73. https://doi.org/10.1159/000210107

48. NHS Business Services Authority. *Information Services*. URL: www.nhsbsa.nhs.uk/Documents/Apr_-_Jun_10_Gastro-intestinal.pdf (accessed 30 October 2019).

49. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, *et al.* Guidelines for the content of statistical analysis plans in clinical trials. *JAMA* 2017;**318**:2337–43. https://doi.org/10.1001/jama.2017.18556

50. Belafsky PC, Postma GN, Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical findings. *Laryngoscope* 2001;**111**:979–81. https://doi.org/10.1097/00005537-200106000-00009

51. Vaezi MF. Sensitivity and specificity of reflux-attributed laryngeal lesions: experimental and clinical evidence. *Am J Med* 2003;**115**(Suppl. 3A):97–104. https://doi.org/10.1016/S0002-9343(03)00205-5

52. Schneider GT, Vaezi MF, Francis DO. Reflux and voice disorders: have we established causality? *Curr Otorhinolaryngol Rep* 2016;**4**:157–67. https://doi.org/10.1007/s40136-016-0121-5

53. Kelchner LN, Horne J, Lee L, Klaben B, Stemple JC, Adam S, *et al.* Reliability of speech-language pathologist and otolaryngologist ratings of laryngeal signs of reflux in an asymptomatic population using the reflux finding score. *J Voice* 2007;**21**:92–100. https://doi.org/10.1016/j.jvoice.2005.09.004

54. McGlashan JA, Johnstone LM, Sykes J, Strugala V, Dettmar PW. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2009;**266**:243–51. https://doi.org/10.1007/s00405-008-0708-7

55. Steen IN, MacKenzie K, Carding PN, Webb A, Deary IJ, Wilson JA. Optimising outcome assessment of voice interventions, II: sensitivity to change of self-reported and observer-rated measures. *J Laryngol Otol* 2008;**122**:46–51. https://doi.org/10.1017/S0022215107007839

56. Cohen E, Bolus R, Khanna D, Hays RD, Chang L, Melmed GY, *et al.* GERD symptoms in the general population: prevalence and severity versus care-seeking patients. *Dig Dis Sci* 2014;**59**:2488–96. https://doi.org/10.1007/s10620-014-3181-8

57. Haft S, Carey RM, Farquhar D, Mirza N. Anticholinergic medication use is associated with globus pharyngeus. *J Laryngol Otol* 2016;**130**:1125–9. https://doi.org/10.1017/S002221511600918X

58. Abdul-Hussein M, Freeman J, Castell DO. Cough and throat clearing: atypical GERD symptoms or not GERD at all? *J Clin Gastroenterol* 2016;**50**:e50–4. https://doi.org/10.1097/MCG.0000000000000384

59. Nikkar A, James P, Powell J, Millar I, Carding P, Leslie P, *et al.* Reflux symptomatology: towards better definition of the patient experience. *Clin Otolaryngol* 2012;**37**(Suppl. 1):128–9.

60. Rothman M, Farup C, Stewart W, Helbers L, Zeldis J. Symptoms associated with gastroesophageal reflux disease: development of a questionnaire for use in clinical trials. *Dig Dis Sci* 2001;**46**:1540–9. https://doi.org/10.1023/A:1010660425522

61. Powell J, Nikkar A, Doyle J, Wilson J. Extraesophageal reflux: throat and gastrointestinal patients. *Otolaryngol Head Neck Surg* 2012;**147**:73. https://doi.org/10.1177/0194599812451438a116

62. Doody J, Fenton JE. Troublesome Throat Awareness (tTA) as a contemporary alternative to 'globus pharyngeus'. *Surgeon* 2017;**15**:183–5. https://doi.org/10.1016/j.surge.2017.05.001

63. Rasmussen ER, Schnack DT, Ravn AT. A prospective cohort study of 122 adult patients presenting to an otolaryngologist's office with globus pharyngeus. *Clin Otolaryngol* 2018;**43** 854–60. https://doi.org/10.1111/coa.13065

64. Spantideas N, Drosou E, Bougea A, Assimakopoulos D. Laryngopharyngeal reflux disease in the Greek general population, prevalence and risk factors. *BMC Ear Nose Throat Disord* 2015;**15**:7. https://doi.org/10.1186/s12901-015-0020-2

65. Tang B, Cai HD, Xie HL, Chen DY, Jiang SM, Jia L. Epidemiology of globus symptoms and associated psychological factors in China. *J Dig Dis* 2016;**17**:319–24. https://doi.org/10.1111/1751-2980.12354

66. Deary IJ, Wilson JA, Harris MB, MacDougall G. Globus pharyngis: development of a symptom assessment scale. *J Psychosom Res* 1995;**39**:203–13. https://doi.org/10.1016/0022-3999(94)00104-D

67. Thomas JP, Zubiaur FM. Over-diagnosis of laryngopharyngeal reflux as the cause of hoarseness. *Eur Arch Otorhinolaryngol* 2013;**270**:995–9. https://doi.org/10.1007/s00405-012-2244-8

68. Ruiz R, Jeswani S, Andrews K, Rafii B, Paul BC, Branski RC, Amin MR. Hoarseness and laryngopharyngeal reflux: a survey of primary care physician practice patterns. *JAMA Otolaryngol Head Neck Surg* 2014;**140**:192–6. https://doi.org/10.1001/jamaoto.2013.6533

69. Holcomb AJ, Hamill CS, Irwin T, Sykes K, Garnett JD, Kraft S. Practice patterns of referring physicians in management of the dysphonic patient. *Otolaryngol Head Neck Surg* 2018;**158**:1072–8. https://doi.org/10.1177/0194599818758958

70. Selby K, Cornuz J, Cohidon C, Gaspoz JM, Senn N. How do Swiss general practitioners agree with and report adhering to a top-five list of unnecessary tests and treatments? Results of a cross-sectional survey. *Eur J Gen Pract* 2018;**24**:32–8. https://doi.org/10.1080/13814788.2017.1395018

71. Tosetti C, Nanni I. Use of proton pump inhibitors in general practice. *World J Gastrointest Pharmacol Ther* 2017;**8**:180–5. https://doi.org/10.4292/wjgpt.v8.i3.180

72. Nguyen PV, Tamaz R. Inappropriate prescription of proton pump inhibitors in a community setting. *Can J Hosp Pharm* 2018;**71**:267–71. https://doi.org/10.4212/cjhp.v71i4.2828

73. Ali O, Poole R, Okon M, Maunick S, Troy E. Irrational use of proton pump inhibitors in general practise. *Ir J Med Sci* 2018;**188**:541–4. https://doi.org/10.1007/s11845-018-1891-1

74. Akram F, Huang Y, Lim V, Huggan PJ, Merchant RA. Proton pump inhibitors: are we still prescribing them without valid indications? *Australas Med J* 2014;**7**:465–70. https://doi.org/10.4066/AMJ.2014.2093

75. Halum SL, Postma GN, Johnston C, Belafsky PC, Koufman JA. Patients with isolated laryngopharyngeal reflux are not obese. *Laryngoscope* 2005;**115**:1042–5. https://doi.org/10.1097/01.MLG.0000162656.05715.57

76. Lee YC, Lee JS, Kim SW, Kwon KH, Eun YG. Influence of age on treatment with proton pump inhibitors in patients with laryngopharyngeal reflux disease: a prospective multicenter study. *JAMA Otolaryngol Head Neck Surg* 2013;**139**:1291–5. https://doi.org/10.1001/jamaoto.2013.5556

77. Liu C, Wang H, Liu K. Meta-analysis of the efficacy of proton pump inhibitors for the symptoms of laryngopharyngeal reflux. *Braz J Med Biol Res* 2016;**49**:S0100–879X2016000700704. https://doi.org/10.1590/1414-431X20165149

78. Wei C. A meta-analysis for the role of proton pump inhibitor therapy in patients with laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2016;**273**:3795–801. https://doi.org/10.1007/s00405-016-4142-y

79. Guo H, Ma H, Wang J. Proton pump inhibitor therapy for the treatment of laryngopharyngeal reflux: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol* 2016;**50**:295–300. https://doi.org/10.1097/MCG.0000000000000324

80. Luo H, Ma S, Gao Y, Yan J, Hou J, Xu M. The therapeutic effect of proton pump inhibitor on alleviation of hoarseness symptoms in patients with laryngopharyngeal reflux. *Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2015;**29**:997–1001.

81. Reichel O, Keller J, Rasp G, Hagedorn H, Berghaus A. Efficacy of once-daily esomeprazole treatment in patients with laryngopharyngeal reflux evaluated by 24-hour pH monitoring. *Otolaryngol Head Neck Surg* 2007;**136**:205–10. https://doi.org/10.1016/j.otohns.2006.10.011

82. Vailati C, Mazzoleni G, Bondi S, Bussi M, Testoni PA, Passaretti S. Oropharyngeal pH monitoring for laryngopharyngeal reflux: is it a reliable test before therapy? *J Voice* 2013;**27**:84–9. https://doi.org/10.1016/j.jvoice.2012.08.006

83. de Bortoli N, Nacci A, Savarino E, Martinucci I, Bellini M, Fattori B, *et al.* How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? *World J Gastroenterol* 2012;**18**:4363–70. https://doi.org/10.3748/wjg.v18.i32.4363

84. Sheikh I, Waghray A, Waghray N, Dong C, Wolfe MM. Consumer use of over-the-counter proton pump inhibitors in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2014;**109**:789–94. https://doi.org/10.1038/ajg.2013.421

85. Boltin D, Zvidi I, Raskin M, Kayless H, Schmilovitz-Weiss H, Gingold-Belfer R, *et al.* Effect of postprandial administration of esomeprazole on reflux symptoms in gastroesophageal reflux disease: a randomized, controlled trial. *Dig Dis* 2018;**36**:257–63. https://doi.org/10.1159/000489557

86. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ Open* 2017;**7**:e015735. https://doi.org/10.1136/bmjopen-2016-015735

87. Shiraev TP, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. *Heart Lung Circ* 2018;**27**:443–50. https://doi.org/10.1016/j.hlc.2017.10.020

88. Pezeshkian S, Conway SE. Proton pump inhibitor use in older adults: long-term risks and steps for deprescribing. *Consult Pharm* 2018;**33**:497–503. https://doi.org/10.4140/TCP.n.2018.497

89. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* 2018;**67**:28–35. https://doi.org/10.1136/gutjnl-2017-314605

90. Wan Q-Y, Wu X-T, Li N, Du L, Zhou Y. Long-term proton pump inhibitors use and risk of gastric cancer: a meta-analysis of 926 386 participants. *Gut* 2018;**68**:762–4. https://doi.org/10.1136/gutjnl-2018-316416

91. Tvingsholm SA, Dehlendorff C, Østerlind K, Friis S, Jäättelä M. Proton pump inhibitor use and cancer mortality. *Int J Cancer* 2018;**143**:1315–26. https://doi.org/10.1002/ijc.31529

92. Wilkie MD, Fraser HM, Raja H. Gaviscon Advance alone versus co-prescription of Gaviscon Advance and proton pump inhibitors in the treatment of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2018;**275**:2515–21. https://doi.org/10.1007/s00405-018-5079-0

93. Koufman JA, Johnston N. Potential benefits of pH 8.8 alkaline drinking water as an adjunct in the treatment of reflux disease. *Ann Otol Rhinol Laryngol* 2012;**121**:431–4. https://doi.org/10.1177/000348941212100702

94. Strugala V, Avis J, Jolliffe IG, Johnstone LM, Dettmar PW. The role of an alginate suspension on pepsin and bile acids – key aggressors in the gastric refluxate. Does this have implications for the treatment of gastro-oesophageal reflux disease? *J Pharm Pharmacol* 2009;**61**:1021–8. https://doi.org/10.1211/jpp/61.08.0005

95. Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (rigid vs. flexible laryngoscope). *Laryngoscope* 2005;**115**:2256–61. https://doi.org/10.1097/01.mlg.0000184325.44968.b1

96. Ylitalo R, Lindestad PA, Hertegard S. Is pseudosulcus alone a reliable sign of gastroesophago-pharyngeal reflux? *Clin Otolaryngol Allied Sci* 2004;**29**:47–50. https://doi.org/10.1111/j.1365-2273.2004.00778.x

97. Belafsky PC, Postma GN, Koufman JA. The association between laryngeal pseudosulcus and laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2002;**126**:649–52. https://doi.org/10.1067/mhn.2002.125603

98. Chang BA, MacNeil SD, Morrison MD, Lee PK. The reliability of the Reflux Finding Score among general otolaryngologists. *J Voice* 2015;**29**:572–7. https://doi.org/10.1016/j.jvoice.2014.10.009

99. Weber B, Portnoy JE, Castellanos A, Hawkshaw MJ, Lurie D, Katz PO, Sataloff RT. Efficacy of anti-reflux surgery on refractory laryngopharyngeal reflux disease in professional voice users: a pilot study. *J Voice* 2014;**28**:492–500. https://doi.org/10.1016/j.jvoice.2013.12.009

100. Spyridoulias A, Lillie S, Vyas A, Fowler SJ. Detecting laryngopharyngeal reflux in patients with upper airways symptoms: symptoms, signs or salivary pepsin? *Respir Med* 2015;**109**:963–9. https://doi.org/10.1016/j.rmed.2015.05.019

101. Fusconi M, De Virgilio A, Conte M, Colicchio MG, Gallo A, Greco A, *et al.* The importance of the number of reflux episodes in the diagnosis of laryngopharyngeal reflux disease. *Otolaryngol Head Neck Surg* 2013;**148**:261–6. https://doi.org/10.1177/0194599812466534

102. Wang AJ, Liang MJ, Jiang AY, Lin JK, Xiao YL, Peng S, *et al.* Predictors of acid suppression success in patients with chronic laryngitis. *Neurogastroenterol Motil* 2012;**24**:432–7. https://doi.org/10.1111/j.1365-2982.2011.01873.x

103. Cumpston EC, Blumin JH, Bock JM. Dual pH with multichannel intraluminal impedance testing in the evaluation of subjective laryngopharyngeal reflux symptoms. *Otolaryngol Head Neck Surg* 2016;**155**:1014–20. https://doi.org/10.1177/0194599816665819

104. Peng L, Patel A, Kushnir V, Gyawali CP. Assessment of upper esophageal sphincter function on high-resolution manometry: identification of predictors of globus symptoms. *J Clin Gastroenterol* 2015;**49**:95–100. https://doi.org/10.1097/MCG.0000000000000078

105. Tang Y, Huang J, Zhu Y, Qian A, Xu B, Yao W. Comparison of esophageal motility in gastroesophageal reflux disease with and without globus sensation. *Rev Esp Enferm Dig* 2017;**109**:850–5. https://doi.org/10.17235/reed.2017.4449/2016

106. Gray LP. The relationship of the 'inferior constrictor swallow' and 'globus hystericus' or the hypopharyngeal syndrome. *J Laryngol Otol* 1983;**97**:607–18. https://doi.org/10.1017/S0022215100094688

107. Fuchs HF, Müller DT, Berlth F, Maus MK, Fuchs C, Dübbers M, *et al.* Simultaneous laryngopharyngeal pH monitoring (Restech) and conventional esophageal pH monitoring-correlation using a large patient cohort of more than 100 patients with suspected gastroesophageal reflux disease. *Dis Esophagus* 2018;**31**. https://doi.org/10.1093/dote/doy018

108. Perng DW, Chang KT, Su KC, Wu YC, Wu MT, Hsu WH, *et al.* Exposure of airway epithelium to bile acids associated with gastroesophageal reflux symptoms: a relation to transforming growth factor-beta1 production and fibroblast proliferation. *Chest* 2007;**132**:1548–56. https://doi.org/10.1378/chest.07-1373

109. Lechien JR, Huet K, Khalife M, Fourneau AF, Finck C, Delvaux V, *et al.* Gender differences in the presentation of dysphonia related to laryngopharyngeal reflux disease: a case-control study. *Eur Arch Otorhinolaryngol* 2018;**275**:1513–24. https://doi.org/10.1007/s00405-018-4951-2

110. Gong EJ, Choi KD, Jung HK, Youn YH, Min BH, Song KH, Huh KC. Quality of life, patient satisfaction, and disease burden in patients with gastroesophageal reflux disease with or without laryngopharyngeal reflux symptoms. *J Gastroenterol Hepatol* 2017;**32**:1336–40. https://doi.org/10.1111/jgh.13716

111. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2015;**12**:472–85. https://doi.org/10.1038/nrgastro.2015.117

112. Garcia-Campayo J, Sanz-Carrillo C. A review of the differences between somatizing and psychologizing patients in primary care. *Int J Psychiatry Med* 1999;**29**:337–45. https://doi.org/10.2190/FMJ2-UK3Y-FKB8-DCGN

113. Weijenborg PW, de Schepper HS, Smout AJPM, Bredenoord AJ. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: asystematic review. *Clin Gastroenterol Hepatol* 2015;**13**:251–9.e1. https://doi.org/10.1016/j.cgh.2014.06.025

114. Deary IJ, Wilson JA. Problems in treating globus pharyngis. *Clin Otolaryngol Allied Sci* 1994;**19**:55–60. https://doi.org/10.1111/j.1365-2273.1994.tb01148.x

115. Gale CR, Wilson JA, Deary IJ. Globus sensation and psychopathology in men: the Vietnam experience study. *Psychosom Med* 2009;**71**:1026–31. https://doi.org/10.1097/PSY.0b013e3181bc7739

116. Okland TS, Gonzalez JR, Ferber AT, Mann SE. Association between patient review of systems score and somatization. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:870–5. https://doi.org/10.1001/jamaoto.2017.0671

117. Chen D-Y, Jia L, Gu X, Jiang S-M, Xie H-L, Xu J. Comparison of paroxetine and amitriptyline in the treatment of refractory globus pharyngeus. *Dig Liver Dis* 2016;**48**:1012–7. https://doi.org/10.1016/j.dld.2016.05.025

118. Liu Y, Jia L, Jiang SM, Chen DY, Song JS, Xu J. Serotonin Transporter Gene (SLC6A4) polymorphism may be associated with Chinese globus pharyngeus and its antidepressant effects. *Digestion* 2018;**97**:146–53. https://doi.org/10.1159/000484202

119. Zhou W-C, Jia L, Chen D-Y, Liu Y, Liu J, Jiang SM, *et al.* The effects of paroxetine and amitriptyline on the upper esophageal sphincter (UES) pressure and its natural history in globus pharyngeus. *Dig Liver Dis* 2017;**49**:757–63. https://doi.org/10.1016/j.dld.2017.02.008

120. Rommel N, Van Oudenhove L, Arts J, Caenepeel P, Tack J, Pauwels A. Esophageal sensorimotor function and psychological factors each contribute to symptom severity in globus patients. *Am J Gastroenterol* 2016;**111**:1382–8. https://doi.org/10.1038/ajg.2016.302

121. Nevalainen P, Walamies M, Kruuna O, Arkkila P, Aaltonen LM. Supragastric belch may be related to globus symptom – a prospective clinical study. *Neurogastroenterol Motil* 2016;**28**:680–6. https://doi.org/10.1111/nmo.12764

122. Zerbib F, Dulery C. Facts and fantasies on extraesophageal reflux: a gastroenterologist perspective. *J Clin Gastroenterol* 2017;**51**:769–76. https://doi.org/10.1097/MCG.0000000000000918

123. Tytgat GN. Clinical efficacy of sucralfate in reflux oesophagitis. *Scand J Gastroenterol Suppl* 1987;**140**:29–31.

124. Savarino E, Zentilin P, Marabotto E, Pellegatta G, Coppo C, Brunacci M, *et al.* Drugs for improving esophageal mucosa defense: where are we now and where are we going? *Ann Gastroenterol* 2017;**30**:585–91. https://doi.org/10.20524/aog.2017.0187

125. Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Lifestyle intervention in gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2016;**14**:175–82.e1-3. https://doi.org/10.1016/j.cgh.2015.04.176

126. Scott DR, Simon RA. Supraesophageal reflux: correlation of position and occurrence of acid reflux-effect of head-of-bed elevation on supine reflux. *J Allergy Clin Immunol Pract* 2015;**3**:356–61. https://doi.org/10.1016/j.jaip.2014.11.019

127. Daniilidou P, Carding P, Wilson J, Drinnan M, Deary V. Cognitive behavioral therapy for functional dysphonia: a pilot study. *Ann Otol Rhinol Laryngol* 2007;**116**:717–22. https://doi.org/10.1177/000348940711601002

128. Deary V, Miller T. Reconsidering the role of psychosocial factors in functional dysphonia. *Curr Opin Otolaryngol Head Neck Surg* 2011;**19**:150–4. https://doi.org/10.1097/MOO.0b013e328346494d

129. Deary V, McColl E, Carding P, Miller T, Wilson J. A psychosocial intervention for the management of functional dysphonia: complex intervention development and pilot randomised trial. *Pilot Feasibility Stud* 2018;**4**:46. https://doi.org/10.1186/s40814-018-0240-5

130. Martín-Merino E, Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S. Depression and treatment with antidepressants are associated with the development of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2010;**31**:1132–40. https://doi.org/10.1111/j.1365-2036.2010.04280.x

131. Khalil HS, Reddy VM, Bos-Clark M, Dowley A, Pierce M, Morris C, Jones A. Speech therapy in the treatment of globus pharyngeus: how we do it. *Clin Otolaryngol* 2011;**36**:388–92. https://doi.org/10.1111/j.1749-4486.2011.02326.x

Appendix 1 Screening, recruitment and withdrawal data

The site and time course of screening and recruitment are summarised in *Tables 26* and *27*.

Numbers analysed

Those participants included in each of the analysis sets are summarised in *Table 28*.

The stratified subgroups are summarised in *Table 29*. *Table 29* shows the balance over treatment groups in terms of the baseline severity measured by RSI-HB, with a cut-off score of 20.

During the course of the trial, during analysis of recruitment data for DMC meetings, it was discovered that some patients were mis-stratified in terms of baseline severity, defined by their RSI-HB scores. This affected approximately 10% of patients, as outlined in *Table 30*.

Ineligible patients

Despite treatment withdrawal, patients were followed up in the trial whenever possible. All primary statistical analyses were carried out on an ITT basis, retaining patients in their randomised treatment groups and including protocol-violator and ineligible patients. Ineligible patients were classed as those randomised patients who were subsequently found not to have adhered to the eligibility criteria of the trial. Four ineligible patients were reported (*Table 31*).

A sensitivity analysis was not carried out as the ineligibility rate was not excessive (1%).

TABLE 26 Numbers of patients screened and recruited, by site

	Number of patients	
Site	Screened	Recruited (based on MACRO)
Birmingham	31	10
Brighton	50	9
Glasgow	462	39
Manchester	116	27
Newcastle	399	133
Nottingham	178	70
Stockport	17	11
Sunderland	174	47
Total	1427	346

TABLE 27 Pattern of recruitment over time, by site

	Year																	
	2014								2015									
Site	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August	September	October
Newcastle	1	3	2	3	4	5	4	5	4	3	1	7	7	6	6	3	4	6
Sunderland			3	2	2	2	2	1	0	0	4	0	0	0	0	0	0	0
Nottingham				1	3	7	4	3	4	2	2	0	6	0	1	3	4	1
Brighton												2	3	2	0	0	0	1
Manchester												1	1	0	1	2	0	3
Glasgow																2	0	3
Birmingham																		
Stockport																		
Month total	1	3	5	6	9	14	10	9	8	5	7	10	17	8	8	10	8	14

Green shading shows when sites were open and recruiting.

TABLE 27 Pattern of recruitment over time, by site (*continued*)

	Year																
	2015		2016												2017		
Site	November	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	Total
Newcastle	1	7	4	6	2	3	7	0	4	5	6	2	6	1	5	0	133
Sunderland	0	0	1	1	5	2	4	8	0	1	0	5	2	0	1	1	47
Nottingham	4	2	4	3	1	2	0	1	2	2	1	2	0	2	1	2	70
Brighton	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9
Manchester	0	0	0	2	2	3	1	1	3	0	1	1	0	1	1	3	27
Glasgow	3	4	3	1	2	4	2	0	1	5	2	1	0	2	3	1	39
Birmingham			2	0	1	0	0	2	1	0	1	2	1	0	0	0	10
Stockport					1	1	0	1	1	1	1	2	1	0	2	0	11
Month total	9	13	14	13	14	15	14	13	12	14	12	15	10	6	13	7	346

Green shading shows when sites were open and recruiting.

TABLE 28 Definitions of participant groups for analysis

	Overall		Treatment group			
			Lansoprazole		Placebo	
Time from randomisation to primary end-point visit (visit 2)	Number of participants	Number with RSI at visit 2	Number of participants	Number with RSI at visit 2	Number of participants	Number with RSI at visit 2
< 10 weeks	6	3	2	1	4	2
Between 10 and 14 weeks	5	5	2	2	3	3
Between 14 and 18 weeks (protocol compliance)	**185**	**178**	**87**	**82**	**98**	**96**
Between 18 and 20 weeks	**44**	**42**	**21**	**20**	**23**	**22**
Compliant ITT group (14 to 20 weeks)	**229**	**220**	**108**	**102**	**121**	**118**
Between 20 and 25 weeks	25	25	14	14	11	11
Between 25 and 30 weeks	8	8	3	3	5	5
> 30 weeks	10	6	6	5	4	1
Pragmatic ITT group (all visit 2 at any time)	283	267	135	127	148	140
Missing (16-week visit, RSI visit 2 = RSI at 16 weeks)	63	79	37	45	26	34
Total number randomised	346	346	172	172	174	174

TABLE 29 Proportion of participants in each treatment group, by stratification factor baseline severity (compliant ITT group)

	Participants, *n* (%)		
	Treatment group		
Baseline RSI-HB severity	Lansoprazole (*N* = 172)	Placebo (*N* = 174)	Total (*N* = 346)
Mild (≤ 20)	91 (53)	93 (53)	184 (53)
Severe (> 20)	81 (47)	81 (47)	162 (47)

TABLE 30 Stratification status, by baseline RSI-HB score

	Stratification status	
Randomised as	Correct	Mis-stratified
RSI-HB 'mild' (≤ 20)		
n	169	12[a]
Range	10–20	21–34
RSI-HB 'severe' (> 20)		
n	137	24[a]
Range	21–38	10–20

a A further four patients (two ineligible) are categorised but have missing baseline raw RSI-HB scores entered.
Green shading denotes numbers of patients who were mis-classified at stratification.
Twenty-four patients with baseline RSI-HB between 10 and 20 were mis-stratified as severe.
Twelve patients with baseline RSI-HB of > 20 were mis-stratified as mild.

TABLE 31 Ineligible patients with reasons

Identifier	Reason patient was ineligible	Number ineligible (%)
5010	Ineligible – this patient was randomised in error, then found to be ineligible. No medication received; no outcome data	4 (1)
5101	It was confirmed that the patient did not fulfil exclusion criteria as escitalopram long-term user	
1062	Patient was randomised in error at the start of their washout period and was then found to be ineligible	
2106	Patient was consented and randomised in error, as it was discovered that they were ineligible, so withdrawn immediately	

Withdrawals

In *Table 32*, the frequency column shows the number fitting the visit status in relation to the primary end point. The compliant column shows those with a primary outcome measure within the compliance window, as specified in *Chapter 2*, *Statistical methods*. The pragmatic column shows those with a primary outcome measure at any time, as specified in statistical methods section.

It is seen that 267 patients provided the primary outcome measure (RSI at visit 2), of whom 220 were compliant within 14–20 weeks of randomisation. In total, 125 participants withdrew/were lost to follow-up over the duration of the trial. Sixty of these provided the primary outcome measure. Of 60 withdrawals providing the primary outcome, 43 were compliant within 14–20 weeks of randomisation. The timing of loss or withdrawal is shown in *Table 33*.

Missing data in the primary outcome

The RSI data points that were missing are summarised in *Table 34*.

TABLE 32 Withdrawals and loss to follow-up in terms of the primary end-point visit (visit 2) and outcome measure

Status in relation to primary end-point visit	Treatment group								
	Lansoprazole			Placebo			Combined participants		
		Primary outcome (RSI) (*n*)			Primary outcome (RSI) (*n*)			Primary outcome (RSI) (*n*)	
	n	Compliant	Pragmatic	*n*	Compliant	Pragmatic	*n*	Compliant	Pragmatic
Visit 2 attended; not withdrawn	103	82	100	109	95	107	212	177	207
No visit 2 but not withdrawn	6	0	0	3	0	0	9	0	0
Withdrew before visit 2	7	2	4	8	4	5	15	6	9
Withdrew at visit 2	6	3	4	10	4	9	16	7	13
Withdrew and no visit 2	31	0	0	23	0	0	54	0	0
Withdrew after visit 2	19	15	19	21	15	19	40	30	38
Total withdrawn	63			62			125		
Total	172	102	127	174	118	140	346	220	267

Green shading denotes that the participants have withdrawal/loss to follow-up dates reported in the trial MACRO database.

TABLE 33 Time in weeks from randomisation to withdrawal (or loss to follow-up)

Descriptive statistics	Treatment group		Overall
	Lansoprazole	Placebo	
n	63	62	125
Median (IQR)	19 (8–54)	25 (13–53)	21 (9–53)
Mean (SD)	30.9 (24.8)	31.7 (22.9)	31.3 (23.8)
Range	0–83	0–84	0–84

TABLE 34 Number of RSI items at baseline and 16-week follow-up, with follow-up completed at various times after randomisation

Visit	RSI completeness (total = nine items)	Participants, *n* (%)		
		Treatment group		
		Lansoprazole (*N* = 172)	Placebo (*N* = 174)	Total (*N* = 346)
Baseline (visit 1)	9 items	171 (99)	171 (98)	342 (99)
	1–8 items	0 (0)	2 (1)	2 (< 1)
	Missing	1 (< 1)	1 (< 1)	2 (< 1)
16-week visit (visit 2) (per protocol), 14–18 weeks post randomisation	9 items	82 (48)	96 (55)	178 (51)
	Missing[a]	5 (3)	2 (1)	7 (2)
16-week visit (visit 2) (compliant ITT), 14–20 weeks post randomisation	9 items	102 (59)	118 (68)	220 (64)
	Missing[a]	6 (3)	3 (2)	9 (3)
16-week visit (visit 2) (pragmatic ITT group), any time	9 items	127 (74)	140 (80)	267 (77)
	Missing[a]	8 (5)	8 (5)	16 (5)
No visit 2 at 16 weeks	Missing[b]	**37 (22)**	**26 (15)**	**63 (18)**

a Those denoted as missing at visit 2 have a visit date recorded but no RSI at that visit.
b No visit 2 date or corresponding RSI recorded.

Appendix 2 Details of patients in relation to per-treatment analysis and concomitant medications

Per-treatment analysis

Issue

In most cases in the per-treatment analysis group, medication was dispensed on the same day as randomisation. Four patients did not receive their trial medication at the baseline visit and in a further six there was no note of IMP being issued. However, details of returned medication at the primary end point show that all 10 did receive IMP and they are included in the per-treatment set.

Washout period for prior anti-reflux medication

Recent PPI use is summarised in *Table 35*.

Full washout data were available for 64 out of 68 participants who reported discontinuing PPI use in the previous 12 months (*Table 36*).

The median washout period was 6 weeks. In total, five participants started the trial treatment < 4 weeks after stopping using another PPI. Two were excluded from per-treatment analysis; the other three had between 1 day and 1 week of washout and were included.

TABLE 35 Recent PPI use at randomisation

	Participants, *n* (%)		
	Treatment group		
PPI use	Lansoprazole (*N* = 126)	Placebo (*N* = 136)	Total (*N* = 262)
PPI used in last 12 months?			
Yes	31 (25)	39 (29)	70[a] (27)
No	95 (75)	97 (71)	192 (73)

a 68 out of 70 who said they had been using PPI in the previous 12 months had stopped using it; two were still using it when screened.

TABLE 36 The washout period

	Treatment group		
Washout period (weeks)	Lansoprazole (*N* = 30)	Placebo (*N* = 34)	Total (*N* = 64)
Washout period, *n*	30	34	64
Median (IQR)	5.9 (4.6–8.6)	6.9 (5.0–11.1)	6.1 (4.9–9.8)
Mean (SD)	8.5 (8.5)	9.6 (7.1)	9.1 (7.8)
Range	0.1–44.4	0.6–27.6	0.1–44.4

Compliance with dosage of investigational medicinal product

The time (number of days) on the treatment (T) was calculated as the date of the 16-week follow-up clinic visit minus the date of randomisation, when the trial drug was dispended. The assumed dose is time on the treatment (T) multiplied by 2 to establish the number of capsules expected to have been taken from commencement of treatment (n_E). The number of capsules received by patients (n_P) after randomisation (238 in each kit) was not explicitly recorded in MACRO and was therefore imputed for each patient. The number of capsules returned (n_R) at the 16-week follow-up visit was recorded in MACRO. The observed dose is the number of capsules taken during the course of treatment (n_O) is calculated as $(n_P) - (n_R)$. The percentage of the protocol dose taken is calculated as $(n_O)/(n_E) \times 100$.

Note that it is possible to have an assumed percentage dose of $\geq$ 100% if time on treatment × 2 is greater than the number of capsules provided in the kit. This is truncated to be 100% in *Table 37*, which shows assumed doses taken based on time between dispensing and primary end-point visit, when unused capsules were returned.

Forty-two per cent of patients reported taking the full dose, balanced across randomised groups, and 70% of patients reported taking $\geq$ 90% of the dose, balanced across groups. The median percentage taking the protocol dose is 99% (IQR 86–100%).

The maximum time on treatment is 17 weeks, as per IMP supplied. There were 81 participants, 45 in the lansoprazole group, who did not have any information for the number of capsules returned so were omitted from the per-treatment analysis group. The 81 participants comprised:

- 57 who consented to the trial but did not attend primary end-point visit 2
- 13 who attended the primary end-point visit, some with primary outcome measure, but had no information on returned capsules
- six who did not attend the primary end-point visit, had no primary outcome measure or any information on returned capsules
- five others, of whom three stopped owing to requirement for other medications; one had only a 2-day suspension of treatment; one was lost.

There were five participants with reasons for stopping taking trial medication but no indication as to how many capsules had been taken, or were returned. Three patients took no medication.

TABLE 37 Assessment of doses taken per protocol

	Treatment group		
Dose	Lansoprazole (*N* = 126)	Placebo (*N* = 136)	Total (*N* = 262)
n (%) of patients assumed to have taken full or partial dose			
100%	50 (40)	61 (45)	111 (42)
90–99%	35 (28)	38 (28)	73 (28)
< 90%	41 (33)	37 (27)	78 (30)
Assumed doses used			
Median (IQR)	222 (190–238)	228 (206–238)	224 (198–238)
% protocol dose			
Median (IQR)	97 (83–100)	99 (89–100)	99 (86–100)

Reasons for discontinuing medication

Common reasons for discontinuing or interrupting IMP were as follows:

- lansoprazole, *n* = 33 (some multiple)
  - rash, *n* = 3
  - upper gastrointestinal symptoms, *n* = 8
  - lower gastrointestinal symptoms, *n* = 6
  - holidays, *n* = 5 (mostly interruptions)
  - headaches; unrelated new medical event – miscarriage/diagnosis polyarthritis; erratic eating patterns; concern about medication load; lack of benefit; 1 week's antibiotics, GP prescribed another PPI, belief that symptoms were endocrine in origin.
- placebo, *n* = 30
  - upper gastrointestinal symptoms, *n* = 3
  - lower gastrointestinal symptoms, *n* = 2
  - holidays, *n* = 9 (mostly interruptions)
  - headaches (*n* = 3); breathing difficulty; erratic eating pattern; concern about medication load; lack of benefit; unrelated new medical events (*n* = 2); antibiotics or other temporary therapy needed (*n* = 3), prescribed another PPI.

Concomitant medication

Some form of antacid medication was taken by five participants out of the total cohort at baseline (four in the lansoprazole group). At the end of therapy, six of the lansoprazole group and seven of the placebo group were taking antacid remedies of one sort or another. This had changed to 30 and 25, respectively, at 12 months – a notable rise bearing in mind the smaller total sample at this later time point.

Appendix 3 Baseline data: itemised severity scores for Reflux Symptom Index; Reflux Finding Score scoring

Table 38 gives the itemised scores for the total population at baseline.

There were a few very minor differences when considering the compliant population baseline RSI scores (*Table 39*).

Reflux Finding Score scoring schema and data recording

The RFS total values range between 0 and 26, including items for different subsites of the larynx, indicating level of abnormality. An outline of these areas and the range of scores for each item are shown in *Table 40*.[37] The ranking for each subsite is seen to be inconsistent. Some items have dichotomous scoring, others a 5-point score. The maximum score per feature is not uniform.

TABLE 38 Itemised scores for RSI (item range: 0–5) for the trial population ($n = 342$[a])

RSI item	Mean	SD	Median	IQR
1 – hoarseness	2.4	1.6	3	1–4
2 – throat clearing	3.4	1.3	4	3–4
3 – excess throat mucus	2.9	1.6	3	2–4
4 – difficulty swallowing	1.7	1.6	2	0–3
5 – coughing after eating or lying down	2.1	1.6	2	0–3
6 – breathing difficulties	1.6	1.6	1	0–3
7 – troublesome cough	2.5	1.7	3	1–4
8 – lump in throat	3.5	1.4	4	3–5
9 – heartburn	1.8	1.6	1.5	0–3

a Note that four patients did not have RSI baseline scores.

TABLE 39 Differences in itemised baseline RSI scores in the compliant ITT group ($n = 220$)

RSI item	Mean	SD	Median	IQR
3 – excess throat mucus		1.5		
4 – difficulty swallowing	1.6		2	
5 – coughing after eating or lying down	2.2	1.7	2	1–3.5
8 – lump in throat		1.5		
9 – heartburn	1.9		2	

TABLE 40 Scoring scheme for the RFS assessment (as originally published by Belafsky *et al.*[37])

Assessment item	Scoring options
Subglottic oedema	0 absent, 2 present
Ventricular obliteration	0 absent, 2 partial, 4 complete
Erythema/hyperaemia	0 absent, 2 arytenoids involved, 4 diffuse
Vocal fold oedema	0 absent, 1 mild, 2 moderate, 3 severe, 4 polypoid
Diffuse laryngeal oedema	0 absent, 1 mild, 2 moderate, 3 severe, 4 obstructing
Posterior commissure hypertrophy	0 absent, 1 mild, 2 moderate, 3 severe, 4 obstructing
Granuloma/granulation	0 absent, 2 present
Thick mucus	0 absent, 2 present

Not all laryngeal images were rated using the RFS. Some images were unusable owing to poor quality, particularly from one of the sites where equipment was of a lower grade. In the early stages of the trial, there was a problem with matching the TOPPITS trial identifier to patients' names and this created potential transcription errors before independent assessment. This issue was addressed in the early phase of the trial. Any rating with uncertainty of the identified subject was excluded from the analysis of the trial. Some images were submitted to the secure server twice and were consequently rated twice. When there were two ratings and confidence in the identified trial number, the chronologically first rating was used throughout.

In all, 363 assessments had both a validated identifier and a RFS. Of these, 107 were duplicates, leaving 256 unique identifiable RFS assessments.

In summary, the patient identifier attributable to a small number of images was not certain. There were also some unusable images owing to poor image quality, particularly from one of the sites where equipment was of a lower grade.

Appendix 4 Multivariable analysis of Reflux Symptom Index minus the heartburn/dyspepsia item for the compliant intention-to-treat group

Analysis of covariance for secondary analysis Reflux Symptom Index minus the heartburn/dyspepsia item: compliant intention-to-treat group

The outcome measure RSI-HB score after 16 weeks was initially analysed using ANCOVA methods in order to compare the 16-week RSI-HB scores between the treatment groups while adjusting for potential confounders. The ANCOVA results are shown in *Table 41*.

Adjusted for the effects of site and baseline severity, there is evidence of statistically significant difference in RSI-HB at 16 weeks between randomised treatment groups ($p = 0.026$) but not in favour of active intervention. There is evidence of dependence on baseline severity ($p < 0.001$). The randomised treatment group is not statistically significant when adjusted for other baseline factors. ANCOVA adjusted for stratification variables and other important baseline factors of RSI-HB for the compliant ITT group showed that the average RSI-HB score at 16 weeks in the lansoprazole and placebo groups remained no different once taking into account age, sex, smoking status, alcohol consumption and BMI.

Modelling was then undertaken as with the total RSI score.

Model 1

Model 1 adjusted for stratification factors used at randomisation [recruiting centre (as a random effect) and baseline severity as defined by the binary RSI-HB cut-off value of 20 (as a fixed effect) as covariates in the analysis] (*Table 42*).

There is no statistically significant benefit of lansoprazole, although there is an apparent difference between randomised treatment groups when adjusted for site and baseline binary RSI-HB score. The estimated difference between randomised groups, when accounting for site and baseline severity, estimates that lansoprazole patients have RSI-HB scores at 16 weeks that are 2.5 points higher (worse) than those of placebo patients (95% CI 0.4 to 4.6; $p = 0.02$). RSI-HB at baseline is confirmed as being statistically significantly related to 16-week RSI-HB score and is justified as a stratification factor in the trial design. Patients with severe RSI-HB at baseline are estimated to have RSI-HB scores that are 7.5 points higher (worse) at 16 weeks. The underlying assumptions of the model were not substantially violated.

TABLE 41 The RSI-HB scores at the 16-week follow-up, as response with adjustment for site and baseline severity

Source	Partial SS	df	Mean square	F-ratio	*p*-value
Model	4854.794	9	539.422	8.20	< 0.001
Arm	329.700	1	329.700	5.01	0.026
Site	1646.931	7	235.276	3.58	0.001[a]
Baseline severity	2880.361	1	2880.361	43.80	< 0.001
Residual	13,809.206	210	65.758		
Total	18,664.000	219	85.224		

df, degrees of freedom; SS, sum of squares.
a Site is not a reliable estimate as it cannot be modelled properly in ANCOVA.
Adjusted $R^2 = 0.228$, $n = 220$.

TABLE 42 The RSI-HB results of multilevel mixed-effect linear regression (model 1) (compliant ITT group) ($n = 220$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	2.489	1.086	2.29	0.022	0.360 to 4.617
Site (reference = Birmingham)						
Brighton	Random	–4.468	4.424	–1.01	0.312	–13.138 to 4.202
Glasgow		0.273	3.255	0.08	0.933	–6.106 to 6.653
Manchester		6.265	3.347	1.87	0.061	–0.294 to 12.825
Newcastle		–0.542	2.852	–0.19	0.849	–6.131 to 5.047
Nottingham		–4.423	2.833	–1.56	0.118	–9.977 to 1.130
Stockport		–2.671	3.767	–0.71	0.478	–10.054 to 4.712
Sunderland		–1.992	3.010	–0.66	0.508	–7.892 to 3.907
RSI-HB baseline severity: severe (reference = mild)	Fixed	7.490	1.106	6.77	< 0.001	5.323 to 9.657
Constant		11.681	2.849	4.10	< 0.001	6.097 to 17.264

SE, standard error.
Log-likelihood = –767.507; Wald chi-squared test = 77.34; *p*-value > χ^2 < 0.001. Site statistics are spurious.

Model 2

Model 2 adjusted for the stratification factor recruiting centre (as a random effect) at randomisation and for baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect) (*Table 43*).

When adjusted for site and continuous baseline severity RSI-HB, the placebo group again shows a greater reduction in symptoms. The estimated difference between randomised groups, when accounting for site and baseline severity, indicates that lansoprazole patients have RSI-HB scores at 16 weeks that are 2.0 points

TABLE 43 The RSI-HB results of multilevel mixed-effect linear regression (model 2) (compliant ITT group) ($n = 220$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	2.011	1.020	1.97	0.049	0.012 to 4.010
Site (reference = Birmingham)						
Brighton	Random	–0.094	4.201	–0.02	0.982	–8.327 to 8.139
Glasgow		–0.363	3.040	–0.12	0.905	–6.321 to 5.596
Manchester		4.317	3.140	1.37	0.169	–1.838 to 10.472
Newcastle		–1.355	2.655	–0.51	0.610	–6.559 to 3.849
Nottingham		–4.155	2.662	–1.56	0.119	–9.371 to 1.062
Stockport		–2.067	3.537	–0.58	0.559	–8.999 to 4.865
Sunderland		–1.398	2.831	–0.49	0.621	–6.946 to 4.150
RSI-HB continuous baseline severity	Fixed	0.668	0.074	9.01	< 0.001	0.523 to 0.813
Constant		2.337	3.061	0.76	0.445	–3.664 to 8.337

SE, standard error.
Log-likelihood = –753.829; Wald chi-squared test = 116.72; *p*-value > χ^2 < 0.001.

higher (worse) than those of placebo patients (95% CI 0.0 to 4.0; $p = 0.05$). A 1-unit increase in baseline severity is associated with a 0.67 increase (95% CI 0.5 to 0.8) in 16-week RSI-HB. As before, it is baseline RSI-HB score that remains the most important (positive) correlate of 16-week RSI-HB. The underlying assumptions of the model were not substantially violated.

Model 3

Model 3 adjusted for baseline severity (RSI-HB as a continuous measure) and age, sex, smoking status (binary), alcohol consumption (binary) and BMI (*Table 44*).

The reduction in AIC through simple log or complex (fractional polynomial) transformation was not substantial. In order to build the most parsimonious, clinically interpretable model, age and BMI were retained as untransformed continuous covariates, under the assumption of linearity with outcome. As none of the potential covariates appears to have a significant univariate relationship, model 2 with continuous baseline severity (RSI-HB) and site as covariates remains the optimal model. A sensitivity analysis based on the pragmatic ITT group including all patients with their 16-week primary end-point visit taking place at any time did not change the conclusions.

Reflux Finding Score was not included in the multivariable model as it added no further beneficial fit to the data.

The results of the multilevel mixed-effect linear regression (model 2) for RSI-HB (see *Table 44*) was extended to include RFS baseline assessment scores and report the change in –2log-likelihood and significance of RFS as a covariate in the model.

Model 4

Model 4 is adjusted for baseline RSI-HB (continuous measure), other important baseline factors and RFS baseline assessment. RFS was explored for suitable first-order fractional polynomial transformations (*Table 45*).

TABLE 44 Univariate relationships including transformed continuous covariates (compliant ITT group) ($n = 220$)

Covariate	AIC	Beta	SE	Test statistic	*p*-value
Age					
Continuous	1605.288	–0.003	0.048	–0.06	0.949
Log-transformed	1605.177				
Complex transformation (age^{-2})	1604.592				
BMI					
Continuous	1605.208	0.030	0.103	0.29	0.773
Log-transformed	1605.292				
Complex transformation (BMI^{-2})	1604.590				
Sex (binary – male/female)	1604.122	1.356	1.258	1.08	0.282
Binary smoking ($n = 219$)	1597.239	1.831	1.422	1.29	0.199
Binary alcohol consumption ($n = 217$)	1582.310	–1.803	1.387	–1.30	0.195

SE, standard error.

TABLE 45 Univariate relationships for continuous and transformed RFSs with primary outcome measure (RSI at 16 weeks) (compliant ITT group) ($n = 167$)

Covariate	AIC	Beta	SE	Test statistic	*p*-value[a]
RFS					
Continuous	1237.800	0.195	0.193	1.01	0.314
Log-transformed (RFS + 0.0001)	1236.033				
Complex transformation (RFS^0)	1236.830				

SE, standard error.
a Significance for untransformed covariate.

As the reduction in AIC through transformation was not substantial, the RFS was retained as an untransformed continuous covariate, under the assumption of linearity with outcome.

Building the optimal model was based on a forward selection method; –2log-likelihood was compared with a chi-squared distribution to assess variable inclusion. As the relationship is not significantly related to the RSI score at the primary end point, RFS was not included in the multivariable model because it added no further beneficial fit to the data.

Appendix 5 Secondary analysis of the primary outcome measure (Reflux Symptom Index): pragmatic and per-protocol groups

Pragmatic intention-to-treat group

The pragmatic analysis group comprises those participants completing the primary outcome visit at any time point after randomisation. All 283 participants had second visits, of whom 267 (94%) had usable RSI data. Of these, 135 (48%) were in the lansoprazole group and 148 (52%) were in the placebo group. All total RSI scores were in the range of 0–44, with 40% falling within the RSI population reference range (0–12), balanced across randomised groups. The means and SDs are reported (*Table 46*), with medians, IQRs and ranges, as the RSI score is treated as a continuous measure but is integer in nature.

The RSI appears to have reduced from a median of 21 at baseline to a median of 15 at 16 weeks in both randomised groups. The underlying RSI distribution appeared to be sufficiently normally distributed (overall mean 16.5, median 15) for parametric analysis of the primary outcome (H_0 = mean RSI scores at 16 weeks are equal for both groups; two-tailed $p < 0.05$).

The test statistic $t = 1.020$ and $p = 0.1544$, concluding that there is no statistically significant difference in the RSI score at 16 weeks between lansoprazole and placebo. As predicted, therefore, the reduction in RSI score from baseline to the primary end point was similar across the randomised groups (mean –4.6 in lansoprazole, –5.9 in placebo).

Multivariable analysis of the pragmatic intention-to-treat group

The RSI score after 16 weeks was initially analysed using ANCOVA methods in order to compare the 16-week RSI scores between the treatment groups while adjusting for the effects of the stratification factors at randomisation: recruitment centre and baseline severity (mild: RSI-HB ≤ 20, severe: RSI-HB > 20) (*Table 47*). The null hypothesis of equality, $p = 0.05$, applied throughout.

A further ANCOVA analysis considered age, sex, smoking status, alcohol consumption and BMI.

TABLE 46 Primary outcome measure (RSI) for the pragmatic ITT population

	Time point			
	Baseline (visit 1)		16 weeks (visit 2)	
RSI	Lansoprazole ($n = 127$)	Placebo ($n = 140$)	Lansoprazole ($n = 127$)	Placebo ($n = 140$)
Median (IQR)	21 (16–26)	22 (16–27)	15 (9–25)	15 (8–23)
Mean (SD) [95% CI]	21.7 (7.4)	21.9 (7.0)	17.1 (9.6) [15.5 to 18.8]	16.0 (9.5) [14.4 to 17.6]
Range	10–41	10–43	0–41	0–44

95% CIs are of the mean.

TABLE 47 Primary outcome measure as response with adjustment for site and baseline severity for the pragmatic ITT analysis group

Source	Partial SS	df	Mean square	F-ratio	*p*-value
Model	5021.445	9	557.938	7.46	< 0.001
Arm	138.600	1	138.600	1.85	0.175
Site	1726.855	7	246.694	3.30	0.002[a]
Baseline severity	3475.861	1	3475.861	46.50	< 0.001
Residual	19,211.146	257	74.752		
Total	24,232.592	266	91.100		

df, degrees of freedom; SS, sum of squares.
a The apparent site effect ($p = 0.002$) is spurious – TOPPITS sites were numbered 1 to 8 for the analysis and ANCOVA treats these numbers as numerical rather than indicative of location. Adjusted for the effects of site and baseline severity, there is no statistically significant difference in RSI at 16 weeks between randomised treatment groups ($p = 0.175$).
Adjusted $R^2 = 0.180$; $n = 267$. There was evidence of dependence on baseline severity ($p < 0.001$), justifying its role as a stratification factors in the trial design.

The hypothesis to be tested is H_0: the average RSI scores at 16 weeks are equal for both groups (lansoprazole vs. placebo) with adjustment for baseline stratification variables and also other clinical and demographic baseline factors. A two-sided significance level of $p < 0.05$ is used throughout. Age and BMI were sufficiently normal to include as untransformed data. Alcohol consumption and smoking status had excessive zero scores, thus skewed to the left and so binary alcohol and smoking variables were created with response 'yes' or 'no' (*Table 48*).

TABLE 48 Primary outcome measure as response with adjustment for stratification and other baseline factors (pragmatic ITT group)

Source	Partial SS	df	Mean square	F-ratio	*p*-value
Model	5184.009	14	370.286	4.86	< 0.001
Arm	82.303	1	82.303	1.08	0.300
Site	1605.675	7	229.382	3.01	0.005[a]
Baseline severity	3298.724	1	3298.724	43.32	< 0.001
Age	21.802	1	21.802	0.29	0.593
Sex	166.950	1	166.950	2.19	0.140
Binary smoking	14.841	1	14.841	0.19	0.659
Binary alcohol	36.450	1	36.450	0.48	0.490
BMI	11.665	1	11.665	0.15	0.696
Residual	18,809.583	247	76.152		
Total	23,993.592	261	91.929		

df, degrees of freedom; SS, sum of squares.
a Site not a reliable estimate as it cannot be modelled properly in ANCOVA.
Adjusted $R^2 = 0.172$; $n = 262$.
The conclusion is not affected: site and baseline severity remain significantly related to 16-week RSI. Adjusted for the effects of stratification variable and other baseline factors, there is no statistically significant difference in 16-week RSI between randomised treatment groups ($p = 0.300$).

Statistical modelling of the pragmatic intention-to-treat group

The analysis set is the pragmatic ITT group ($n = 267$). Analysis is carried out on a complete-case basis (analysing only those cases with complete information on all variables). Missing observations were examined to determine both the extent of and the reason for such omissions. Any missing data are described for each model. The use of multiple imputation techniques was considered for the secondary outcome data and covariate data. The rationale was that missing data to a sufficient extent of > 10% would necessitate imputation. Data were not missing to this extent for the pragmatic ITT group so multiple imputation was not used.

Multilevel mixed-effect linear regression was used to model the 16-week RSI outcome measure for the pragmatic group. Three models were developed.

Model 1

Model 1 adjusted for stratification factors used at randomisation: recruiting centre (as a random effect) and binary baseline severity as defined by the binary RSI-HB cut-off value of 20 (as a fixed effect) as covariates in the analysis. Modelling site as a random effect demonstrates no impact of site on RSI score at 16 weeks, as anticipated, and demonstrates the advantage of modelling these data more appropriately.

The RSI-HB score at baseline is confirmed as being statistically significantly related to 16-week RSI scores, and justified as a stratification factor in the trial design. Patients with 'severe' RSI scores at baseline are estimated to have RSI scores that are 7 points higher (worse) than patients with mild severity scores at baseline at 16 weeks.

There is no statistically significant difference between randomised groups, lansoprazole compared with placebo ($p = 0.165$), when adjusted for site and baseline binary RSI-HB.

Model 2

Model 2 adjusted for the stratification factor recruiting centre (as a random effect) at randomisation and for baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect). A 1-unit increase in baseline RSI-HB severity was associated with a 0.7-unit increase (95% CI 0.6 to 0.9) in 16-week RSI. There was no statistically significant difference between randomised groups, lansoprazole compared with placebo ($p = 0.264$), when adjusted for site and baseline continuous RSI-HB.

Model 3

Model 3 adjusted for baseline severity (RSI-HB as a continuous measure) and other important clinical and demographic baseline factors, specifically age, sex, smoking status, alcohol consumption and BMI. (Alcohol and smoking were treated as binary variables; see above.)

Conclusion

As none of the potential covariates appears to have a significant univariate relationship with the RSI score at the primary end point ($p > 0.1$ for all), model 2 with continuous baseline severity (RSI-HB) and site remains the optimal model.

Per-protocol population

During the DMC closed session held on 9 March 2018, the DMC discussed the different analysis groups. The chairperson felt that a sensitivity analysis including only patients who complied with the protocol (16 weeks $\pm$ 2 weeks) could be useful to support the primary analysis. The numbers available for this analysis are 178 out of 346 (51% of the trial population), with 82 out of 172 (48%) in the lansoprazole treatment group and 96 out of 174 (55%) in the placebo group.

The summary statistics showed the randomised groups to be similar at baseline and for the RSI score to reduce similarly in both randomised groups at 16 weeks (the primary outcome) (*Table 49*).

TABLE 49 Primary outcome measure (RSI) at 16 weeks for the per-protocol population

	Primary outcome measure: RSI 16-week follow-up (visit 2)		
	Treatment group		
RSI	Lansoprazole	Placebo	Total
n	82	96	178
Median (IQR)	15 (9–26)	13 (7–23)	13.5 (8–24)
Mean (SD)	16.9 (10.0)	15.4 (10.1)	16.1 (10.1)
95% CI of mean	14.7 to 19.1	13.4 to 17.5	14.6 to 17.6
Range	0–41	0–44	0–44

Overall, 47% of participants were within the normal range at the primary end point for the per-protocol population, balanced across randomised treatment groups. Proceeding to the previously employed multivariate strategies, the conclusion is not affected: site and baseline severity remain significantly related to 16-week RSI. Adjusted for the effects of stratification variables and other baseline factors, there was no statistically significant difference in 16-week RSI between randomised treatment groups ($p = 0.586$).

Statistical modelling of the per-protocol group

In the statistical modelling, as before, model 2 adjusted for the stratification factor recruiting site (as a random effect) at randomisation and for baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect). The log-likelihood statistics show that the continuous baseline severity substantially improves the model fit (reduction in –2log-likelihood) compared with the previous model with binary severity stratification factor above. A 1-unit increase in baseline severity is associated with a 0.7-unit increase (95% CI 0.5 to 0.9) in 16-week RSI. There is no statistically significant difference between randomised groups, lansoprazole compared with placebo ($p = 0.522$), when adjusted for site and baseline continuous RSI-HB. The estimated difference between randomised groups, when accounting for site and baseline severity, indicates that lansoprazole patients are estimated to have RSI scores at 16 weeks that are 0.81 points higher (worse) than placebo (95% CI –1.7 to 3.3; $p = 0.52$). As none of the potential covariates appeared to have a significant univariate relationship with the RSI score at the primary end point ($p > 0.1$ for all), model 2 with continuous baseline severity (RSI-HB) and site remains the optimal model.

Appendix 6 Secondary analysis of the primary outcome measure having excluded the heartburn component of Reflux Symptom Index (Reflux Symptom Index minus the heartburn/dyspepsia item): pragmatic group

Means, SDs, medians, IQRs and ranges are reported (*Table 50*) as the score is treated as a continuous measure but is integer in nature.

The randomised groups are similar in both treatment groups at baseline. A comparison of differences of unadjusted 16-week RSI-HB scores for pragmatic ITT group tested H_0: the mean RSI-HB scores at 16 weeks are equal for both groups (lansoprazole vs. placebo; two-sided $p < 0.05$). The test statistic, $t = 1.518$, $p = 0.130$, concludes that there is no statistically significant difference in the RSI-HB scores at 16 weeks between lansoprazole and placebo.

As before, ANCOVA multivariate analysis was followed by statistical modelling. Model 2 adjusted for the stratification factor recruiting centre (as a random effect) at randomisation and for baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect). As none of the potential covariates appears to have a significant univariate relationship with the RSI-HB score at the primary end point ($p > 0.1$ for all), model 2 with continuous baseline severity (RSI-HB) and site remains the optimal model.

TABLE 50 The RSI-HB for the pragmatic ITT population

	Time point			
	Baseline (visit 1)		16 weeks (visit 2)	
RSI-HB	Lansoprazole group ($n = 127$)	Placebo group ($n = 140$)	Lansoprazole group ($n = 127$)	Placebo group ($n = 140$)
Median (IQR)	19 (15–24)	20 (15–24)	14 (9–23)	13 (7.5–19.5)
Mean (SD)	20.0 (6.9)	20.0 (6.5)	16.0 (9.0)	14.3 (8.8)
95% CI of mean	18.8 to 21.2	18.9 to 21.1	14.4 to 17.5	12.8 to 15.8
Range	10–38	10–38	0–39	0–39

Appendix 7 Analysis of covariance of Reflux Symptom Index at 12 months

The outcome measure is RSI score after 12 months and it was initially analysed using ANCOVA methods, as detailed previously, in order to compare the 12-month RSI scores between the treatment groups while adjusting for potential confounders. Adjusted for the stratification effects of site and baseline severity, there was no statistically significant difference in RSI at 12 months between randomised treatment groups ($p = 0.069$). A secondary ANCOVA analysis considered age, sex, smoking status, alcohol consumption and BMI (*Table 51*).

There was no statistically significant difference in RSI at 12 months between randomised treatment groups on ANCOVA ($p = 0.256$), but site and baseline severity remain significantly related to 12-month RSI. Age and sex also appear to be significantly related to 12-month RSI when all stratification and baseline characteristics are included in the model.

Model 1

Model 1 adjusted for stratification factors used at randomisation [recruiting centre (as a random effect) and binary baseline severity as defined by the binary RSI-HB cut-off value of 20 (as a fixed effect)] as covariates in the analysis (*Table 52*).

There is no statistically significant difference between randomised groups, lansoprazole compared with placebo, when adjusted for site and baseline binary RSI-HB. The difference between randomised groups, when accounting for site and binary baseline severity, indicates that lansoprazole patients are estimated to have RSI scores at 12 months that are 2.5 points higher (worse) than those of placebo patients (95% CI –0.1 to 5.0; $p = 0.06$). The underlying assumptions of the model were not substantially violated.

TABLE 51 The RSI at 12 months as response with adjustment for stratification and other baseline factors

Source	Partial SS	df	Mean square	F-ratio	*p*-value
Model	6034.890	14	431.064	5.66	< 0.001
Arm	99.122	1	99.122	1.30	0.256
Site	2660.900	7	380.129	4.99	< 0.001[a]
Baseline severity	3019.474	1	3019.474	39.62	< 0.001
Age	444.648	1	444.648	5.83	0.017
Sex	298.691	1	298.691	3.92	0.049
Binary smoking	4.754	1	4.754	0.06	0.803
Binary alcohol	58.667	1	58.667	0.77	0.382
BMI	123.473	1	123.473	1.62	0.205
Residual	12,422.082	163	76.209		
Total	18,459.972	177	104.277		

df, degrees of freedom; SS, sum of squares.
a Site is not a reliable estimate as it cannot be modelled properly in ANCOVA.
Adjusted $R^2 = 0.269$; $n = 178$.

TABLE 52 Results of multilevel mixed-effect linear regression (model 1) at 12 months post randomisation (compliant ITT group) ($n = 181$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	2.469	1.311	1.88	0.060	–0.100 to 5.038
Site (reference = Birmingham)						
Brighton	Random	–19.058	6.094	–3.13	0.002	–31.003 to –7.113
Glasgow		–8.713	4.942	–1.76	0.078	–18.400 to 0.973
Manchester		–0.717	4.923	–0.15	0.884	–10.367 to 8.933
Newcastle		–8.616	4.453	–1.93	0.053	–17.344 to 0.112
Nottingham		–13.138	4.461	–2.95	0.003	–21.881 to –4.395
Stockport		–10.709	5.177	–2.07	0.039	–20.856 to –0.563
Sunderland		–9.029	4.626	–1.95	0.051	–18.096 to 0.037
RSI-HB baseline severity: severe (reference = mild)	Fixed	8.233	1.314	6.27	< 0.001	5.658 to 10.808
Constant		19.149	4.405	4.35	< 0.001	10.515 to 27.784

SE, standard error.
$n = 181$; log-likelihood = –646.428; Wald chi-squared test = 73.49; *p*-value > χ^2 < 0.001.

Model 2

Model 2 adjusted for the stratification factor recruiting centre (as a random effect) at randomisation and for baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect) (*Table 53*).

A 1-unit increase in baseline severity of RSI-HB is associated with a 0.7-unit increase in 12-month RSI score (95% CI 0.6 to 0.9). There is no statistically significant difference between randomised groups, lansoprazole compared with placebo, when adjusted for site and baseline continuous RSI-HB. The difference between randomised groups, when accounting for site and baseline severity, indicates that lansoprazole patients are estimated to have RSI scores at 12 months that are 1.7 points higher (worse) than those of placebo patients (95% CI –0.7 to 4.1; $p = 0.157$). The underlying assumptions of the model were not substantially violated.

Model 3

Model 3 adjusted for baseline severity (RSI-HB as a continuous measure) and other important clinical and demographic baseline factors, specifically age, sex, smoking status, alcohol consumption and BMI (*Table 54*).

The reduction in AIC through simple log or complex (fractional polynomial) transformation was not substantial and continuous covariates were therefore retained as untransformed. As none of the potential covariates appears to have a significant univariate relationship with the 12-month RSI score, model 2 with continuous baseline severity (RSI-HB) and site remains the optimum model.

TABLE 53 Results of multilevel mixed-effect linear regression (model 2) at 12 months post randomisation (compliant ITT group) ($n = 181$)

Model	Type	Beta	SE	Test statistic	*p*-value	95% CI (beta)
Group: lansoprazole (reference = placebo)	Fixed	1.730	1.222	1.42	0.157	–0.666 to 4.126
Site (reference = Birmingham)						
Brighton	Random	–12.195	5.701	–2.14	0.032	–23.369 to –1.022
Glasgow		–7.452	4.611	–1.62	0.106	–16.489 to 1.585
Manchester		–1.609	4.592	–0.35	0.726	–10.608 to 7.391
Newcastle		–7.999	4.153	–1.93	0.054	–16.139 to 0.141
Nottingham		–11.125	4.161	–2.67	0.007	–19.280 to –2.970
Stockport		–8.324	4.842	–1.72	0.086	–17.813 to 1.165
Sunderland		–6.729	4.313	–1.56	0.119	–15.182 to 1.724
RSI-HB continuous baseline severity	Fixed	0.739	0.087	8.51	< 0.001	0.569 to 0.909
Constant		7.188	4.483	1.60	0.109	–1.598 to 15.974

SE, standard error.
Log-likelihood = –633.722; Wald chi-squared test = 111.85; *p*-value > $\chi^2 = 0.000$.

TABLE 54 Univariate demographic relationships including transformed continuous covariates for RSI response at 12 months (compliant ITT group) ($n = 178$)

Covariate	AIC	Beta	SE	Test statistic	*p*-value
Age					
Continuous	1330.032	0.013	0.05	0.22	0.828
Log-transformed	1330.079				
Complex transformation (age^3)	1329.639				
BMI					
Continuous	1329.971	0.042	0.128	0.33	0.743
Log-transformed	1330.079				
Complex transformation (BMI^{-2})	1329.417				
Sex (binary – male/female)	1330.058	0.224	1.527	0.15	0.884
Binary alcohol consumption ($n = 176$)	1315.883	–1.781	1.690	–1.05	0.293
Binary smoking ($n = 177$)	1321.686	2.307	1.737	1.33	0.186

SE, standard error.

Appendix 8 Consideration of the weight of baseline Reflux Finding Score in modelling the primary outcome: Reflux Symptom Index at 16 weeks

Reflux Symptom Index was not included in the multivariable model because it added no further beneficial fit to the data.

The multilevel mixed-effect linear regression (model 2) for RSI-HB (see *Table 53*) was extended to include RFS baseline assessment scores and report the change in –2log-likelihood and significance of RFS as a covariate in the model.

Model 4 is adjusted for baseline RSI-HB (continuous measure), other important baseline factors and RFS baseline assessment. RFS was explored for suitable first-order fractional polynomial transformations (*Table 55*).

As the reduction in AIC through transformation was not substantial, RFS was retained as an untransformed continuous covariate, under an assumption of linearity with outcome.

Building the optimal model was based on a forward selection method; –2log-likelihood was compared against a chi-squared distribution to assess variable inclusion. As the relationship is not significantly related to the RSI score at the primary end point, RFS was not included in the multivariable model because it added no further beneficial fit to the data.

TABLE 55 Univariate relationships for continuous and transformed RFS with primary outcome measure (RSI at 16 weeks) (compliant ITT group) ($n = 167$)

Covariate	AIC	Beta	SE	Test statistic	*p*-value[a]
RFS					
Continuous	1237.800	0.195	0.193	1.01	0.314
Log-transformed (RFS + 0.0001)	1236.033				
Complex transformation (RFS^0)	1236.830				

SE, standard error.
a Significance for untransformed covariate.

Appendix 9 Comprehensive Reflux Symptom Score total and subscale 16-week follow-up scores descriptive analysis: compliant intention-to-treat analysis group (n = 220)

The CReSS total and subscale scores at the primary end point (16 weeks) are summarised by randomised treatment group and overall using descriptive statistics in *Table 56* and at the 12-month follow-up in *Table 57*. The means, SDs, medians, IQRs and ranges are reported as the score is treated as a continuous measure but is integer in nature. Box plots showing CReSS total and subscales at the three time points are shown in *Figures 17–20*.

A higher CReSS indicates more severe symptoms. The CIs for lansoprazole and placebo overlap for all scales, showing that the differences are not significant. Summary statistics show CReSS total and subscale scores to reduce in both randomised groups at 16 weeks. Summary statistics also show CReSS total and subscale scores to continue to reduce in both randomised groups by 12 months (*Table 58*).

The 16-week and 12-month total CReSS is lower than at baseline in both groups. The three subscale CReSSs are shown in *Figures 18–20*. All box plots show medians, IQRs and overall ranges.

There were two participants in the compliant ITT group with CReSS total scores completely missing at baseline. A further three participants had partially missing data. Two participants had CReSS oesophageal scores completely missing at baseline. Two participants had partially missing data. Two participants had CReSS upper airway scores completely missing at baseline. Another participant had partially missing data. Two participants in the compliant ITT group had CReSS pharyngeal scores completely missing at baseline.

The box plots show how the CReSS total and subscales change over the course of the trial visits, shown separately for the treatment groups. For all CReSS scales, a similar larger drop is seen between baseline and 16 weeks for both treatment groups.

Relationship of Comprehensive Reflux Symptom Score and Reflux Symptom Index (primary outcome)

Simple log and fractional polynomial transformations were considered for CReSS total and subscale scores to investigate better fit than under the assumption of linearity with RSI at 16 weeks (see *Table 57*), when the best-fitting transformation is selected based on a reduction in AIC. The reduction in AIC through simple log or complex (fractional polynomial) transformations was not substantial. In order to build the most parsimonious, clinically interpretable model, the CReSS total and subscale scores were retained as untransformed continuous covariates, under the assumption of linearity with outcome.

Comprehensive Reflux Symptom Score univariate analysis

The univariate analysis is based on fitting a univariate model of each baseline CReSS domain score as a potential predictor of RSI at 16 weeks (*Table 59*).

TABLE 56 The CReSS total and subscale scores at the primary end point (16 weeks, visit 2) for the compliant ITT population

	Total (range: 0–170)		Oesophageal subscale (range: 0–85)		Upper airway subscale (range: 0–85)		Pharyngeal subscale (range: 0–25)	
CReSS	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group
n	102	118	102	118	102	118	102	118
Median (IQR)	36 (15 to 55)	27.5 (14 to 48)	12 (4 to 26)	11.5 (5 to 22)	12 (5 to 21)	8 (4 to 18)	6 (2 to 10)	4 (2 to 8)
Mean (SD)	38.9 (27.7)	34.7 (28.3)	16.4 (14.7)	16.2 (14.9)	13.6 (9.8)	11.3 (10.0)	7.0 (5.6)	5.7 (5.2)
95% CI	33.4 to 44.3	29.6 to 39.9	13.5 to 19.3	13.5 to 18.9	11.6 to 15.5	9.5 to 13.2	5.9 to 8.1	4.7 to 6.6
Range	2–140	0–158	0–75	0–76	0–38	0–45	0–21	0–23

TABLE 57 Transformations of continuous CReSS total and subscale score covariates and relationship with RSI at 16 weeks ($n = 215$)

Factors	AIC	Beta	SE	Test statistic	*p*-value[a]
Total CReSS					
Continuous	1543.889	0.175	0.023	7.76	< 0.001
Log-transformed	1550.044				
Complex transformation (total CReSS$^{0.5}$)	1543.519				
Oesophageal					
Continuous	1571.588	0.230	0.044	5.22	< 0.001
Log-transformed	1592.283				
Complex transformation (oesophageal$^{0.5}$)	1569.072				
Upper airway					
Continuous	1534.297	0.502	0.059	8.53	< 0.001
Log-transformed	1585.946				
Complex transformation (upper airway^{2})	1532.443				
Pharyngeal					
Continuous	1579.617	0.491	0.114	4.29	< 0.001
Log-transformed	1590.116				
Complex transformation (pharyngeal^{1})	1579.617				

SE, standard error.
a For the continuous untransformed covariate.

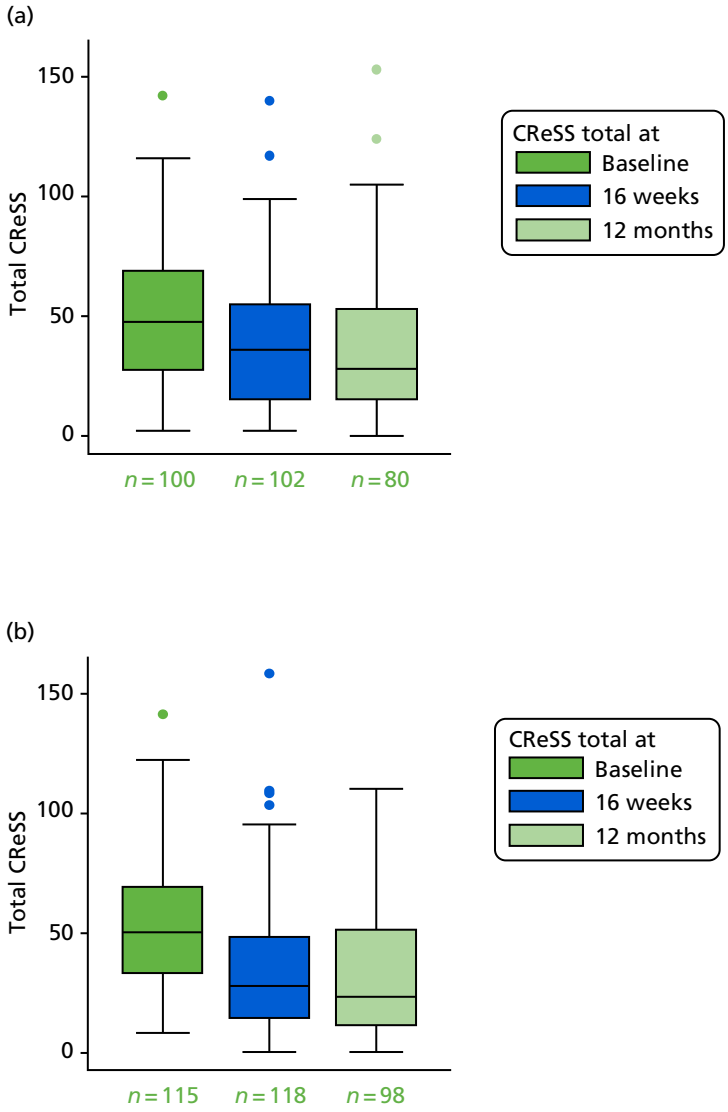

FIGURE 17 The CReSS total scores at baseline and follow-up visits for the compliant ITT population (median, IQR and overall range). (a) Lansoprazole; and (b) placebo.

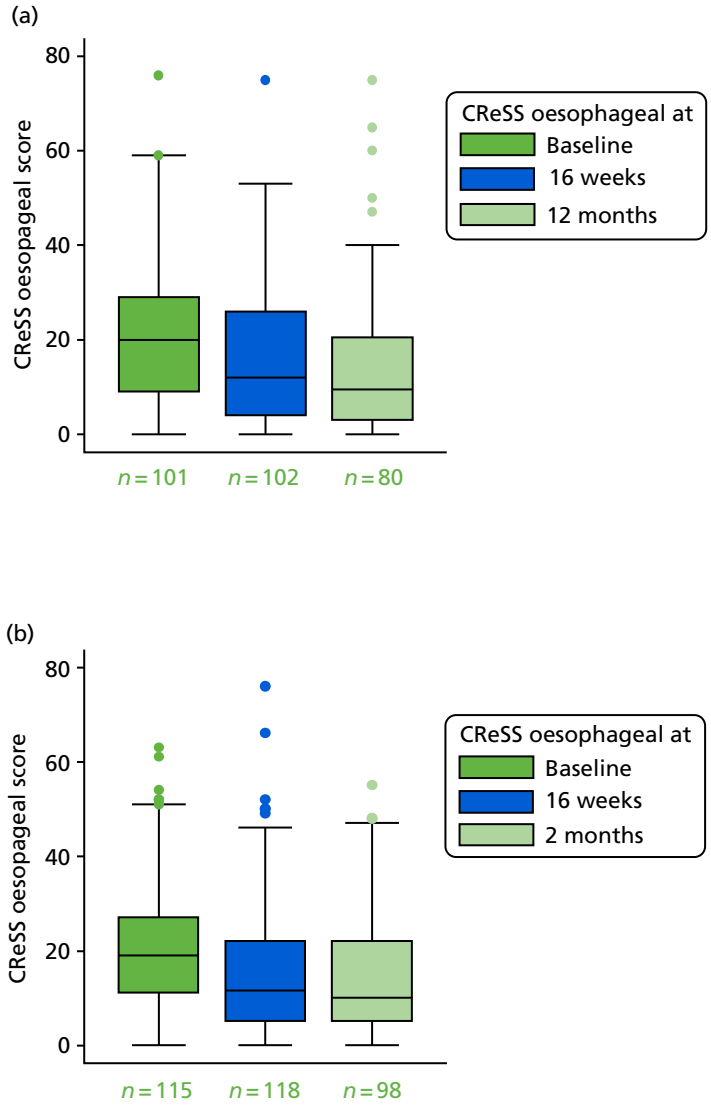

FIGURE 18 The CReSS oesophageal subscale scores at baseline and follow-up for the compliant ITT population. (a) Lansoprazole; and (b) placebo. The 16-week and 12-month CReSS oesophageal subscale score is lower than at baseline in both treatment groups.

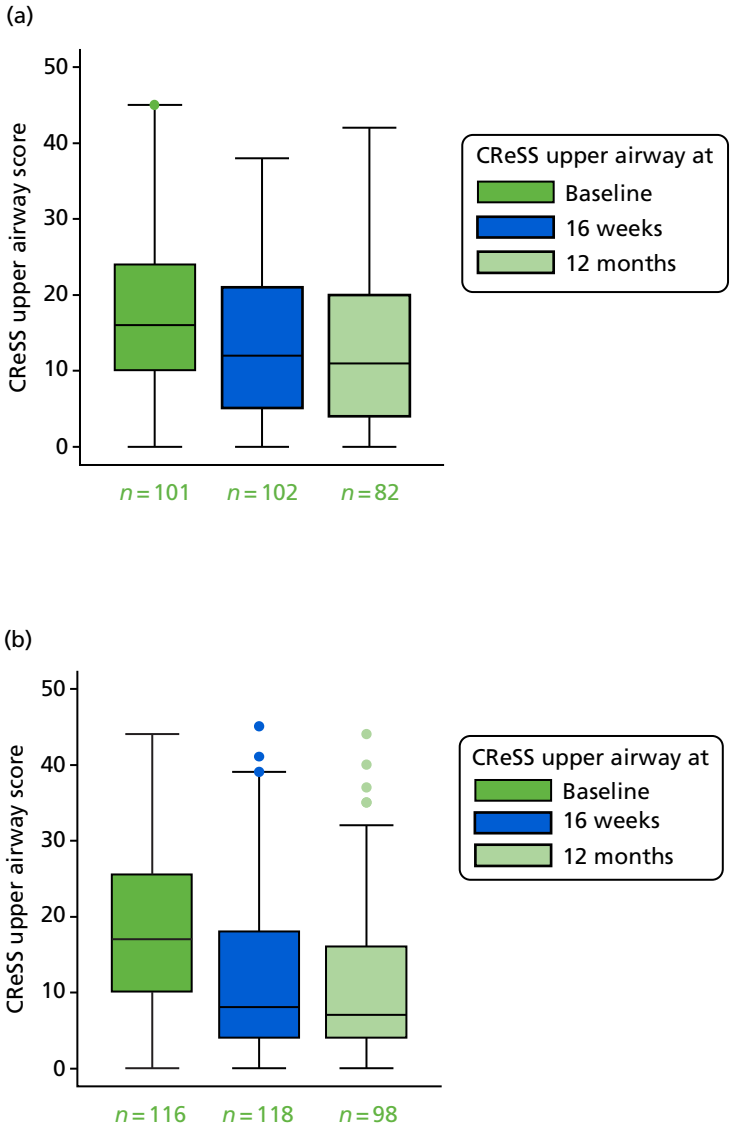

FIGURE 19 The CReSS upper airway subscale scores at baseline and follow-up visits for the compliant ITT population. (a) Lansoprazole; and (b) placebo. The 16-week and 12-month CReSS upper airway score is lower than at baseline in both treatment groups.

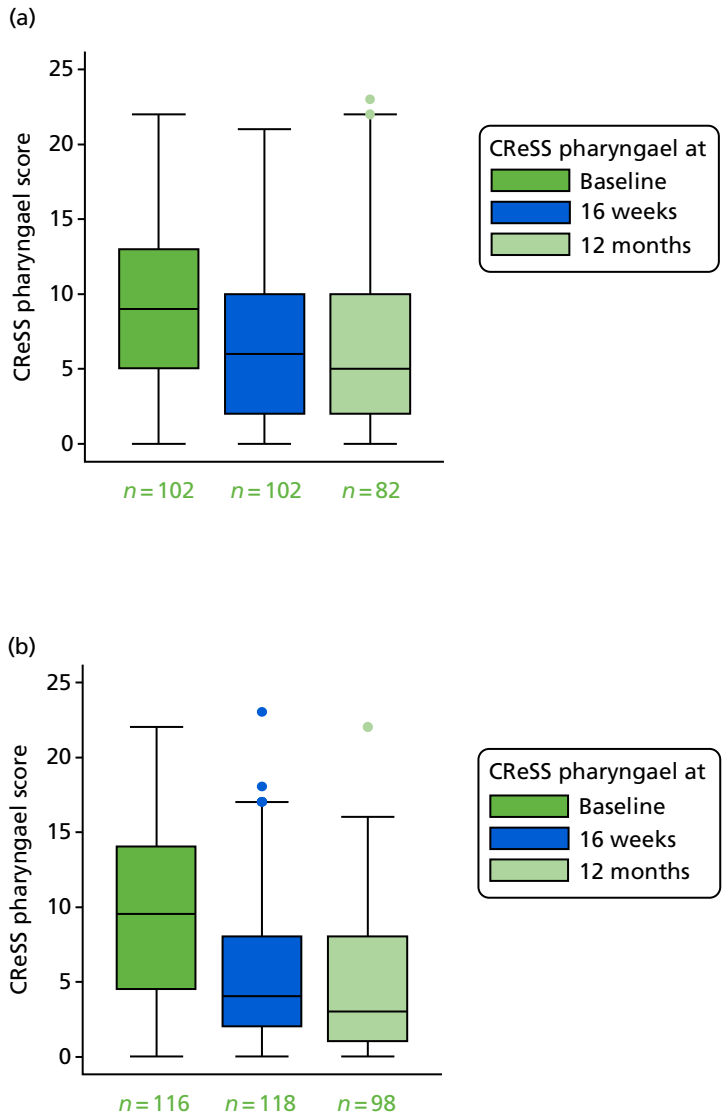

FIGURE 20 The CReSS pharyngeal subscale scores at baseline and follow-up for the compliant ITT population. (a) Lansoprazole; and (b) placebo. The 16-week and 12-month CReSS pharyngeal subscale score is lower than at baseline in both treatment groups.

TABLE 58 The CReSS total and subscale scores at the 12-month follow-up (visit 3) for the compliant ITT population

	12-month follow-up (visit 3)							
	Total (range: 0–170)		Oesophageal subscale (range: 0–85)		Upper airway subscale (range: 0–45)		Pharyngeal subscale (range: 0–25)	
CReSS	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group	Lansoprazole group	Placebo group
n (%)	80 (78)	98 (83)	80 (78)	98 (83)	82 (80)	98 (83)	82 (80)	98 (83)
Median (IQR)	28 (15–53)	23 (11–51)	9.5 (3–20.5)	10 (5–22)	11 (4–20)	7 (4–16)	5 (2–10)	3 (1–8)
Mean (SD)	36.6 (30.7)	31.8 (25.9)	15.4 (16.0)	15.3 (13.5)	12.9 (11.0)	10.3 (10.0)	6.3 (5.8)	4.6 (4.7)
95% CI	29.8 to 43.5	26.6 to 36.9	11.8 to 18.9	12.6 to 18.0	10.5 to 15.3	8.3 to 12.3	5.0 to 7.6	3.7 to 5.6
Range	0–153	0–110	0–75	0–55	0–42	0–44	0–23	0–22

TABLE 59 Univariate models for RSI at 16 weeks with baseline severity represented by baseline RSI-HB or any one of the baseline CReSS total/subscales ($n = 215$)

Baseline severity measure	AIC	Beta	SE	Test statistic	*p*-value
Total CReSS	1543.889	0.175	0.023	7.76	< 0.001
CReSS oesophageal	1571.588	0.230	0.044	5.22	< 0.001
CReSS upper airway	1534.297	0.502	0.059	8.53	< 0.001
CReSS pharyngeal	1579.617	0.491	0.114	4.29	< 0.001
RSI-HB	1524.924	0.754	0.082	9.24	< 0.001

SE, standard error.

Baseline CReSS total and subscales appear to be significant predictors of the primary outcome (RSI) at 16 weeks. All increases in CReSS domain scores result in an increase in RSI. A 1-unit increase in (1) baseline CReSS total results in a 0.18-unit increase in RSI at 16 weeks, (2) baseline CReSS oesophageal subscale results in a 0.23-unit increase, (3) baseline CReSS upper airway subscale results in a 0.50-unit increase and (4) baseline CReSS pharyngeal results in a 0.49-unit increase. It appears that baseline RSI-HB remains the single most important predictor of the primary outcome – a 1-unit increase results in a 0.75-unit increase in 16-week RSI.

Comprehensive Reflux Symptom Score multivariable analysis

Table 60 summarises each of the baseline CReSS domains' individual significance (presented with RSI-HB) when included individually in a multivariable model for RSI at 16 weeks, adjusted by site and baseline RSI-HB.

Baseline CReSS total and subscales, with the exception of the pharyngeal subscale, are significant predictors of RSI at 16 weeks, independent of and in addition to RSI-HB. A 1-unit increase in all baseline CReSS domains results in an increase in RSI at 16 weeks (total score, 0.06 increase; oesophageal subscale, 0.09 increase; upper airway, 0.2 increase).

TABLE 60 Summary of multivariable models[a] for RSI at 16 weeks and baseline CReSS domain predictors ($n = 215$)

CReSS domains in model[a]	AIC	Beta	SE	Test statistic	*p*-value	95% CI (beta)
None	1525.460					
RSI-HB		0.723	0.080	9.02	< 0.001	0.565 to 0.879
Total CReSS	1522.308	0.064	0.028	2.28	0.022	0.009 to 0.119
RSI-HB		0.568	0.104	5.47	< 0.001	0.365 to 0.772
Oesophageal	1523.397	0.085	0.042	2.03	0.043	0.003 to 0.168
RSI-HB		0.654	0.086	7.60	< 0.001	0.485 to 0.822
Upper airway	1521.063	0.206	0.081	2.55	0.011	0.047 to 0.364
RSI-HB		0.518	0.112	4.62	< 0.001	0.299 to 0.738
Pharyngeal	1527.460	0.001	0.113	0.01	0.995	–0.220 to 0.221
RSI-HB		0.721	0.093	7.79	< 0.001	0.540 to 0.903

SE, standard error.
a Model adjusted by site (not presented) and baseline RSI-HB (continuous measure).

Comparison of Comprehensive Reflux Symptom Score total and subscales and Reflux Symptom Index minus the heartburn/dyspepsia item as baseline severity measures

The baseline severity as provided by the baseline CReSS total and subscale scores were investigated to see if they explained variability in the data better than baseline RSI-HB. The modelling process for the compliant ITT group was repeated including CReSS baseline severity as an alternative to RSI-HB (*Table 61*).

The results in *Table 61* show that all baseline CReSS total and subscales are significant predictors of the primary outcome when adjusted by site.

The model with a substantially better fit to the data lowest AIC is that including baseline RSI-HB severity measure with an AIC of 1525.4. The best-fitting model based on only baseline CReSS severity measures is the model including CReSS upper airway with an AIC of 1539.4. This covariate explains more variability in the RSI score at 16 weeks than the total CReSS but nevertheless performs less well than RSI-HB. The addition of CReSS upper airway score to RSI-HB, in a model adjusted by site, results in a better-fitting model with the lowest AIC of 1521.1 (see *Table 60*).

TABLE 61 Multivariable models comparing the ability of baseline CReSS and continuous RSI-HB scores, adjusted by site, to predict RSI at 16 weeks ($n = 215$; model 5)

Multivariable model[a] baseline severity measure	AIC	Beta	SE	Test statistic	*p*-value
Total CReSS	1548.332	0.164	0.023	7.18	< 0.001
CReSS oesophageal	1572.542	0.210	0.044	4.81	< 0.001
CReSS upper airway	1539.431	0.471	0.059	7.92	< 0.001
CReSS pharyngeal	1578.926	0.444	0.110	4.02	< 0.001
RSI-HB	1525.460	0.723	0.080	9.02	< 0.001

SE, standard error.
a Adjusted by site.

Appendix 10 Laryngopharyngeal Reflux – Health Related Quality of Life tabulated thermometer and domain scores

The groups are seen to be balanced, with similar scores across treatment groups and quality-of-life domains at baseline in the 'thermometers', which are part of the scoring system; a score of 3 or 4 indicates a small effect and scores of 2 and 1 indicate minimal to no effect on quality of life (*Table 62*).

At the end of treatment (primary end point) (*Table 63*), mean voice, coughing, clear throat, general subscale scores and overall scores were reduced in both groups.

There is a further reduction in the 12-month visits for scale and thermometer scores (*Tables 64* and *65*).

TABLE 62 Baseline thermometers of LPR-HRQL scales

	Treatment group								
	Lansoprazole			Placebo			Overall		
Scale	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range
Voice	101	2 (1–5)	1–10	116	2 (1–5)	1–10	217	2 (1–5)	1–10
Cough	99	3 (1–6)	1–10	116	2.5 (1–5)	1–10	215	3 (1–5)	1–10
Clear	101	4 (2–6)	1–10	116	3 (1–6)	1–10	217	4 (2–6)	1–10
General	102	4 (2–7)	1–10	116	3 (2–6)	1–10	218	3.5 (2–6)	1–10

TABLE 63 Primary end-point (16 weeks) thermometers for LPR-HRQL scales

	Treatment group								
	Lansoprazole			Placebo			Overall		
Scale	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range
Voice	100	2 (1–4)	1–10	117	1 (1–3)	1–10	217	1 (1–3)	1–10
Cough	102	2 (1–4)	1–10	117	1 (1–3)	1–10	219	2 (1–4)	1–10
Clear	102	2 (1–5)	1–10	117	2 (1–5)	1–10	219	2 (1–5)	1–10
General	102	2 (1–5)	1–10	117	2 (1–5)	1–10	219	2 (1–5)	1–10

TABLE 64 The LPR-HRQL scores at the 12-month follow-up (compliant ITT group)

Scale	Descriptive statistics	Scores					
		Raw			Standardised		
		Treatment group			Treatment group		
		Lansoprazole	Placebo	Total ($n = 220$)	Lansoprazole	Placebo	Total
Voice (raw range: 0–72)	Number complete	82	99	181	82	99	181
	Median (IQR)	6 (6 to 11)	6 (3 to 12)	6 (6 to 11)	–0.42 (–0.42 to –0.11)	–0.32 (–0.68 to 0.41)	–0.32 (–0.42 to 0.05)
	Mean (SD)	12.8 (16.0)	8.6 (8.3)	10.5 (12.5)	0 (1)	0 (1)	0 (1)
	95% CI	9.3 to 16.3	7.0 to 10.3	8.7 to 12.3	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
	Range	0 to 68	0 to 39	0 to 68	–0.80 to 3.46	–1.04 to 3.67	–1.04 to 3.67
Cough (raw range: 0–36)	Number complete	82	99	181	82	99	181
	Median (IQR)	3 (0 to 11)	1 (0 to 6)	2 (0 to 9)	–0.44 (–0.76 to 0.44)	–0.50 (–0.64 to 0.19)	–0.50 (–0.64 to 0.44)
	Mean (SD)	7.0 (9.2)	4.6 (7.2)	5.7 (8.2)	0 (1)	0 (1)	0 (1)
	95% CI	5.0 to 9.0	3.2 to 6.0	4.5 to 6.9	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
	Range	0 to 36	0 to 36	0 to 36	–0.76 to 3.17	–0.64 to 4.37	–0.76 to 4.37
Clear (raw range: 0–36)	Number complete	82	99	181	82	99	181
	Median (IQR)	4.5 (0 to 10)	2 (0 to 6)	3 (0 to 9)	–0.32 (–0.87 to 0.35)	–0.39 (–0.70 to 0.25)	–0.39 (–0.70 to 0.25)
	Mean (SD)	7.1 (8.2)	4.4 (6.3)	5.7 (7.3)	0 (1)	0 (1)	0 (1)
	95% CI	5.3 to 8.9	3.2 to 5.7	4.5 to 6.7	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
	Range	0 to 30	0 to 26	0 to 30	–0.87 to 2.80	–0.70 to 3.41	–0.87 to 3.41
General (raw range: 0–30)	Number complete	81	99	180	81	99	180
	Median (IQR)	3 (0 to 6)	2 (0 to 6)	2 (0 to 6)	–0.30 (–0.78 to 0.19)	–0.30 (–0.69 to 0.48)	–0.30 (–0.69 to 0.32)
	Mean (SD)	4.8 (6.2)	3.6 (5.1)	4.1 (5.6)	0 (1)	0 (1)	0 (1)
	95% CI	3.5 to 6.2	2.5 to 4.6	3.3 to 5.0	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
	Range	0 to 28	0 to 28	0 to 28	–0.78 to 3.76	–0.69 to 4.77	–0.78 to 4.77
Overall (raw rescaled range: 0–100)	Number complete	79	97	176	79	97	176
	Median (IQR)	12 (2 to 22)	7 (1 to 18)	8 (2 to 20)	–0.30 (–0.73 to 0.15)	–0.35 (–0.68 to 0.23)	–0.35 (–0.69 to 0.23)
	Mean (SD)	18.8 (22.5)	13.9 (19.2)	16.0 (20.8)	0 (1)	0 (1)	0 (1)
	95% CI	13.7 to 23.8	10.0 to 17.8	13.0 to 19.2	–0.2 to 0.2	–0.2 to 0.2	–0.1 to 0.1
	Range	0 to 91	0 to 94	0 to 94	–0.83 to 3.23	–0.72 to 4.15	–0.83 to 4.15

TABLE 65 The 12-month follow-up thermometers of LPR-HRQL scales

	Treatment group								
	Lansoprazole			Placebo			Overall		
Scale	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range	*n*	Median (IQR)	Range
Voice	80	1 (1–3)	1–10	98	1 (1–2)	1–10	178	1 (1–3)	1–10
Cough	81	2 (1–4)	1–10	98	1 (1–2)	1–10	179	1 (1–3)	1–10
Clear	81	2 (1–5)	1–10	99	1 (1–3)	1–10	180	2 (1–4)	1–10
General	81	2 (1–4)	1–10	99	2 (1–3)	1–9	180	2 (1–4)	1–10

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