TOPPITS

Trial **o**f **P**roton **P**ump **I**nhibitors in **T**hroat **S**ymptoms

Protocol

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2. Protocol signature page

2.1 Protocol authorisation signatories

Signature …… Date ……

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Signature …… Date ……

Dr Nick Steen, Statistician

Signature …… Date ……

Dr Lesley Hall, Senior Trial Manager

2.2 Principal Investigator signature

I confirm that I have read and understood protocol version 3.0 dated 7 December 2015. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

Site Name/I.D……

3. Contents Page

4. Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AR/ADR	Adverse Reaction/Adverse Drug Reaction
CI	Chief Investigator
CReSS	Comprehensive Reflux Symptom Score
DMEC	Data Monitoring & Ethics Committee
e-CRF	electronic Case Report Form
ENT	Ear Nose and Throat
EOR	Extra Oesophageal Reflux
GORD	Gastro-oesophageal Reflux Disease
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LPR	Laryngopharyngeal Reflux
LPR-HRQL	Laryngopharyngeal Reflux – Health Related Quality of Life
MA	Marketing Authorisation
PI	Principal Investigator
PPI	Proton Pump Inhibitor
RSI	Reflux Symptom Index
RSI-HB	Reflux Symptom Index – Heart Burn
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

5. Responsibilities

Sponsor: The nominated Sponsor for the study is The Newcastle upon Tyne Hospitals NHS Foundation Trust who will undertake a Research Governance Risk Assessment prior to commencement of the study.

Funder: The Health Technology Assessment (HTA) Programme (Ref No: 11/NE/0136) is funding this study. Contact at HTA: Alexa Cross, Programme Manager, National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS. Email: a.cross@southampton.ac.uk.

Trial Management: The study will be managed through the Newcastle Clinical Trials Unit (a UK CRC registered CTU). A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The trial management group will consist of the Chief Investigator (Prof Janet Wilson), Co-Investigator (Mr James O'Hara), Senior Trial Manager (Mr Chris Speed), Trial Manager (Dr Vanessa Hogan) and statistician (Dr Nick Steen). The day-to-day management of the trial will be co-ordinated by the Trial Manager.

Principal Investigator: The Principal Investigator will have overall responsibility for the conduct of the study at a particular trial site

Trial Management:

The following functions falling under the responsibility of the Sponsor will be delegated to Professor Janet Wilson:

- Authorisation and Ethics Committee Opinion (including CTA request, research ethics committee opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)

- Good Clinical Practice and Trial Conduct (including GCP arrangements, management of IMP, data monitoring, emergency & safety procedures)

- Pharmacovigilance (including defining & recording adverse events/reactions, reporting SUSARs, notifying investigators of SUSARs, ensuring SAEs are reviewed by an appropriate committee for safety monitoring, annual listings & safety report).

- Administration of funding for the study

Trial conduct at site:

Investigator responsibilities:

- Study conduct and the welfare of study subjects

- Familiarity with the use of the investigational medicinal product as described in the product information, appropriate storage, and administration according to the protocol and drug accountability. Ensuring investigational medicinal product is not used for any purposes other than the conduct of the study.

- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events

- Screening and recruitment of subjects
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event
- Obtaining local approval and abiding by the policies of Research Governance
- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, and any national legislation implementing the EU Clinical Trials Directive (2001/20/EC) and subsequent amendments.
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained.
- Obtaining written informed consent from participants prior to any study specific procedures.
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File (TMF).
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study.
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining study documentation and compliance with reporting requests
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms
- Documenting appropriate delegation of tasks to study personnel e.g. Pharmacist, Research Nurse, Investigator(s)
- Ensuring data collected is accurate, timely & complete
- Providing updates on the progress of the trial
- Ensuring subject confidentiality is maintained during the project and archival period
- Ensuring archival of study documentation for a minimum of 15 years following the end of the study, unless local arrangements require a longer period

6. Protocol Summary

Short title:	TOPPITS
Protocol version:	3.0
Protocol date:	7 December 2015
Chief Investigator:	Professor Janet Wilson
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	Health Technology Assessment, Clinical Evaluation and Trials
Study design:	A randomised double-blind, placebo controlled trial with internal feasibility pilot.
Study Intervention:	Treatment with either 30mg (twice daily) dose of the proton pump inhibitor lansoprazole or placebo on a 1:1 basis for 16 weeks.
Primary objective:	To compare the symptomatic response in patients with persistent throat symptoms at the end of four months (16 weeks) therapy of treatment with lansoprazole versus placebo
Secondary objective:	(i) To explore the feasibility of study recruitment by means of an internal pilot trial rehearsal whose data will be included in the main data for analysis (ii) To compare the end of four months (16 weeks) treatment symptom responses with those at 12 months (iii) To determine the utility of the Reflux Symptom Index (RSI) questionnaire, the Comprehensive Reflux Symptom Score (CReSS) questionnaire items and subscales, endolaryngeal examination findings as scored by the Reflux Finding Score, and patient demographics including age; gender; smoking; Body Mass Index (43-45) as potential baseline determinants of treatment response. (iv) To compare the patient reported side effects and compliance with treatment and use of any other over-the-counter medication use in both arms. (v) To compare changes in disease-specific quality of life (LPR-HRQL) in the two arms.
Primary outcome:	The change in Reflux Symptom Index (RSI) at four months in the treatment and placebo groups in an intention to treat analysis.
Number of study sites:	seven
Study population/size:	30 patients will be recruited and randomised during the pilot feasibility study. A further 302 patients will be recruited during the full trial. This gives a total of 332.
Study duration:	42 months

7. Background

7.1 Background

TOPPITS addresses the problem of adults with persistent throat symptoms such as globus, catarrh, throat discomfort, clearing, recurring dysphonia or excess mucus. In one UK survey, 6% of the middle aged female population had had a persistent feeling of the something in the throat (globus) in the previous three months (1). Globus is also reported to account for up to 4% of Ear Nose and Throat (ENT) referrals to secondary care (2). Throat clearing is the commonest single symptom in any voice clinic. Equally familiar are intermittent hoarse voice, and post nasal drip (3). It is claimed that 55 % of patients referred to a voice clinic have symptoms of Extra Oesophageal Reflux (EOR), while an English study of primary care attenders indicated that 25% had recent experience of persistent upper respiratory symptoms (4). In the general population, the lifetime incidence of milder variants of globus (a feeling of a lump in the throat) is over 40% (5). In 2010-2011, the Hospital Episode Statistics online database of NHS activity lists 1,142,404 first ENT consultations. A conservative estimate is that 5% of these patients were referred for very common throat symptoms like throat clearing, fluctuating voice change, catarrh and chronic throat discomfort, which equates to over 57,000 NHS patients referred to secondary care that year annum in England alone. Some patients experience anxiety as they fear 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 which 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).

EOR symptoms have long been recognised as having a strong placebo response (28). The original evidence that reflux might affect the upper airway came from animal experiments, and the term “acid laryngitis” was coined 40 years ago (29). Intracellular reactivation of acidified pepsin may explain pepsin activity at weakly acid pH,.(30, 31). There is a growing trend to treat throat symptom patients empirically with proton pump inhibitors (PPIs), but most controlled studies fail to demonstrate a significant benefit of PPI over placebo (9, 12, 32). Our UK Evidence Based Medicine EOR conference concluded that: “Studies assessing PPIs in EOR suffer from variable study design and quality, small numbers and heavy selection bias and use a variety of different treatment regimes. The small proportion of controlled studies demonstrating overall benefit of PPI over placebo(19) may incorporate a disproportionate improvement in heartburn, known to respond promptly to antacid therapies, without due regard to the upper airway symptoms per se” (33, 34). There was little evidence on other pharmaceuticals such as H2 antagonists (35, 36).In the Patient and Public Involvement background work for this proposal, individual interviews conducted with several patients encompassing both young professionals and retired patients. All fully support 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.

7.2 Patients

Participants will be adult patients newly referred to secondary care otolaryngology clinics with persistent (over six weeks) unexplained throat symptoms, principally dysphonia, throat pain, globus sensation (feeling of something stuck in the throat), throat clearing, post nasal drip or mucus excess, also night time unexplained cough or choking.

7.3 Treatment choice in TOPPITS

The acid suppression approach has been in vogue for over a decade, on the basis that recurring upper respiratory symptoms are atypical manifestations of gastro-oesophageal reflux - so called Extra-oesophageal Reflux (EOR), or laryngopharyngeal reflux, (LPR). Over half of UK otolaryngologists prescribe proton pump inhibitors (PPIs) for persistent throat symptoms in the absence of structural pathology (6). Our early systematic review (9) of studies that used PPIs as an empiric treatment modality for suspected laryngopharyngeal reflux identified fourteen uncontrolled studies and one unblinded, nonrandomised 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 or inadequate blinding of the results were among typical limitations. Although uncontrolled series reported positive results, randomised, controlled trials 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 ear, nose and throat practice in the UK is based on poor levels of evidence from uncontrolled studies. A later meta-analysis (10) included further studies, notably that of Vaezi (11), and concluded that PPI therapy 'may offer a modest but nonsignificant clinical benefit' over placebo. The authors also concluded that validated diagnostic guidelines may facilitate the recognition of likely responders. The 2007 meta analysis included five RCTs, only two of which had more than 22 participants and only one randomised over 100 patients. The conclusion was that there was no overall benefit of therapy and that further work was needed to identify likely responders. (12) Finally the most recent meta-analysis included seven placebo-controlled trials totalling 396 patients with varying doses over four weeks to four months' duration, and again showed PPI therapy lacked evidence of efficacy in those suspected of LPR. Rather, high placebo response levels suggested a much more complex and multifactorial pathophysiology (13) Like previous authors, the reviewers concluded that further studies are needed to characterize subgroups of patients with reflux-associated laryngeal symptoms that might benefit from treatment with PPI.

The message has also filtered through to primary care that PPIs are a reasonable "empirical" treatment strategy for this group of patients. (Almost since their introduction, in the late 1990's of course, PPIs have constituted the largest sector of the NHS community drugs bill - £238m in 1999; 5.6% (7)). A recent review of throat symptom patients referred to the Newcastle upon Tyne Ear Nose and Throat department indicated that almost 30% had taken antireflux medication in the previous 12 months. Proton-pump inhibitors are highly efficient in reducing gastric acid secretion. The annual NHS expenditure on proton pump inhibitors is over £300 million. (Generic omeprazole, lansoprazole and pantoprazole are the NHS QIPP endorsed low-cost PPIs). Without the proposed research we see nothing to stop the increasing 'belief' in EOR as a prime cause of upper respiratory symptoms as the theory is supported by prominent laryngological enthusiasts, some respiratory medicine experts and of course the pharmaceutical industry. If all putative patients referred to otolaryngologists were treated with PPI, the costs are estimated at £4 million per annum. Although the link of EOR 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 increasing. Aside from the substantial direct NHS cost of the antacid therapy, there are hidden costs. 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 alluded to above (13). Perpetuating a simplistic, unscientific, unselective strategy of giving 'all comers' with upper respiratory symptoms antireflux therapy misses the opportunity to intervene more appropriately in those with such generalised somatic sensitivity. Other dimensions overlooked through over-reliance on antacid include management of the fatigue shown to accompany functional hoarseness, and

anecdotal reports from our own patients of significant impact on employment, particularly in today's communication-conscious era.

The TOPPITS trial aims to quantify, and to characterise, the effect of proton pump inhibitor therapy compared to placebo. Our comprehensive package of patient centred outcomes allow us to assess which specific throat symptoms respond; whether any patient characteristics can predict such a treatment response, derive improved estimates of impact on quality of life, and define the proportion of likely non-responders, for whom alternative therapeutic approaches may be more appropriate.

PPIs 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. Commonest complaints are headache, diarrhoea, abdominal pain, and nausea. Except for diarrhoea, the adverse effects of PPIs seem independent of age, dosage, or duration of treatment. The diarrhoea seems to be due to altered gut flora secondary to the loss of acid secretion (overall incidence of diarrhoea is less than 5%). 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, prompting recent NHS guidance on prioritising the best value choices.

- We propose to use Lansoprazole in TOPPITS as it is among those recommended by the NHS Quality Innovation Productivity and Prevention strategy
- In TOPPITS, as is typical of LPR studies, we propose twice daily treatment to minimise the risk of gastro-oesophageal reflux occurring at night (8).
- Lansoprazole has a lower unit cost than omeprazole - NHS Prescribing Data (January-March 2010) indicate that Omeprazole is the most commonly prescribed PPI, 4.9 million items (unit cost £4.9, total £24.2million), while lansoprazole totalled 3.8 million items, at a somewhat lower unit cost £3, total £11.4 million. www.**nhs**bsa.**nhs**.uk/Documents/Apr_-_Jun_10_Gastro-intestinal.pdf

The clinical side effects of PPI use include rebound hypersecretion after cessation of PPI therapy making it hard to wean some patients off PPIs – and of course reinforcing the notion that they were necessary in the first place (37, 38). Rarer side effects include, pneumonia (39), *Clostridium difficile* (40) infections, acute renal inflammation (41) and fractures of hip, wrist, and spine (42) Nonetheless, PPIs remain popular in the absence of other clear throat symptom treatment choices, despite their cost – hence the timeliness of the present proposal.

7.4 Measuring Treatment response

The most frequently used primary outcome measure in the assessment of persistent, hard to explain throat symptoms is the Reflux Symptom Index (RSI). This 9 item, self-administered questionnaire was introduced a decade ago and is scored on a Likert scale –total score 0-45(14). Our own patient reported outcome measure is the Comprehensive Reflux Symptom Score (CReSS) (15). The CRESS is a 34 item questionnaire of oesophageal and extra-oesophageal 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: gastrointestinal; an upper airway factor – relating to cough, breathing, mucus and hoarseness; and a third, obstruction / choking globus factor. The continuing use of the RSI alongside other variables by ourselves and others has at least allowed the summation of studied in some of the prior attempted evidence synthesis

exercises. One thing 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 patients with a score greater than 10(4). 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, gastro-oesophageal reflux.

Excluding the gastro-oesophageal item, 8% of GP attenders had an RSI over 10 due to the remaining, extra-oesophageal items. In a recent UK population study, there was a similar 7.5% overall prevalence of suspected LPR in adults (4). Our study using CReSS demonstrated wide separation of 103 volunteers, mean score under 7, from 177 throat patients – mean score 31(15).

8. Research Objectives

This is a non-commercial study to determine the clinical effectiveness of the proton pump inhibitor lansoprazole compared with placebo in patients referred to secondary care with persistent throat symptoms.

8.1 Primary Objective:

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

8.2 Secondary Objective:

1. To explore the feasibility of study recruitment by means of an internal pilot trial rehearsal whose data will be included in the main data for analysis.

2. To compare the end of four months' (16 weeks) treatment symptom response with those at 12 months.

3. To determine the utility of the Reflux Symptom Index (RSI) questionnaire, the Comprehensive Reflux Symptom Score (CReSS) questionnaire items and subscales, endolaryngeal examination findings as scored by the Reflux Finding Score, and patient demographics including age; gender; smoking; Body Mass Index (43-45) as potential baseline determinants of treatment response. (Hence generating improved characterisation of the subgroup of suspected LPR patients most likely to benefit from acid suppression therapy).

4. To compare the patient-reported side effects and compliance with treatment and use of any other over-the-counter medication use in both arms.

5. To compare changes in disease-specific quality of life (LPR-HRQL) in the two arms.

9. Study Design

This is a multi-centre, Phase III, randomised, double blind, placebo-controlled trial, with internal feasibility pilot, carried out in secondary care. Patients will be randomised into two parallel streams on a 1:1 ratio stratified by centre and baseline severity (two groups, on the basis of the Reflux Symptom Index score). Following successful demonstration of recruitment in three sites in the internal pilot, a definitive trial will be conducted over 30 months. Patients with persistent throat symptoms will be identified and recruited from Ear Nose and Throat clinics.

9.1 Intervention

The active intervention is a 16 week course of a 30mg twice daily dose of the proton pump inhibitor lansoprazole

9.2 Duration of Study

Feasibility Pilot

We shall originally set up three research sites – Newcastle, Sunderland and Nottingham. Participant recruitment will commence for a total of six months. Each site will be able to recruit 10 participants. At the end of month six we will submit a report to NIHR HTA. Our early stopping criterion [for lack of feasibility] is the failure to recruit 30 patients in the pilot. The process will be overseen by the Data Monitoring and Ethics Committee and the Trial Steering Committee prior to consideration by HTA who will decide whether to release the full funding.

Full Trial

A further 302 participants (332 participants in total) will be recruited over seven centres: Newcastle, Sunderland, Nottingham, Manchester, Brighton, Glasgow and Birmingham.

9.3 Primary outcome measure

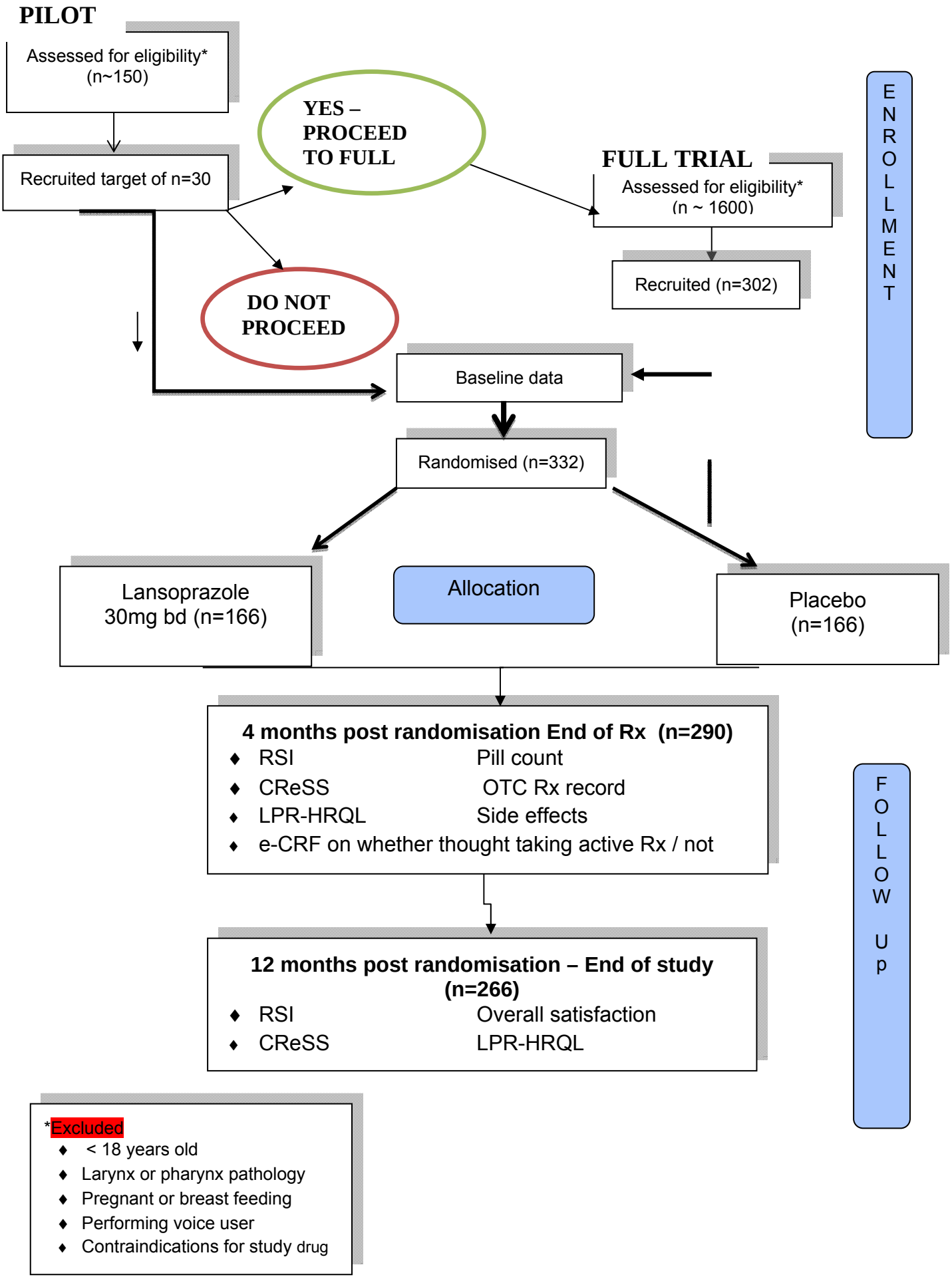
The RSI remains the 'area standard', and despite well–rehearsed limitations (15) remains our chosen primary outcome in the present proposal. Some reported studies have a baseline RSI only just above the normal level, others considerably higher. An observational study of 455 patients in Korea, in whom the mean RSI score fell from 15 at baseline to 5.6 after 12 weeks' of the proton pump inhibitor rabeprazole (17). A baseline RSI scores in a much smaller but comparative study of 62 patients treated with esomeprazole were considerably higher - >20 (14). On the other hand I rabeprazole RCT like the Korean descriptive study had baseline RSI scores around 14 (19), mean baseline RSI scores were closer to those of Lee (around 14). Despite these differences in baseline severity, both of these most recent trials showed a benefit from a three month trial of acid suppression – but Lam (19) continued follow up for a further six weeks, when the effect disappeared, while Reichel's final measurement point was the end of therapy (18).

Throat symptoms impact on general health status measures (20, 21). A tool specifically designed to assess throat symptom patients is the LaryngoPharyngeal Reflux Health Related Quality of life (LPR HRQL) tool (22, 23), which has also been validated in a Swedish population (24). Its 43 items are grouped into four domains and an overall impact category and the tool appears responsive to change (11).

The change in Reflux Symptom Index (RSI) at four months in the treatment and placebo groups in an intention to treat analysis. The 9 item RSI allows comparison with previous studies as it offers ten years' of comparative data in the literature. We plan however to report both the total score (0-45) and the score omitting the heartburn item (0-40), which we and others note can skew the results in favour of PPI in past small trials. Inclusion of the total RSI aligns our output with other publications which have not taken separate account of the RSI heartburn item. Our proposed analysis will also address the issue of presentation of simple mean end scores in other papers, with wide deviations and often with a mean out with the normal reference range. We shall further explore this outcome according to our stratification variables of centre and baseline severity.

9.4 Secondary outcome measures

- RSI changes as above, at twelve months after randomisation.
- Quality of life: Change in LPR-HRQL total score and subscale at four and twelve months.
- Laryngeal mucosal changes - increased 'Reflux Finding' Scores – are widely prevalent in both normal volunteers (64 - 86%) (25) and in throat symptom patients (38-51%). The best predictor of EOR is pseudosulcus (67-90% positive predictive value) (26, 27), but this is a rare finding. We propose to assess the RFS scored 0-29 by an independent observer, blind to treatment group as a response predictor, alongside patient characteristics – age; gender; smoking; Body Mass Index and the total and the Comprehensive Reflux Symptom Score (CReSS) total and three subscales – oesophageal (14 items), upper airway (8 items) and pharyngeal (7 items).
- Estimates of compliance (pill count), side effects. Current and/or planned use of over the counter medication.
- Patient reported satisfaction.


PILOT
Assessed for eligibility* (n~150)
Recruited target of n=30
YES – PROCEED TO FULL
DO NOT PROCEED
FULL TRIAL
Assessed for eligibility* (n ~ 1600)
Recruited (n=302)
ENROLLMENT
Baseline data
Randomised (n=332)
Lansoprazole 30mg bd (n=166)
Allocation
Placebo (n=166)
4 months post randomisation End of Rx (n=290)
RSI
CReSS
LPR-HRQL
e-CRF on whether thought taking active Rx / not
Pill count
OTC Rx record
Side effects
12 months post randomisation – End of study (n=266)
RSI
CReSS
Overall satisfaction
LPR-HRQL
FOLLOW Up
*Excluded
< 18 years old
Larynx or pharynx pathology
Pregnant or breast feeding
Performing voice user
Contraindications for study drug

9.5 Definition of end of study

The end of study will be the last participant's final study contact, at twelve months follow up.

10. Participant Population.

Participants will be adult patients newly referred to secondary care otolaryngology clinics with persistent (over six weeks) unexplained throat symptoms, principally dysphonia, throat pain, globus sensation (feeling of something stuck in the throat), throat clearing, post nasal drip or mucus excess, also night time unexplained cough or choking.

10.1 Inclusion criteria

- Referred with a persistent (over six weeks) primary throat symptom – globus, hoarseness, throat clearing, throat discomfort, choking spasms excess mucus/postnasal drip, otherwise unexplained night time cough or choking.
- Score of 10 or more on the non-heartburn items of the Reflux Symptoms Index (RSI).
- Patient has capacity to provide fully informed consent to participate in the study.

10.2 Exclusion criteria

- Those with an RSI score excluding the lower GI item of less than 10
- Patients who are not willing to undergo flexible endoscopy could not by definition be included.
- Inability to complete the relevant questionnaires.
- Patients under 18 years old.
- Endoscopic evidence of specific laryngopharyngeal pathology that would ordinarily be treated by surgical intervention or be investigated by specific investigations. This includes suspected neoplasia/ dysplasia, prominent Reinke's oedema or unilateral vocal fold polyp, vocal cord palsy, and rarities such as amyloid, Wegener's, sarcoid.
- Confirmed or likely, current or prior malignancy of head and neck or oesophagus.
- Performing voice users including singers, actors, media workers (e.g. voice-over artists, radio DJs).
- Pregnant or lactating woman. Woman of child bearing potential must be using adequate contraception.
- Currently on acid suppressant, acid neutralisers and alginates and unwilling to discontinue for a four weeks pre study washout period (PPI); 24 hours for alginate or acid neutraliser. For those discontinuing PPI, ad hoc alginate use is allowed until the final 24-48 hours of the washout period prior to reassessment.
- Prior adverse reaction to proton pump inhibitor.
- Severe hepatic dysfunction.
- Patients taking clopidogrel or warfarin
- Patients taking Phenytoin.
- Patients taking systemic antifungal treatment (specifically itraconazole, ketoconazole, posaconazole and voriconazole).

- HIV positive/ patients taking Antiviral medications (atazanavir, nelfinavir, raltegravir, saquinavir, tipranavir).
- Patients taking digoxin, cyclosporine, methotrexate, erlotinib, lapatinib, tacrolimus, sucralfate, escitalopram, fluvoxamine, St John's wort, clozapine, Ulipristal or Cilostazol.
- Previous participation in this study.
- Use of other investigational study drugs within 30 days prior to study entry.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS MUST NOT BE USED.

11. Screening, Recruitment and Consent

11.1 Identification and screening of participants

Potential participants may be identified through routine clinic outpatient appointments by their treating physician (the PI at site, or a colleague). There will be more than ten consultants at some of the recruiting sites, who may initially be referred potential participants. The PI and colleagues will ensure that all physicians are informed about the nature and purpose of TOPPITS.

At the initial clinic appointment a routine consultation and clinical examination will take place. Any patient with persistent throat symptoms will be asked to complete the RSI form and the total, less the heartburn item computed. If a patient scores 10 or more non heartburn items the physician will inform the patient of the trial and offer them participation.

If a patient scores 10 or more on the RSI-HB, and is interested in the TOPPITS trial, he/she will be given a PIS, watch a DVD explaining study procedures and be invited to attend a dedicated TOPPITS clinic at a subsequent date convenient for them, arranged by the Research Nurse. A screening log will be completed for all potential participants screened, including reasons for ineligibility and / or refusal to participate.

Potential participants may also be screened using their primary care referral letters. PIs at site will be responsible for posting invite letters and Patient Information Sheets to these potential participants. Patients will also watch the trial information DVD. These patients will be booked straight onto a TOPPITS trial clinic.

11.2 Recruitment

Eligible patients who have received the PIS through the routine clinic outpatient appointment or through the invite process will then attend a dedicated TOPPITS trial clinic, where any outstanding queries will be answered, followed by an invitation to participate by the consultant or research nurse. They will have already received the PIS and watched the study DVD. They will be given time to discuss the study further in this clinic. Those wishing to have further time to consider may attend a subsequent clinic, if they decide to participate at a later stage. At the first trial clinic appointment, eligibility will be confirmed by the investigator, for all patients considered for the study and subsequently included or excluded.

11.3 Consent

Informed consent discussions will be undertaken, and consent obtained, by appropriately-delegated site study staff (this will be documented on the Delegation Log), including medical staff and Research Nurses. The Consent Form will be signed and dated by the participant and the member of site staff obtaining consent.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant will specifically consent to his/her GP being informed of his/her participation in the study.

The right to refuse to participate without giving a reason must be respected.

Consent should be obtained prior to any washout period required, which in turn will be prior to randomisation.

Patients taking acid suppressants, acid neutralizers or alginates prior to involvement in/being approached to take part in the TOPPITS trial must undergo a four week washout period of

PPIs, or 24 hours for alginates or acid neutralisers, before they start taking TOPPITS trial medication (prescribed as part of Clinic Visit 1). Participants will be provided with a 'washout period card' confirming when the washout period started, in case they attend a GP or clinic appointment prior to Visit 1. This card can then be shown to the GP/consultant to try and ensure the participant does not take/is not prescribed acid suppressants, acid neutralizers or alginates.

Due to the small subject population, the Patient Information Sheet, Consent Form and questionnaires for the study will be available only in English. Interpreters may be arranged for all visits of patients who require them either for verbal translation or for hearing impaired subjects wishing to take part in the study, via local NHS arrangements. As per local custom, qualified interpreters may be used to explain the consent form and information sheet, and finding the most direct communication will be a priority.

12. Study Medication / Intervention Details

12.1 Intervention

Randomisation to treatment group will be in a 1:1 ratio. Full details of the allocation method are given in section 13.

Participants will receive either 60mg lansoprazole daily (divided into 2 equal daily doses) or placebo (divided into 2 equal daily doses) for 16 weeks.

12.2 Study Drug

The basis for the Investigation Medicinal Products (IMPs) is commercially available lansoprazole 30mg gastro-resistant capsules. (Marketing Authorisation PL 30306/0149). These are available as plain white (no markings) gelatine gastro-resistant capsules filled with white to off-white enteric-coated pellets. For purposes of blinding, placebo matched capsules will be manufactured using standard white gelatine capsules (not DR/enteric coated) containing white to off-white sugar spheres.

12.3 Manufacture

MODEPHARMA is responsible for arranging the IMP's manufacture as well as project management and assistance relating to the IMPs for the trial. The IMP packaging/manufacturing and final QP release for clinical trial use will be undertaken by Piramal Healthcare UK Ltd, a clinical supplies company licensed for the manufacture and release of IMPs by the MHRA (MIA-IMP 29595).

The lansoprazole 30mg capsules will be procured from approved commercial wholesale channels and repacked in a trial specific way. The matching placebo capsules will be formulated and manufactured by Primal Healthcare and subsequently also packaged in a trial specific way, identical to the active capsules.

The study medication will be shipped directly from Piramal to the trial sites following site initiation.

Please refer to the Summary of product Characteristics and Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo product.

12.4 Storage

Investigators must store study medication in a safe controlled place with no access for unauthorised personnel. Trial medication will be stored in a secure and controlled environment at ambient temperature,

Investigators will provide patients with instructions on how to store the medication at home. Trial participants will be advised to store medication at ambient temperature and out of the reach of children.

12.5 Study administration

The study medication (IMPs) will be labelled according to the requirements of Annex 13. Following site initiation, IMPs will be received at the trial sites from the final Qualified Person releasing site at Piramal Healthcare UK Ltd. Study medication is for use by trial participants only.

All active and placebo capsules will be blister packed and subsequently placed in randomised treatment packs for 332 patients in two groups. Each patient will receive 1 x 16 week packs each containing 238 capsules. Each of the treatment packs and corresponding blisters will be labelled according to Annex 13 guidelines. All blisters and treatment packs will bear unique randomisation numbers and the randomisation system will allocate the correct treatment pack to a patient during the trial. The study medication will be dispensed at visit 1 (Randomisation).

Side effects will be documented by the participant throughout the course of the trial and will be assessed by the clinical team

Study medication will be prescribed by a study clinician according to the protocol, and dispensed to the patient or clinical staff according to local pharmacy policy. Patients in possession of their study medication shall return all trial supplies in their original packaging (even if empty) to the study clinician or Pharmacist at visit 3 (four month follow-up visit). All returned, or unused, study medication will be stored in Pharmacy until the end of the study, or until the Trial Manger has completed appropriate reconciliation.

At the end of the study, any surplus or unused stock will be reconciled and destroyed.

Documentation of prescribing, dispensing and return of study medication shall be maintained for study records.

12.6 Concomitant Medication

For management of concomitant therapies, please refer to the lansoprazole Summary of Product Characteristics. A complete listing of all concomitant medication received during the treatment phase must be recorded for study purposes.

12.7 Early Termination

Patients withdrawing or withdrawn from the study should complete final study assessment in the form of an early termination visit. This visit should include all of the twelve month assessments if possible.

13. Randomisation

A blocked allocation (permuted random blocks of variable length) system will be used to allocate patients in a 1:1 ratio stratified by centre and baseline severity (two groups, on the basis of the Reflux Symptom Index score). Block size will not be disclosed to the investigators and the computer-generated allocation list will be produced by an individual not otherwise involved with the study in order to ensure concealment of allocation. Randomisation will be administered centrally via Newcastle Clinical Trials Unit using a secure web based system. The PI or delegated personnel named on the delegation log will obtain the randomisation number via this system (http://apps.ncl.ac.uk?random/ - available 24 hours a day).

Details of a nominated CTU contact for randomisation will be notified to sites.

Randomisation will generate a treatment number for each participant that links to the corresponding allocated study drug (blinded), in accordance with block size and strata. The treatment number must be clearly documented by the investigator on the trial prescription to ensure the study pharmacist dispenses the correct study medication

14. Blinding

Assignment to either lansoprazole or placebo arm will be blinded to both the participant and investigators/assessor (double-blind). A set of sealed code-break envelopes will be kept either in pharmacy or in the site file at participating hospitals; these envelopes should be opened only in an emergency, with authorisation from the Chief Investigator. If the code is broken, details including the participant number, who broke the code, why and when shall be recorded and maintained in the site file. Code breaks will not be routinely opened for participants who complete study treatment. Following a code break, should a clinician wish to supply clinical lansoprazole, this must then be supplied from normal routine pharmacy stock and not clinical trial supplies.

At the final visit, the integrity of the blind will be assessed by asking the participant: “Do you think you were taking lansoprazole or the dummy pill? Why do you think this?”

The blind should be maintained until all the trial data have been collected and the database locked. Upon reaching this point participants will be unblinded and informed as to whether they received lansoprazole or placebo. If participants in the lansoprazole arm wish to continue to take lansoprazole, this decision will be made in consultation with their treating clinician. Patients on placebo may wish to take lansoprazole; again this decision will be made in consultation with their treating clinician.

15. Study Data

15.1 Assessments/Data Collection

Screening
Potential participants will either have an initial consultation with an Ear, Nose and Throat clinician following primary care referral for assessment of throat symptoms. This consultation is likely to be with a clinician not directly involved in recruitment. If the patient's RSI (minus heartburn score) is greater or equal to 10 then the patient will be informed about the TOPPITS study. If the patient is initially interested, then a Patient Information Sheet will be provided and an appointment made at the dedicated TOPPITS clinic. Patient details will be relayed to the PI and research nurse to organise the clinic appointment. In some centres potentially suitable patients may be identifiable through scrutiny of referral letters. In that event, the PIS is posted out ahead of the clinic and the patient booked directly to the TOPPITS screening clinic.

Potential participants may also be screened using their primary care referral letters. The PI at site will be responsible for sending out an invitation letter and Patient Information Sheet to the patients in the post, detailing the study. These patients will be booked straight onto a TOPPITS clinic.

TOPPITS Clinic Visit 1 - Consent and Randomisation

A suitable appointment for the patient will be made for the TOPPITS clinic to see the PI, or clinician on the delegation log, and research nurse. Further verbal information will be offered about the trial and patient questions answered. As the Patient Information Sheet was previously provided and the patient has willingly attended the TOPPITS clinic, consent, randomisation and provision of medication can occur at this visit. If the patient wishes further time to consider, then a second appointment can be arranged at a later date. If the patient wishes to take part in the study the following measures will be taken following written consent:

- Body Mass Index
- Standardised Medical History Proforma to include:
  - Age / Sex
  - Smoking status (pack years for current or ex-smokers)
  - Alcohol consumption
  - Past Medical History
  - Current Medications
  - (Record if used a PPI in the last 12 months. Check stopped PPI if previously taking one)
  - Allergies
- Completion of the questionnaires:
  - Reflux Symptom Index
  - Comprehensive Reflux Symptom Score
  - Laryngopharyngeal Reflux Health Related Quality of Life

Laryngoscopy assessment of the larynx and pharynx will be performed by the clinician using a laryngoscope. Local anaesthetic and decongestant spray will be offered to all patients. An

image will be taken to allow an independent clinician to score the appearances using the Reflux Finding Score at a later date. This image will be anonymised and securely stored and transferred. Where possible all imaging will be by a videoendoscope (digital) camera.

The patient will then be randomised via the NCTU online randomisation system and receive four-month supply of active Lansoprazole 30mg bd or matched placebo bd. Patients previously taking a PPI must have been off the medication for four weeks before taking the study medication.

A standard throat symptom advice sheet will be offered to all participants.

TOPPITS Clinic Visit 2 - Follow-up 1

This will occur four months following recruitment and be conducted in the TOPPITS clinic. Patients will be phoned and reminded by the research nurse to return medication packaging to facilitate a pill count. This will be recorded.

- Completion of the questionnaires will be repeated:
  - Reflux Symptom Index
  - Comprehensive Reflux Symptom Score
  - Laryngopharyngeal Reflux Health Related Quality of Life
- e-CRF on whether patient is thought to be taking study drug or placebo

A further examination of the throat will not take place.

Information will be gathered on adverse events.

Information will be gathered on reasons for stopping medication if appropriate and whether any other over the counter or prescription medication have been used in the previous four month related to throat or upper gastrointestinal symptoms. It will also be recorded which treatment arm the clinician believes the participant received during the trial.

TOPPITS Clinic Visit 3 - Final Follow-up

This will occur twelve months following recruitment and be conducted in the TOPPITS clinic.

- Completion of the questionnaires will be repeated:
  - Reflux Symptom Index
  - Comprehensive Reflux Symptom Score
  - Laryngopharyngeal Reflux Health Related Quality of Life

A further examination of the throat will not take place unless clinically indicated out with the study context.

Information will be gathered on whether any other over the counter or prescription medication have been used in the previous eight months related to throat or upper gastrointestinal symptoms, and an overall satisfaction scale recorded.

15.2 Table of Events

Time	Additional Visit for GP Referrals only Basic assessment of eligibility and interest	All participants Visit 1 TOPPITS Baseline visit Confirmation of eligibility, consent and Randomisation	All participants Visit 2 Follow-up 1	All participants Visit 3 Final Follow-up
	Screening +/-2-4 weeks	Consent and Randomisation	Month 4 +/- 2 weeks	Month 12 +/- 2 weeks
Study Discussed in outline / detailed PIS & DVD viewed	X	X		
Informed Consent		X		
Medical History		X		
RSI questionnaire	X	X	X	X
CReSS Questionnaire		X	X	X
LPR-HRQL Questionnaire		X	X	X
Video laryngoscopy digital image capture for later independent RFS scoring by expert blind to participant study group		X		
Randomisation (after all eligibility checked)		X		
Study medication dispensed		X		
Study medication returned			X	
Adverse events			X	X
Concomitant medications		X	X	X

15.3 Data Handling and Record Keeping

Data that is collected as part of this study is under the responsibility of the Chief Investigator, Professor Janet Wilson.

Data will be recorded by authorised site staff on electronic Case Report Forms (eCRF) to allow statistical analysis of the study to take place. Data transferred from site to the secure validated database by remote access will be secure and encrypted.

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site and patients will be identified by a unique study number.

Caldicott approval will be sought to enable the collection of personal identifiable information as part of this study i.e. during the consenting process.

The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be retained in accordance with the NCTU SOP NCTU:DM-006 Data Security and local policy.

16. Statistical Considerations

16.1 Statistical Analysis

The primary outcome measure of change in RSI score after four months will be analysed using analysis of covariance (ANCOVA) methods in order to compare the change in RSI between the trial arms while adjusting for potential confounders including the stratification variables used at randomisation of centre and baseline severity (as defined by the binary RSI cut off) as covariates in the analysis. We will also consider adjusting for gender, age, Body Mass Index, baseline laryngeal appearance scores by the RFS, and categories of symptoms. Not all covariates mentioned above will necessarily be included in the final model but will be considered during the model selection process.

Should data be found to be non-Normally distributed the use of transformations or non-parametric approaches will be considered although as ANCOVA is generally robust to departures from Normality the above approach is likely to be followed. More basic exploratory analyses may be undertaken using the 2-sample t-test or non-parametric alternatives.

The analysis of secondary outcomes will follow a broadly similar strategy when considering questionnaire scores or the change in questionnaire scores. The proportion with follow-up RSI scores within versus out with the published normal range will be analysed using a logistic regression approach, once more adjusting for the covariates as described for the primary outcome above.

The primary analysis will be carried out on an intention-to-treat basis; other analysis groups, such as per-protocol, may be considered subsequently. Outcome data will be analysed at the end of the study. There are no planned interim analyses and a full statistical analysis plan will be developed prior to the start of analysis. Safety data will not be subject to statistical analysis. Data with missing observations due to loss to follow-up will be examined to determine both its extent and whether it is missing at random or is informative. If data is missing to a sufficient extent, the use of appropriate multiple imputation techniques will be considered.

16.2 Sample Size Calculation

The primary outcome measure is the change in the RSI score from baseline to the four month assessment. We believe a clinical effect of 0.4 (equivalent to a difference in change of RSI of 3.1 given an SD of 7.7 (47)) is a reasonable target based on prior LPR therapy studies. Further, a 0.4 effect size is of smaller magnitude than the effect of phonomicrosurgery or speech therapy. A similar effect size is predicted from the more limited amount of published data available on the LPR-HRQL. For a 2-sample t-test, 90% power and at the 0.05 significance level, allowing for 20% loss to follow-up, we require 332 patients (166 in each arm of the study) to give 266 (133 in each arm) completing the study. The figure of 20% we believe is a more realistic estimate. There are two other fairly recent reports of LPR drug studies with under 7% drop out rates. Our NHS experience, however, suggests that this is overly optimistic for a trial of this kind. As the literature is well populated with underpowered low impact studies, we prefer to err on the side of caution and hence our sample allows for a 20% attrition rate, [this is a somewhat higher attrition than in the original submission as we feel the required loss of the two month review will distance some participants from the process. Also the final follow-up is now six months' more remote from the end of therapy]. As stated elsewhere, however, if recruitment and retention exceed our prediction, we are in a position to close recruitment in advance of the planned stop date.

Participant recruitment into the pilot phase will be for a total of six months. We estimate that each site will be able to recruit 10 participants per three month block once the study is established. However, as research studies usually take some time to become embedded into practice, we have calculated recruitment across the whole trial based on lower recruitment in in three sites during the first six months. Our predicted recruitment allows for each of the three sites to recruit at 30% (three patients) in the first three months, and 70% (7 patients) in the second three months. We aim for those three sites to be recruiting to full target (10 patients per three months) thereafter in the main trial, with equivalent run in for the remaining three sites.

As discussed, our six month pilot aims to recruit a minimum of 30 participants, who are retained in the main study until the final 12 months' review of the main study. Thereafter the first three centres should be in a position to randomise one patient most weeks for 60 clinics during the 18 months of trial recruitment = a further 180 patients; while the three later recruiting centres will recruit over 16 months and assuming that their recruitment will also be at a lower rate initially, these three sites should be able to recruit a minimum of 122 in that period (30 + 180 + 122 = 332), perhaps slightly more. In other words the revised strategy offers a realistic prospect of comfortably achieving the required number of main trial participants.

17. Compliance and Withdrawal

17.1 Assessment of compliance

Where feasible, visit windows of +/- 14 days should ensure visit attendance; non-attendance for study visits will prompt follow-up by telephone.

Compliance with study medication will be assessed by checking and recording the remaining number of capsules at the end of therapy by a member of the study team. Study drug accountability will be assessed and documented by local pharmacy before being destroyed.

17.2 Withdrawal of participants

Study drug must be discontinued if:

- the participant decides they no longer wish to continue
- cessation of study drug is recommended by the investigator

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study drug in the event of intervening pregnancy, inter-current illness, Adverse Events, Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from study medication will be asked to confirm whether they are still willing to provide the following.

- Study specific data at follow-up visits four months and twelve months
- ‘End of study data’ as per visit at twelve months, at the point of withdrawal
- If participants agree to any of the above, they will be asked to complete a confirmation of withdrawal form to document their decision.

Participants who withdraw from the study will not be replaced.

18. Data Monitoring, Quality Control and Quality Assurance

18.1 Discontinuation rules

An internal pilot has been incorporated to function as a feasibility study and a TOPPITS trial rehearsal. The stop criterion is failure to recruit 30 patients in six months at three sites. The process will be overseen by The Data Monitoring and Ethics Committee and the Trial Steering Committee prior to consideration by HTA who will decide whether to release the full funding

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring & Ethics Committee and/or Trial Steering Committee, Sponsor, regulatory authority or ethics committee concerned.

18.2 Monitoring, quality control and assurance

The trial will be managed through Newcastle Clinical Trials Unit. The Trial Management Group (TMG) will include:

Professor Janet Wilson (Chief Investigator), Mr James O'Hara (Co-Investigator), Dr Nick Steen (Trial Statistician), Dr Lesley Hall (Senior Trial Manager) and Miss Gillian Watson (Trial Manager).

The Principal Investigators will be responsible for the day-to-day study conduct at site.

Newcastle Clinical Trials Unit will provide day-to-day support for the sites and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

Quality control will be maintained through adherence to Newcastle Clinical Trials Unit's SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

A brief overview of the monitoring plan should be provided in the study protocol (specific details may be further outlined in a separate monitoring plan document).

18.3 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC) (two physicians not connected to the trial, one statistician) will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMEC will have access to unblinded study data. The committee will meet at least three times, at the start, middle and end of the study.

The DMEC will be chaired by Dr John de Caestecker, a consultant gastroenterologist at Leicester General Hospital. The independent clinician will be Mr Kim Ah See, a consultant ENT Head and Neck surgeon at Aberdeen Royal Infirmary. The Independent statistician is to be confirmed.

18.4 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial. The remit of the TSC will be in line with HTA expectations as follows:

- To provide advice, through its Chair, to the Chief Investigator, the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.

- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.
- To ensure the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.
- To ensure appropriate ethical and other approvals are obtained in line with the project plan.
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments.
- To provide advice to the investigators on all aspects of the trial.

The TSC will be chaired by Professor Robert C. Heading, honorary Professor in the School of Medicine, Pharmacy and Health at Durham University. The Independent clinician will be Mr Iain Swan, a Clinical Senior Lecturer in Surgery at the University of Glasgow and honorary Consultant ENT Surgeon at Glasgow Royal Infirmary. Two independent lay members, Mr Philip Pickard and Mr Mark Pope have agreed to be on the TSC along with independent statistician Dr Victoria Allgar. Also on the TSC will be the Chief Investigator, Professor Janet Wilson, Co-Investigator Mr James O'Hara, the study statistician, Senior Trial Manager and Trial Manager. Observers from the HTA and a representative of the Sponsor will be invited to all TSC meetings and will receive minutes of TSC meetings regardless of attendance.

The TSC and DMEC will meet during the pilot phase. Any recommendations they make to discontinue the trial, continue or continue with changes will be followed.

18.5 Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the Trial Manager. The main areas of focus will include consent, Serious Adverse Events, essential documents in study files and drug accountability & management.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study file. The presence of a copy in the patient hospital notes will be confirmed for 100% participants.
- All original consent forms will be compared against the study participant identification list.
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification).
- The presence of essential documents in the investigator site file and study files will be checked.
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study.
- Drug accountability and management will be checked.

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission.

- All documentation essential for study initiation will be reviewed prior to site authorisation.

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as Sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit trial-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents. Written confirmation from participants to accept this level of monitoring and access by researchers, in confidence, to their medical records, will also be incorporated on the study Consent Form.

19. Pharmacovigilance

19.1 Adverse event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, “treatment” includes all investigational agents (including placebo) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

19.2 Adverse Reaction (AR)/Adverse Drug Reaction (ADR)

Any untoward and unintended responses to an Investigational Medicinal Product (IMP) which related to any dose administered to that subject. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as Adverse Reactions. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship.

19.3 Causality

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All AEs judged as having a reasonable suspected causal relationship to the IMP(s) (i.e. definitely, probably or possibly related) are considered to be Adverse Reactions. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

19.4 Unexpected Adverse Reaction

An Adverse Reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:- (a) In the case of a product with a marketing authorisation, in the Summary of Product Characteristics for that product; (b) in the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question.

19.5 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An Adverse Event, Adverse Reaction or Unexpected Adverse Reaction, respectively, that (at any dose)-

- Results in death
- Is life-threatening (refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

19.6 Suspected, Unexpected Serious Adverse Reaction (SUSAR)

An Adverse Reaction that is both unexpected and serious. An Adverse Reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information.

19.7 Severity (intensity) of Adverse Events and Adverse Reactions

Severity of all AEs and ARs will be graded on a three-point scale of intensity (mild, moderate, severe):

- Mild: Discomfort is noticed, but there is no disruption of normal daily activities.
- Moderate: Discomfort is sufficient to reduce or affect normal daily activities.
- Severe: Discomfort is incapacitating, with inability to work or to perform normal daily activities.

An AE or AR may be severe but not serious.

19.8 Expected Adverse Reactions:

Most Adverse Events and Adverse Drug Reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drug used in this study. The side effects for lansoprazole are shown below in the table.

Adverse drug reactions such as dizziness, vertigo, visual disturbances and somnolence may

occur (see table below). Under these conditions the ability to react may be decreased.

Frequencies are defined as common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

	Common	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders		Throm-bocytopenia, eosinophilia, leucopenia	Anaemia	Agranulocytosis, pancytopenia	
Metabolism and nutritional disorders					Hypomagnesaemia
Psychiatric Disorders		Depression	Insomnia, hallucination, confusion		
Nervous system Disorders	Headache, dizziness		Restlessness, vertigo, paraesthesia, somnolence, tremor		
Eye disorders			Visual disturbances.		
Gastrointestinal Disorders	Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat		Glossitis, candidiasis of the oesophagus, pancreatitis, taste disturbances	Colitis, stomatitis	
Hepatobiliary disorders	Increase in liver enzyme levels		Hepatitis, jaundice		
Skin and subcutaneous tissue disorders	Urticaria, itching, rash		Petechiae, purpura, hair loss, erythema multiforme, photosensitivity	Stevens-Johnson syndrome, toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia Fracture of the hip, wrist or spine			
Renal and urinary disorders			Interstitial nephritis		

Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Fatigue	Oedema	Fever, hyperhidrosis, angioedema, anorexia, impotence	Anaphylactic shock	
Investigations				Increase in cholesterol and triglyceride levels, hyponatremia	

Rebound acid hypersecretion and protracted dyspepsia may occur after stopping prolonged treatment with a proton pump inhibitor.

For a full list of expected undesirable effects of lansoprazole, please refer to the Summary of Product Characteristics for lansoprazole.

19.9 Protocol Specifications

For purposes of this protocol:

- All non-Serious Adverse Reactions will be recorded at Visits 3 and 4.
- Any Serious Adverse Events will be recorded throughout the duration of the trial until four weeks after trial therapy is stopped
- Serious Adverse Events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration.
- Serious Adverse Events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Serious Adverse Events exclude elective or scheduled treatment for pre-existing conditions that did not worsen during the study.

19.10 Recording & Reporting Serious Adverse Events or Reactions:

All Adverse Events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning Adverse Event reporting should be directed to the Chief Investigator in the first instance. A flowchart (figure 1) is given below to aid in the reporting procedures.

19.11 Adverse Event (including Adverse Reaction):

All non-Serious Adverse Events / Reactions during drug treatment will be reported on the study CRF and sent to Newcastle Clinical Trials Unit within four weeks of the form being due. Severity of AEs will be graded on a three-point scale (mild, moderate, severe). Relation of the AE to the treatment should be assessed by the investigator at site. The individual

investigator at each site will be responsible for managing all Adverse Events / Reactions according to local protocols.

19.12 Serious Adverse Event / Reaction (SAE/SAR, including SUSARs):

All SAEs, SARs & SUSARs during drug treatment shall be reported to the Chief Investigator within 24 hours of the site learning of its occurrence. The initial report can be made by completing a specific structured SAE reporting form and sending it either by fax, email or electronic equivalent (SoHo66 fax to email system) the electronic Serious Adverse Event CRF which will automatically send email notification to the Chief Investigator, Senior Trial Manager, Trial Manager and Sponsor. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to the treatment should be assessed by the investigator at site, as should the expected or unexpected nature of any Serious Adverse Reactions.

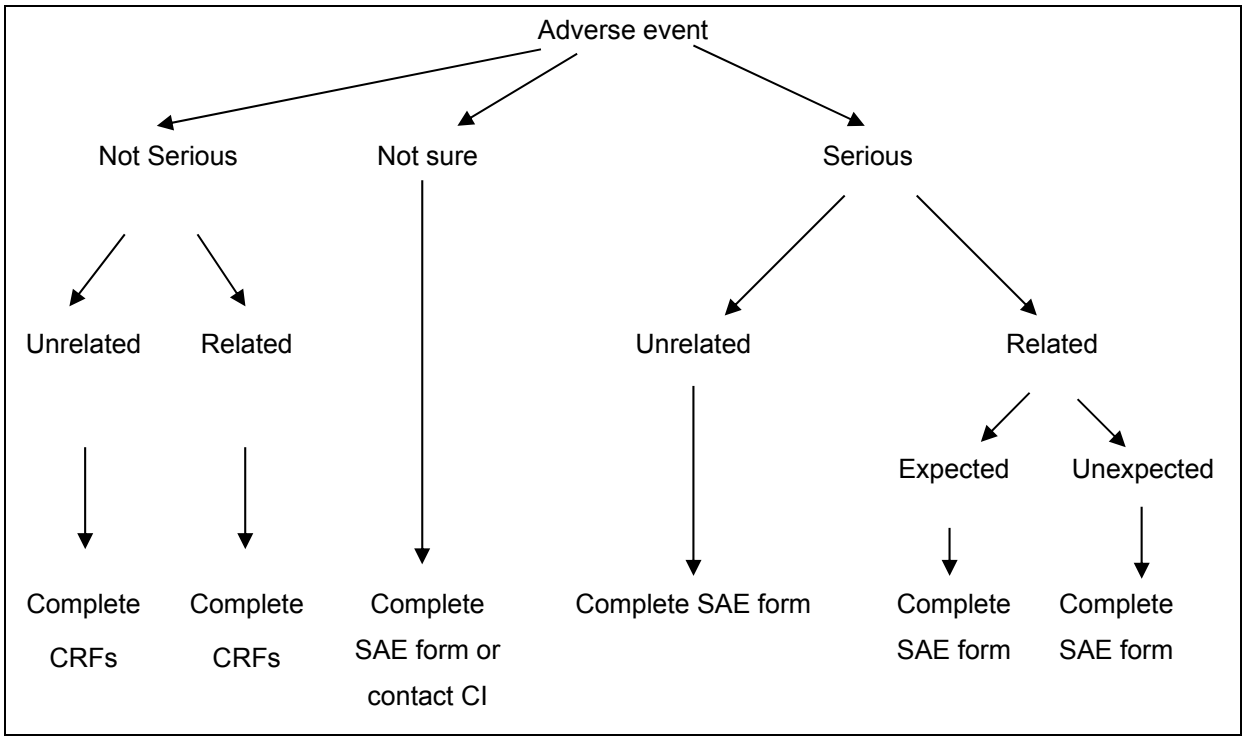
The MHRA and main REC will be notified by the Trial Management Team (on behalf of the Sponsor) of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. SUSARS will be reported using a CIOMS 1 form, specifying the EudraCT number, CTA number, protocol number and study name, and the data elements listed in Annex 3 of Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006.

All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis.

The Chief Investigator will ensure The Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SUSARs in accordance with local trust policy.

Local investigators should report any SUSARs and / or SAEs as required by their local Research & Development Office.

Figure 1



Contact details for reporting SAEs and SUSARs
Please send SAE form(s) via [Fax: 01915800039/electronic CRF]
or
Tel: 01912083819 (Mon to Fri 08.00– 16.00)

19.13 Pregnancies

If a female participant does become pregnant while participating in the trial, study drug(s) will be discontinued immediately. Details of the pregnancy should be reported to the Chief Investigator within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome. Additional follow-up will no longer be required once the infant is determined to be healthy.

20. Ethics & Regulatory Issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. All members of the research team and the investigators at each of the participating sites will be trained in those aspects of Good Clinical Practice appropriate to their role in the trial.

A favourable ethical opinion and Clinical Trial Authorisation from relevant Competent Authority(ies) will be sought prior to commencement of the study. Local approvals will be sought before recruitment may commence at each site. The Newcastle Clinical Trials Unit in its capacity as The Study Coordination Centre will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets will be provided to all eligible subjects. Eligible subjects may also be shown a DVD that explains more about the study. Written informed consent will be obtained prior to any study procedures.

21. Confidentiality

21.1 Safeguarding confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by a unique study identification code only. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

21.2 Long term data storage

At the end of the study, original questionnaires, Case Report Forms and Consent Forms will be securely archived for 15 years following publication of the last paper or report from the study, in line with Sponsor policy and Standard Operating Procedures. This will allow any queries or concerns about the data, conduct or conclusions of the study to be resolved.

22. Insurance and Finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

NIHR Health Technology Assessment Programme is funding the study.

23. Study Report / Publications

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review articles and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report.

Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results, on which the TOPPITS user forum patient involvement group will take a lead.

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