

Helicobacter eradication to prevent ulcer bleeding in aspirin users: a large simple randomised controlled trial

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SYNOPSIS

Title	Helicobacter eradication to prevent ulcer bleeding in aspirin users: a large simple randomised controlled trial
Acronym	HEAT
Short title	Helicobacter Eradication Aspirin Trial
Chief Investigator	Prof Christopher Hawkey
Objectives	<p>The research has three primary objectives:</p> <ol style="list-style-type: none"> 1. Medical: To test the hypothesis that a one week course of <i>Helicobacter pylori</i> (<i>H. pylori</i>) eradication in patients using aspirin ≤ 325mg daily will reduce the incidence of subsequent adjudicated peptic ulcer bleeding that results in hospitalisation. 2. Economic: To test the hypothesis that the intervention has a positive net monetary benefit. 3. Methodological: To establish a methodology for large simple outcomes studies using electronically extracted Primary Care follow-up data, to reduce costs to a level that enables outcomes studies of clinically important questions to be done without the need for industry support.
Trial Configuration	Double-blind, placebo-controlled randomised multi-centre study
Setting	Primary Care
Sample size estimate	The sample size calculation assumes event rates of 4 per 1000 per year in the intervention arm and 8 per 1000 per year in the control arm, giving an incidence rate ratio of 0.5 comparing the intervention with the control arm. With a 5% two sided significance level and 90% power then a total of 87 events are required to detect this. Using the assumed event rates then 8000 person-years are required per study arm to obtain this number of events. With an average of 2.5 years of follow-up then 3300 participants are needed per study arm (6600 total). This accounts for a 2% loss to follow-up rate.
Number of participants	From our pilot study we expect 33,000 to respond (from 170,000 invited) and that ~6,600 will be <i>H. pylori</i> positive; 3300 of these will be randomised to eradication treatment and 3300 to placebo.
Eligibility criteria	<p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Males and females ≥ 60 years of age at the date of screening. 2. Subjects who are taking aspirin ≤ 325mg daily and who have had 4 or more 28-day prescriptions in the last year. 3. Subjects who are concurrently using other anti-platelet agents are allowed to enter the study.

	<ol style="list-style-type: none"> 4. Subjects who are willing and able to undergo a breath test for <i>H. pylori</i>, including fasting for 6 hours, and whose result is unequivocally positive (results of breath test will be determined post-screening). 5. Subjects who are willing to give permission for their paper and electronic medical records to be accessed and abstracted by trial investigators. 6. Subjects who are willing to be contacted and interviewed by trial investigators, should the need arise for adverse event assessment, etc. 7. Subjects must be able to communicate well with the investigator or designee, to understand and comply with the requirements of the study and to understand and sign the written informed consent. <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Subjects who are currently prescribed proton-pump inhibitors or H2-receptor antagonists. 2. Subjects who are currently prescribed oral non-steroidal anti-inflammatory drugs (NSAIDs). 3. Subjects who have a known intolerance or allergy to <i>H. pylori</i> eradication treatment. 4. Subjects who are taking drugs with a clinically significant interaction with <i>H. pylori</i> eradication treatment (see Appendix 3). 5. Subjects who are terminally ill or suffer from a life-threatening co-morbidity. 6. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication (eg. alcoholism, substance abuse, debilitating psychiatric conditions or inability to provide informed consent). 7. Subjects currently participating in another interventional clinical trial or who have taken part in a trial in the previous three months.
Description of interventions	Participants will be randomised to receive active or placebo <i>H. pylori</i> eradication treatment. Active treatment will consist of seven days of lansoprazole 30mg twice daily, clarithromycin 500mg twice daily and metronidazole 400mg twice daily. Placebo will be manufactured to match the active drug where possible. Participants will continue to take aspirin at their prescribed dose.
Duration of study	The trial will continue until 87 adjudicated events have occurred, which would occur after a mean 2.5 patient years of follow-up, if trial assumptions are correct.
Randomisation and blinding	A positive breath test result will trigger web-based randomisation (stratified by centre) and despatch of active or placebo treatment, in a double-blind fashion.
Outcome measures	<p>Primary outcome measure: Rates of hospitalisation because of definite or probable peptic ulcer bleeding.</p> <p>Secondary outcome measures will include: Other causes of GI bleeding (adjudicated) are predicted not to be affected by <i>H. pylori</i> eradication. This will act as a specificity control.</p>

	<p>Cardiovascular outcomes (APTC endpoint, MI and stroke, unadjudicated) are predicted not to be affected.</p> <p>The incidence of detected uncomplicated ulcers.</p> <p>Ulcer site (Duodenal vs. Gastric).</p> <p>GP-recorded and patient-reported dyspepsia.</p> <p>Need for proton pump inhibitor (PPI) prescription or other antiulcer/dyspepsia medication.</p>
Statistical methods	<p>Cox proportional hazards models will be used to analyse time to first episode of hospitalisation because of definite or probable peptic ulcer bleeding, to estimate a hazard ratio and 95% confidence interval comparing treatment arms, adjusted for stratum (centre). In addition to our primary intention to treat analysis, several other analyses will also be undertaken. We will conduct similar analyses restricted to those who confirm that they have both received and taken eradication treatment. We will use data from those that present with ulcer bleeding and undergo <i>H. pylori</i> eradication, together with results from the 10% follow-up sample, to estimate the effect of becoming <i>H. pylori</i> negative compared to remaining <i>H. pylori</i> positive on event rates.</p>
Economic analysis	<p>An incremental economic analysis will be conducted comparing treated patients with controls, using an NHS perspective. Resource parameters relevant to this will include that attributable to testing and treatment, complications from eradication and prescribing, admissions and referral to ICU, length of stay and re-bleeds. Health and clinical outcomes to be considered in this analysis include dyspepsia, gastric bleeds, gastric mortality, stroke, AMI and APTC endpoints, in terms of the probability of their occurrence and their resource consumption.</p> <p>The economic modelling will employ Markov decision models over the lifetime of the patient and use Monte Carlo microsimulation. The model will include risks of events captured in the trial and controls for adherence, age and sex-adjusted mortality risk.</p> <p>We expect <i>H. pylori</i> eradication to dominate; in the event that it does not, we will conduct secondary economic analysis that considers patient utilities. Probabilities of entering relevant disease states post-intervention will be captured in the trial and validated utility weights will be taken from literature and CEA registries, and attached to these health states to allow generation of QALYs.</p>

ABBREVIATIONS

AE	Adverse Event
AMI	Acute Myocardial Infarction
APTC	Anti-Platelet Trialists' Collaboration
BPU	Bleeding Peptic Ulcer
CCG	Clinical Commissioning Group
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CRN	Clinical Research Network
CRF	Case Report Form
CSP	Coordinated System for gaining NHS Permissions
CTU	Clinical Trials Unit
CVD	Cardiovascular Disease
DU	Duodenal Ulcer
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General Practitioner
GU	Gastric Ulcer
HES	Hospital Episode Statistics
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HRG	Healthcare Resource Group
HTA	Health Technology Assessment programme
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IMP(D)	Investigational Medicinal Product (Dossier)
INB	Incremental Net Benefit
INMB	Incremental Net Monetary Benefit
ITT	Intention To Treat
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NEC	Not Elsewhere Classified
NHS	National Health Service
NIHR	National Institute for Health Research
NOS	Not Otherwise Specified
NRES	National Research Ethics Service
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCT	Primary Care Trust
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Proton Pump Inhibitor
PSSRU	Personal Social Services Research Unit

QALY	Quality-Adjusted Life Year
QP	Qualified Person
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UGI	Upper Gastrointestinal

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1. TRIAL BACKGROUND INFORMATION AND RATIONALE

1.1 SEARCH STRATEGY

We undertook literature searches using the following 2 strategies to identify the systematic published evidence:

Strategy 1: “Aspirin AND *Helicobacter pylori* AND peptic ulcer OR stomach (gastric) ulcer OR duodenal ulcer” applied to the Cochrane Database of Systematic Reviews [1], CRD Database of Abstracts and Review of Effects (DARE) [2], Ovid Medline (1996-2010) [3] and PubMed (limited by the term “meta analysis” [4] and via “Systematic reviews” [5]), supplemented by manual searching of Clinical Evidence (BMJ) [6] and the Gastroenterology section of the National Library of Health [7].

Strategy 2: “Peptic ulcer OR stomach ulcer OR duodenal ulcer (Prevention and Control, Therapy) AND Aspirin was searched in Ovid MedLine [3].

1.2 IMPORTANCE OF THE TOPIC

In 2007 peptic ulcer was recorded as the cause of death of 2833 people (2558 aged 60+) in England and Wales, principally because of bleeding [8]. In the same year, Hospital Episodes Statistics (HES) recorded 12,864 admissions in England for gastric duodenal or peptic ulcer haemorrhage (9787 in people aged 60+) [9]; ten years ago aspirin was identified as the single commonest cause [10]. Since then the UK use has risen by 75% [11] and there has been a rise in ulcer bleeding attributed to increased aspirin use [12].

1.3 ASPIRIN

Approximately 28% of the 12 million people aged 60+ in England take aspirin 75-300mg [13]. Four systematic reviews of randomised controlled trials with relevant interpretable data on the effects of aspirin ≤ 325 mg/day on upper GI or peptic ulcer bleeding were identified [14-17]. In a setting of secondary prevention, such as proposed for the trial, aspirin increased the risk of upper GI bleeding by 2.5 (1.4-4.7) fold (attributable risk ~23%) [14], and similar results have been seen in other settings [15-17] and for co-use of aspirin with coxibs [18,19]. Values for upper GI bleeding or dyspepsia or ulcer range between 1.6 and 3.1-fold [15-22]. In the pilot study for this trial, aspirin increased upper GI bleeding 3.15 (2.94-3.37) fold [23]. The estimated excess risk ranges between 0.12% per annum and 0.45% per annum (all cases, regardless of *H. pylori* status) [12,13,14,16] but is likely to be higher in our population, since the average age in trials (~60 years) is the minimum proposed for our study and we, like others, found an age gradient with a 1.5 fold higher event rate in patients aged 65-75 vs. 55-65 [23]. A formula derived from epidemiological studies predicts an excess risk of 0.69 for a population of 70 year olds (70% men) [24].

1.4 HAEMOSTASIS

Aspirin increases the risk of bleeding at sites such as brain, skin and nose where the capacity of high doses to cause ulcers is not a factor. Equally clopidogrel, another anti-platelet drug which has no known ulcerogenic capacity, is associated with ulcer bleeding to an extent similar to aspirin [25,26]. In contrast to higher doses (and NSAIDs), aspirin 75-300mg daily does not appear to cause ulcers in largely *H. pylori* negative volunteers, at least over 1 month [27]. The best explanation of the discrepancy between this finding and aspirin's clear effect on the risk of ulcer bleeding [14-24, 26] is that, in this situation like others, it mainly acts via an anti-

haemostatic effect to provoke bleeding in ulcers caused by another agent. The only plausible candidate for the role of ulcerogen is *H. pylori*.

1.5 H. PYLORI

In support of this hypothesis, an endoscopy study of patients taking aspirin found ulcers were increased 5.1 fold in *H. pylori* positive versus *H. pylori* negative subjects (22.5% versus 4.9%) [22]. Epidemiological studies estimate that *H. pylori* increases the risk of upper GI bleeding in aspirin users by between 2.5 and 4.7 fold [28,29]. In both situations, the increase is principally for duodenal ulcer, compatible with a dominant ulcerogenic role for *H. pylori* with aspirin acting to provoke bleeding, as also seen with other antiplatelet agents [25,26].

1.6 H. PYLORI ERADICATION

In studies of patients who had already experienced ulcer bleeding [30,31], the effect of successful *H. pylori* eradication was to reduce recurrent ulcer bleeding to rates that were similar to those seen in patients taking PPIs (2.0% over 6 months and 5.5% over 12 months respectively). Unfortunately neither study had a simple control group of patients taking aspirin and not undergoing eradication. However rates following eradication were similar to those seen in patients on a PPI, which in NSAID users in the same study reduced recurrent ulcer bleeding fourfold; indirect evidence in support of an effect of similar magnitude for *H. pylori* eradication in aspirin users [30].

1.7 PROTON PUMP INHIBITORS (PPIs)

Whilst PPIs reduce the incidence of endoscopic ulcers [20] and ulcer bleeding [21] in at-risk patients on aspirin, they are now recognised to come at a significant medical cost (e.g. increased risks of *C. difficile* infection) [32], as well as possibly interfering with the efficacy of clopidogrel [33]. The data from the secondary prevention studies [30, 31] suggest that use of PPIs may add nothing to the benefits of *H. pylori* eradication. If this hypothesis is correct, *H. pylori* eradication is likely to be highly cost effective because a single intervention would reduce subsequent hazards on a continuing lifelong basis.

1.8 POTENTIAL MEDICAL AND FINANCIAL IMPACT OF H. PYLORI ERADICATION

Based on results from the ACTION trial [34], life expectancy is 14.0 years for men and 16.0 years for women aged 65 or more, with an average indication for aspirin such as angina. If aspirin is continued lifelong and our hypothesis that *H. pylori* eradication reduces the annual rates of hospitalisations for ulcer bleeding from 0.8% to 0.4% (see Section 5.1) is correct, then we would expect an overall lifetime reduction of 5.6 events per 100 patients for men (14.0 x 0.4) and 6.4 (16.0 x 0.4) for women.

Assuming 25% of the 9.6 million people in England aged 65+ are *H. pylori* positive [23] and 25% take aspirin (70% men) [13], the strategy would result in a reduction in hospital admissions by approximately 35,000 (5.6% of 420,000 men and 6.4% of 180,000 women) and premature deaths by 3,500 (assuming 10% mortality).

In a previous economic evaluation [35], one of our group used published treatment pathway data [36] and consultation with clinical experts to estimate the costs of management of upper gastrointestinal bleeds. At 2003 UK prices, this totalled £8900 per episode for medical in-patient

management in patients of all ages, £15,900 per episode for surgical in-patient management and £17,000 for management of a re-bleed [37]. A recent analysis of costs across Europe (including the UK) comes to broadly similar conclusions [38]. A very conservative estimate of the cost of admission for a bleeding peptic ulcer is therefore in excess of £10,000 at today's prices. Age is a major factor in prolonging length of stay, which is a key cost driver, and £10,000 is likely very conservative for this older than average population. On current evidence, a cost of £15,000 per admission seems reasonable for the population we will be studying. Thus the avoidable cost of 35,000 admissions may be at least £350 million, a substantial saving even if fairly extreme sensitivity analyses are applied.

Figures for patients participating in the proposed trial (assuming all ultimately undergo eradication treatment) are prevention of 585 hospitalisations and 59 deaths at a saving of approximately £5.85 million, potentially making the trial itself a cost effective therapeutic intervention.

A valuable component of the trial will be an economic assessment of the monetary value of the proposed treatment, based on data from direct observations in the trial. This will be extended beyond direct costs of hospitalisation to include the costs of avoidable events and mortality associated with *H. pylori*, avoidable events and mortality associated with non-use of aspirin, avoidable post-bleed complications and alternative treatment with PPIs, as well as potential benefits of a possible expansion in aspirin use that a positive result might stimulate.

1.9 IMPORTANCE OF TRIAL DESIGN

An important component of this study is the attempt to develop low-cost, streamlined, simplified methodologies to bring outcome studies within the capability of academic investigators. New MHRA guidelines from 1 April 2011 are helpful to this aspiration. This guidance suggests that this is a Type A trial because it only uses established medical products given for their licensed indications and “no higher than the risk of standard medical care”.

As defined in MHRA document ‘Risk-adapted approaches to the management of clinical trials of investigational medicinal products’ (version 10 October 2011), Type A status has potential implications for:

- the need for authorisation by the competent authority
- the content of the Clinical Trials Authorisation application
- IMP management
- safety surveillance
- trial documentation
- GCP inspection

1.10 FEASIBILITY

All key steps of this study have been validated in large numbers of patients. In our MRC-funded pilot study (EudraCT Number 2007-003577-74, REC Reference 07/H0408/109) we wrote to 2525 patients, with 47% replying, and 33% of those invited suitable. Of the suitable patients, 24% were *H. pylori* positive with successful eradication in 91%. Of the enrolled patients, 92% were aged 60+. These data establish the study's feasibility.

2. DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

2.1 DESCRIPTION

Active treatment will consist of seven days of lansoprazole 30mg, clarithromycin 500mg and metronidazole 400mg all given twice daily. This is one of the authorised recommended regimens for *H. pylori* eradication in adults. The control group will receive placebos (identical where possible) to the same regimen.

Lansoprazole (CAS: 103577-45-3); 30mg capsules (generic).

Clarithromycin (CAS: 81103-11-9); 500mg tablets (generic).

Metronidazole (CAS: 99616-64-5); 400mg tablets (generic).

A full list of the characteristics for these medications can be found in Appendix 1.

2.2 MANUFACTURE

MODEPHARMA is responsible for arranging the IMPs' manufacture as well as project management and assistance relating to the IMP for the trial. The actual manufacturing and final QP release of the IMPs will be undertaken by Piramal Healthcare UK Ltd (Licence Number 29595).

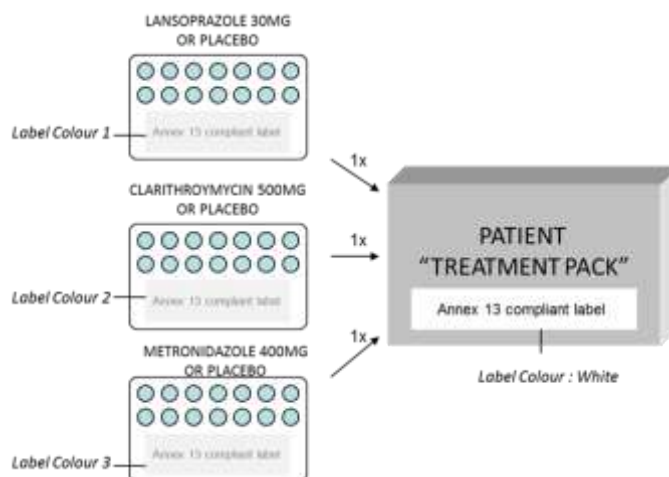
Comparator products of clarithromycin 500mg tablets, metronidazole 400mg tablets and lansoprazole 30mg capsules will be procured. Placebos for these three products will be developed and manufactured by Piramal Healthcare UK Ltd.

IMPs will be manufactured, packaged, and QP released for clinical trial use by Piramal Healthcare UK Ltd. The study medication will be shipped directly from Piramal to the storage facility in the central Trial Coordinating Centre.

Project managers at MODEPHARMA will work with the trial team to provide full support surrounding the trial IMP including the preparation of the IMPD.

2.3 PACKAGING AND LABELLING

Both active and placebo eradication treatment for the trial will be packaged under QP control by Piramal Healthcare UK Ltd. All IMPs will be supplied in blister strips of 14 tablets (7 days' worth), with a colour-coded Annex 3 compliant label attached. The appropriate three blister strips will be put together in a carton to make up individual treatment packs, which will also be labelled in accordance with Annex 3. This label will have spaces for addition of the patient randomisation number, name and date.



2.4 STORAGE, DISPENSING AND RETURN

Trial medication will be stored in a secure and controlled environment at ambient temperature. This will only be accessible to authorised trial personnel; the CI, the Trial Manager, and other appropriate designees at the Trial Coordinating Centre. The storage facility (i.e. a “satellite Pharmacy”) will be assessed by the Clinical Trials Pharmacist at Nottingham University Hospitals NHS Trust at the beginning of the study to assure suitability, and all procedures regarding access control and accountability will be verified.

Trial participants will be advised to store medication at ambient temperature, and out of the reach of children.

All trial medication will be distributed from the Trial Coordinating Centre to the trial participants by post. On randomisation, a trial prescription will be generated for each patient which will assign the patient to a specific treatment pack number. The prescription will be signed by the CI or appropriate designee.

Study drug will be dispensed by designated members of the study team, who will have received training appropriate to their role from the Clinical Trials Pharmacy at Nottingham University Hospitals NHS Trust. All dispensing will be checked by a second authorised member of the study team, and at least one of these two members of study personnel will be a registered nurse, with training in drug dispensing. Clear accountability logs of this process will be maintained, along with training logs.

All procedures relating to the dispensing and return of study medication will be authorised by the Clinical Trials Pharmacist at Nottingham University Hospitals NHS Trust. In addition to this, spot-checks and auditing of the dispensing process will occur as the trial progresses, to ensure that all procedures are adhered to.

At the end of the study, any surplus or unused stock will be reconciled and destroyed. Study participants will not be asked to return their empty medication packaging.

2.5 PLACEBO

MODEPHARMA will arrange the manufacture of placebo tablets or capsules (identical where possible) for the active eradication treatment medications by Piramal Healthcare UK Ltd. Placebo blister strips and patient treatment packs will match those of the active substances, and will be labelled in the same way, to maintain the blind.

2.6 KNOWN SIDE EFFECTS

Full details of trial medication, including drug interactions, are given in Appendix 1.

3. TRIAL OBJECTIVES AND PURPOSE

3.1 PURPOSE

Use of aspirin for cardiovascular prophylaxis (and potentially cancer prevention [39]) is widespread and increasing. The main hazard is ulcer bleeding. This is usually associated with *H. pylori* infection. It is important to determine whether this can be reduced or prevented by *H. pylori* eradication. Given the scale of aspirin use, its continuing increase and its contribution to ulcer bleeding, how to deal with this problem is arguably the most important question with regard to current iatrogenic medicine.

3.2 PRIMARY OBJECTIVES

The research has three **primary objectives**:

1. **Medical**: To test the hypothesis that a one week course of *H. pylori* eradication in patients using aspirin ≤ 325 mg daily will reduce the incidence of subsequent adjudicated peptic ulcer bleeding that results in hospitalisation.
2. **Economic**: To test the hypothesis that the intervention has a positive net monetary benefit.
3. **Methodological**: To establish a methodology for large simple outcomes studies using electronically extracted Primary Care follow-up data, to reduce costs to a level that enables outcomes studies of clinically important questions to be done without the need for industry support.

3.3 SECONDARY OBJECTIVES

Secondary medical objectives include evaluating the effect of *H. pylori* eradication on other GI and cardiovascular outcomes, detailed in Section 4.1.2.

4. TRIAL DESIGN

4.1 TRIAL CONFIGURATION

Double-blind, placebo-controlled randomised multi-centre study of the effects of *H. pylori* eradication treatment on subsequent ulcer bleeding in infected individuals taking aspirin ≤ 325 mg daily. The trial will use methods validated during the MRC-funded pilot study.

See Appendix 2 for flow-diagram of the trial.

4.1.1 Primary endpoint

The primary outcome is the rate of hospitalisation due to peptic ulcer bleeding in patients who enter the randomised study (only the first event per patient will be analysed), adjudicated by a blinded Committee as definite or probable. The Committee will use definitions validated in the TARGET study [19]. The TARGET adjudication process is better than alternatives because it uses endpoints that are clinically recognised, precisely aligned with the goals of the trial and highly discriminative. This was demonstrated by a greater separation in rates of ulcer complications between NSAIDs and COX-2 inhibitors in TARGET compared to comparable studies.

4.1.2 Secondary endpoint

- i. Other causes of GI bleeding (adjudicated); these are predicted not to be affected by *H. pylori* eradication and will act as a specificity control.
- ii. Cardiovascular outcomes (APTC endpoint, MI and stroke, unadjudicated); these are predicted not to be affected.
- iii. The incidence of detected uncomplicated ulcers.
- iv. Ulcer site (Duodenal Ulcer vs. Gastric Ulcer).
- v. GP-recorded and patient-reported dyspepsia.

- vi. Need for PPI prescription or other antiulcer/dyspepsia medication.

These outcomes will be determined from GP records; outcomes ii. – vi. will not be formally adjudicated.

4.1.3 Safety endpoints

The primary endpoint of the trial is a safety assessment. Other safety endpoints will include adverse events (patient-reported), serious adverse events (including deaths), and hospitalisations. Adjudicated ulcer bleeding (the primary endpoint) will be formally assessed as part of the trial; the other safety endpoints will be presented descriptively.

4.1.4 Stopping rules and discontinuation

Formal stopping rules will be defined in the IDMC charter, which would be used to advise the Trial Steering Committee. The following are the instances where the IDMC may consider it advisable to terminate the study:

- If the two treatments arms are found to be convincingly different or convincingly not different
- Side effects or toxicity too severe and/or frequent for this patient group (e.g. pseudomembranous colitis, which will be monitored carefully)
- IDMC consider data are of poor quality
- Flaws in design or conduct of the study come to light
- Accrual too slow to complete the study
- Adherence to treatment proving difficult or unacceptably poor
- External new information on the treatment comes to light
- Resources inadequate to complete trial

If the trial is prematurely terminated or discontinued, the University of Nottingham will promptly notify the investigators. After notification, the investigator must contact all participating subjects within 90 days and all trial materials must be collected and all data completed to the greatest extent possible.

4.2 RANDOMISATION AND BLINDING

A randomisation schedule will be developed by the Nottingham University Clinical Trials Unit (CTU). There will be separate randomisation sequences for each region. In each region, randomisation will use permuted blocks of randomly varying size. The medication will be packed according to the randomisation schedule.

Randomisation will be via a web-based randomisation system, to which only authorised individuals will have access. This will be managed by Nottingham CTU. On confirmation of an unequivocally positive breath test, trial personnel will access the randomisation system to generate a patient-specific randomisation number and allocation of a treatment pack. This pack will be posted to the patient together with the associated letter and other documentation detailed in Section 4.6.3. Unequivocally negative breath tests will trigger a standard letter (or email) to the patient to inform them of their result. Patients with borderline breath tests will not be randomised, but a letter will be sent to the patient and their GP.

4.2.1 Maintenance of randomisation codes and procedures for breaking code

Codebreaks for this trial are highly unlikely, as study treatment consists of just a one week course of eradication treatment, with licensed, well-used drugs. Each patient enrolled into the study will be provided with a trial participation card, giving their randomisation number and contact details for the local Study Site Coordinator (GP) responsible for the study at their GP practice, and also for the relevant Regional Centre. Patients will be instructed to carry this card with them at all times. The contact details can be used by other healthcare professionals to ascertain details of the trial or for emergency unblinding if required. Should emergency unblinding be necessary (for medical reasons), the code can be broken via the web-based randomisation system (the password for breaking the code will be held by a Clinical Trials Pharmacist at Nottingham University Hospitals NHS Trust). In such a situation, the Central Trial Coordinating Centre must be informed as soon as possible.

At the end of the study, all patients who were randomised (i.e. were confirmed as *H. pylori* positive) will be informed of whether they were allocated active or placebo treatment, and hence at this point the blind will be broken for all patients.

4.3 TRIAL MANAGEMENT

The **Sponsor** of the trial will be the University of Nottingham. The trial will be managed from the Central Trial Coordinating Centre in Nottingham, with a designated **Trial Manager**. The **Trial Management Group** (TMG), led by the Chief Investigator, will meet regularly to discuss the design and progress of the trial. Advice will be sought by this Group on relevant decisions from local patient and public involvement groups.

The trial will be overseen by a **Trial Steering Committee** (TSC). This will comprise an independent chair, a statistician or triallist with experience of similar large scale community based trials, a clinician with expertise in the relevant clinical area, the Trial Manager, the Chief Investigator plus at least one Principal Investigator and a lay member. The TSC will meet at the start of the study and then yearly thereafter, unless more frequent meetings are required. They will be responsible for defining the stopping rule for the study. An **Independent Data Monitoring Committee** (IDMC) will be established. The IDMC will comprise an independent chair, a statistician with clinical trials expertise and a clinician with expertise in the relevant clinical area (e.g. a gastroenterologist).

Trial Monitoring will be by Nottingham CTU.

A three person **GI Adjudication Team** will each independently adjudicate possible ulcer bleeding endpoints and achieve consensus by resolving discrepancies at teleconference, as previously done in the TARGET study.

The **Chief Investigator** will be based in the Trial Coordinating Centre, and will have overall responsibility for the trial, and for issuing trial medication to eligible participants. **Regional Centres** will co-ordinate the study sites in their area, lead by a regional **Principal Investigator**. Regional centres will be responsible for recruiting and liaising with local study sites.

A **study site** will be a participating general practice. Each practice will have at least one **Study Site Coordinator** who will be a primary care physician. The study site coordinator will be responsible for selecting suitable patients from the general practice population.

4.4 DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The trial will continue until at least 87 adjudicated events have accrued. We anticipate that approximately 2.5 patient years of follow-up will be needed to achieve 87 events. All patients entered into the trial will spend a minimum of 6 months as a participant.

4.4.1 End of trial

The end of the trial is defined as reaching the required number of endpoints (87), with every randomised subject participating for at least 6 months.

4.5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.5.1 Recruitment

All trial recruitment will be in a Primary Care setting. There will be six trial centres: Nottingham, Durham, Birmingham/Oxford, Southampton, Northern Ireland and Scotland, and the trial will recruit from CCGs (former PCTs) / health boards around these regions across the whole of the UK.

Participating GPs will identify eligible patients at their practice using an automated MiQuest search (provided by TCR (Nottingham) Ltd) as per the inclusion / exclusion criteria that will then be checked against the patients' medical records. The GP will sign a statement to confirm that all patients to be contacted are eligible for the trial, and that they are happy for these patients to be consented, breath-tested and randomised (if *H. pylori* positive).

At this point, an electronic screening log will be generated based on the GP-approved list of patients from the MiQuest search. The following information will be stored in the trial database: screening number, patient initials, date of birth, anonymised MiQuest number, and anonymised NHS Number. The patients' NHS number is required to be able to uniquely identify each patient, should the practice lose their data and require a back-up. It will be anonymised as follows:

- At the practice, the patients' NHS number will be encrypted (using the AES-256 encryption standard) prior to being uploaded to the trial database.
- The unique encryption key, to allow decryption of the NHS number, is the NHS number itself. Therefore, there is absolutely no way that this information can be decrypted outside of the practice. In this instance, the encrypted NHS number is not a strong identifier for the patient.

The GP practice will invite suitable patients to participate in the trial by sending a REC-approved letter, together with a copy of the approved Participant Information Sheet and Consent Form. Each letter of invitation sent out will have a unique screening number that will be used for future identification of any patients taking part in the trial.

4.5.2 Inclusion criteria

1. Males and females ≥ 60 years of age at the date of screening.
2. Subjects who are taking aspirin ≤ 325 mg daily and who have had 4 or more 28-day prescriptions in the last year.
3. Subjects who are concurrently using other anti-platelet agents are allowed to enter the study.
4. Subjects who are willing and able to undergo a breath test for *H. pylori*, including fasting for 6 hours, and whose result is unequivocally positive (results of breath test will be determined post-screening).
5. Subjects who are willing to give permission for their paper and electronic medical records to be accessed and abstracted by trial investigators.
6. Subjects who are willing to be contacted and interviewed by trial investigators, should the need arise for adverse event assessment, etc.
7. Subjects must be able to communicate well with the investigator or designee, to understand and comply with the requirements of the study and to understand and sign the written informed consent.

4.5.3 Exclusion criteria

1. Subjects who are currently prescribed proton-pump inhibitors or H₂-receptor antagonists.
2. Subjects who are currently prescribed oral non-steroidal anti-inflammatory drugs (NSAIDs).
3. Subjects who have a known intolerance or allergy to *H. pylori* eradication treatment.
4. Subjects who are taking drugs with a clinically significant interaction with *H. pylori* eradication treatment (see Appendix 3).
5. Subjects who are terminally ill or suffer from a life-threatening co-morbidity.
6. Subjects whose behaviour or lifestyle would render them less likely to comply with study medication (eg. alcoholism, substance abuse, debilitating psychiatric conditions or inability to provide informed consent).
7. Subjects currently participating in another interventional clinical trial or who have taken part in a trial in the previous three months.

Prohibited concomitant medications are listed in Appendix 3.

4.5.4 Informed consent

For this trial, research nurses will be obtaining informed consent, as delegated by the Principal Investigator at each regional centre. The research nurses will receive considerable training on informed consent, the trial, and the treatment in question, prior to trial start.

All participants will provide written informed consent. The informed consent form will be signed and dated by the participant before they enter the trial or undergo any interventions. Participants will have received a Participant Information Sheet in advance of their consent visit, allowing them ample time to consider their participation (at least 24 hours). The research nurse will explain the details of the trial, and will answer any questions that the participant has concerning study participation.

One copy of the informed consent form will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the site file at the GP practice (practice staff will be asked to scan this into the patients' electronic GP record).

Should there be any subsequent amendment to the final protocol which might affect participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

4.5.5 Expected duration of participant participation

The trial will continue until 87 adjudicated events have accrued, which would occur after a mean 2.5 patient years of follow-up if trial assumptions are correct. Patients are therefore expected to be participating in the study for a period of 2-3.5 years (including one week of treatment).

4.5.6 Removal of participants from therapy or assessments

Subjects will be free to withdraw from the trial at any time, whether during the trial treatment period (which only lasts for one week) or thereafter by withdrawing consent for the collection of follow-up data.

It is possible that participants may have their study medication stopped by their GP due to side effects of the eradication treatment, although this is not likely to be common because of the short treatment duration. The participants will be made aware that this will not affect their future care. Participants will be informed (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Patients who discontinue *H. pylori* eradication treatment before completing the course will remain subject to assessment. Patients are asked to complete a log of their treatment dosing, and so variation in adherence can be considered in the trial analysis.

Patients who discontinue aspirin during the trial will be assessed as trial participants up to the point that they discontinue aspirin and will be assessed separately thereafter, as the goal of the trial is to assess prevention of aspirin-associated endpoints. They will only be included in the secondary analysis, as the primary analysis is intention to treat.

4.6 TRIAL REGIMEN

4.6.1 Patient Identification and Screening

Patients (~170,000) identified from GP records as being suitable for the trial will be written to by their GP practice with full information about the trial, and invited to participate (and allocated a patient screening number, see Section 4.5.1). Those patients who respond to the Regional Centre to express an interest will be contacted by telephone, to give them further information and allow them to ask questions.

Suitable patients (~33,000) will be invited to attend a screening visit at their GP practice (or other suitable convenient location, such as a Clinical Research Facility or local hospital). They will be asked to fast, and not smoke, for 6 hours prior to this visit, and will be sent a letter/email to reiterate this and confirm their appointment time.

Inclusion/exclusion criteria will be checked and the patient consented by an appropriately trained research nurse. Following consent the research nurse will perform a brief baseline assessment, including BP measurement and demographics, and the patient will perform a breath test. Basic information on current medications, including aspirin use in the last 12 months, and any relevant blood test results and medical history will be extracted electronically from the patients' medical notes to the trial database.

4.6.2 Breath Test for *H. pylori*

'Helicobacter Test INFAI' is a breath test kit used to determine the presence of *H. pylori* in the stomach (EMA product number EMA/H/C/000140). It is a commonly-used breath-testing kit for *H. pylori* detection, and is currently widely-used within the NHS. The test will be conducted by suitably trained research nurses during the patient's screening visit. Occasionally, the nurse may train the patient on the use of the test during the visit, but then ask them to complete this at home and post back to the research team (for example, if the patient has forgotten to fast, or is found to have taken recent antibiotics). The breath testing kits are designed to be completed independently by patients, and contain full details of the correct procedure to follow.

Patients must have fasted for 6 hours before testing (and refrain from smoking) and should be free of antibiotic or antisecretory medication for the previous 4 and 2 weeks respectively. The patients will be asked to collect 2 baseline samples of breath. They will then drink a liquid test meal (200ml orange juice or 1g citric acid in 200ml water) to delay stomach emptying followed by a test solution containing 75mg ¹³C-urea. Thirty minutes later they will collect further 2 breath samples. If *H. pylori* is present in the stomach, there will be a significant increase in the amount of ¹³Carbon in the second set of breath samples.

Test kits will be provided directly from INFAI UK Ltd, York for the purposes of this research study, and will be labelled with the study name. The kits will be posted back to INFAI UK Ltd for analysis.

4.6.3 Randomisation

Patients will be informed that they will be told of the results of their breath test via the post, and will receive eradication treatment / placebo should this be positive.

H. pylori positive patients (~6600) will be randomised to receive eradication treatment (3300) or placebo (3300). Treatment will be dispatched to the patients by post from the Trial Coordinating Centre. Included with the treatment will be a record form on which the patient will confirm receipt, log dose timings and record any adverse effects.

4.6.4 Patient Follow-Ups

Patients will not be required to attend any routine face-to-face follow-up visits, but will be given multiple contact methods (email, telephone, event form and pre-paid envelope) to inform their Regional Centre following any hospital admission or change of GP or address. They will also carry a trial participant ID card (posted with the treatment) which asks admitting hospitals to inform the Regional Centre of admissions. We will contact patients on an annual basis to ask them for information regarding any hospitalisations they have experienced in the previous year.

GP records will be interrogated annually (more frequently as the trial nears completion) by searching for relevant read codes to identify any hospital admission possibly due to acute GI bleeding, as well as current health and prescribing information. Our pilot study showed that Primary Care records are not sufficiently precise on their own because more generic codes such as “Gastrointestinal Bleeding” are used, so we will take an inclusive approach to identifying patients with possible endpoints and use scrutiny of the hospital records of these patients to achieve enough precision for accurate judgement by the Adjudication Committee. GPs will add an alert to each patient’s electronic record to allow easy identification of trial participants. NHS Trust permissions will be required for the study team to be able to access the medical records of the admitting hospital; these will be sought when required / after notification that a hospitalisation has occurred.

Patients experiencing an adjudicated endpoint will undergo further *H. pylori* breath testing, to define their status.

Also, in order to confirm that we have achieved similar eradication rates to those seen in the pilot study, we will re-test a 10% sample of all trial participants at the end of the study. This sample will be identified prospectively, to enable us to also collect quality of life data. These patients will be sent an EQ-5D questionnaire for completion with their study medication, and will repeat this questionnaire and have a second breath test at the end of the study (which may be sent to them by post for completion at home).

After study completion, patients will be informed of the study’s outcome and the treatment they received will be identified, enabling them and their GP to take an evidence-based decision about undergoing eradication treatment. If the trial supports eradication therapy as appropriate, this will represent a small amount of work for GP practices but will, by then, be the standard of care.

4.6.5 Compliance

Study medication will be delivered by post, including a report form asking the patient to record the date of receipt, to ensure that we have a robust method of verification. The patient will also be asked to log times of dosing each day and any adverse effects. Patients will receive a telephone call approximately 7 (4 -10) days following despatch of medication and will be reminded to complete and return the record sheet. For analysis, adherence will also be estimated from eradication rates measured in the 10% sample of patients who will be retested at the end of the study (see Section 4.6.4). A similar method was validated during the pilot study, where a 91% eradication rate was achieved. As a result, we will not be collecting empty medication containers for compliance verification.

4.6.6 Accountability for drugs & placebos

Once received from MODEPHARMA, the patient treatment packs will be stored securely at ambient temperature. Accurate accountability logs will be maintained of medication in stock, and temperature logs of the storage area maintained (see Section 2.4).

On confirmation of an unequivocally positive breath test, trial personnel at the Trial Coordinating Centre will access the web-based randomisation system to generate a patient-specific

randomisation number and allocation of a treatment pack. This will be logged on accountability logs along with the date of despatch. The date of receipt by the patient will also be logged.

4.6.7 Management of study drug overdose

This will be in accord with the recommendations of the individual drug Summary of Product Characteristics. Patients are only provided with 7 days' worth of eradication treatment as part of the trial, and therefore it is unlikely that participants will experience a study drug overdose. The Summary of Product Characteristics for each of the study drugs do not report any toxic effects at the maximum dosages that patients could receive on this trial (i.e. should they consume 7 days' worth of all drugs at the same time). The Study Site Coordinator will use clinical judgement in treating the symptoms of a suspected overdose.

5. STATISTICS

5.1 ASSUMPTIONS

Unless otherwise stated, our analysis concerns first events following trial entry. Our power calculations are based on assumptions derived from event rates in published randomised clinical trials and observational studies. Based on an average of the rates of ulcer bleeding in control patients in RCTs and observational studies we assume a rate of 0.16% per annum, in patients not taking aspirin. If aspirin increases the bleeding rate 2.5 fold we would predict an ulcer bleeding rate in patients ≥ 60 years old on aspirin of 0.4% per annum. This is slightly but not significantly lower than the average rate recorded in the literature (0.43% per annum). We assume approximately 25% of patients are *H. pylori* positive (as in our pilot study) and that infection increases the risk threefold (a conservative estimate compared to the odds ratio of 5.1 for endoscopic ulcers [22] and 4.7 from epidemiological observations [29]). These assumptions translate into an ulcer bleeding rate of 0.8% per annum in the 25% of patients who are on aspirin and *H. pylori* positive, and 0.27% per annum in the 75% of patients on aspirin who are *H. pylori* negative. We think it is plausible that this value is slightly higher than the 0.16% seen in *H. pylori* negative patients not on aspirin.

5.2 SAMPLE SIZE

The sample size calculation assumes event rates of 4 per 1000 per year in the intervention arm and 8 per 1000 per year in the control arm, giving an incidence rate ratio of 0.5 comparing the intervention with the control arm.

With a 5% two sided significance level and 90% power then a total of 87 events are required to detect this. This calculation uses the sample size formula in the McMahon and MacDonald paper [40] (p332; calculation of T). The continuity corrected version of the formula was used.

Using the assumed event rates then 8000 person-years are required per study arm to obtain this number of events. With an average of 2.5 years of follow-up, then 3300 participants are needed per study arm (6600 total). This accounts for a 2% loss to follow-up rate.

The trial will be event-driven and continue until 87 adjudicated events have occurred. This offers some protection against the possibility of errors in our assumptions.

5.3 PRIMARY ANALYSIS

Cox proportional hazards models will be used to analyse time to first episode of hospitalisation because of definite or probable peptic ulcer bleeding, to estimate a hazard ratio and 95% confidence interval comparing treatment arms, adjusted for stratum (centre).

Analyses will be presented adjusted only for any centre effect (primary analysis) and also adjusted for both centre effect and for important prognostic factors (these will be specified in advance of the analysis).

The analysis will be carried out blind to treatment group. A secondary analysis will compare the primary outcome between treatment arms in those who do or do not continue using aspirin (defined as no prescription for three consecutive months) and on those who continue aspirin and do not take a PPI.

In addition to our primary intention to treat analysis, several other analyses of the primary outcome will also be undertaken. We will conduct similar analyses restricted to those who confirm that they have both received and taken eradication treatment. We will investigate the extent of influence of adherence by comparing the rates of the primary outcome variable between treatment arms in separate analyses of those reporting full adherence to trial medication and/or continued aspirin use (defined as aspirin use with no breaks in prescription of three consecutive months or more) without a PPI and those reporting less than full adherence.

We will use data from those that present with ulcer bleeding and undergo *H. pylori* eradication, together with results from the 10% follow-up sample, to estimate the effect of becoming *H. pylori* negative compared to remaining *H. pylori* positive on event rates.

5.4 PROPOSED SUB-GROUP ANALYSES

To assess whether the effect of the intervention on upper GI ulcer bleeding varies with age, a term for the interaction between treatment arm and age will be added to the Cox proportional hazards model and assessed for significance using a likelihood ratio test. If there is a significant interaction with age then estimates of the treatment effect will be presented in different age groups.

5.5 SECONDARY ANALYSIS

Descriptive analyses will be carried out to summarise baseline characteristics and outcome variables by treatment group, using means and standard deviations or medians and interquartile ranges as appropriate for continuous measures and numbers and percentages for categorical variables.

The rates of experiencing first events of GI bleeding not due to peptic ulcer, cardiovascular outcomes, and an uncomplicated ulcer, will be compared between treatment arms using Cox regression to estimate hazard ratios and 95% confidence intervals, adjusted for stratum. Patient reported dyspepsia will be analysed using Cox regression analysis of the first patient report by the patient. All instances of GP recorded dyspepsia and prescription of antiulcer/dyspepsia medication (PPI, H2 antagonist, antacid, alginate) will be compared

between arms using Poisson regression to calculate rate ratios and 95% confidence intervals. Assumptions of these Poisson analyses will be checked including an assessment of residuals and influential observations and checking for over-dispersion. If there is significant over-dispersion negative binomial regression will be used instead of Poisson regression.

Analyses will be presented adjusted only for stratum, and adjusted for stratum and important prognostic factors.

5.6 DEATHS AND COMPETING RISKS

A significant number of patients will die during the course of the study. We estimate this will amount to around 430 if the age distribution of participants and age related mortality rates are similar to that recorded for the UK from the Office of National Statistics. These will be presented descriptively.

5.7 MISSING DATA

We will present numbers with missing data in the participants' baseline characteristics and will describe numbers lost to follow-up by treatment group.

5.8 FOLLOW-UP PERIOD

A follow-up period of 2.5 years is an estimate because the trial will be event driven. As detailed elsewhere, the maximum follow-up period is likely to be 3.5 years, and the minimum follow-up period will be 6 months.

5.9 ASSESSMENT OF SAFETY

Adjudicated ulcer bleeding, which is the primary endpoint, will be analysed as described in Section 5.3. Other safety data will be presented descriptively.

6. ECONOMIC ANALYSIS

We will conduct an incremental economic analysis comparing treated patients with control patients. The analysis will compare resource use between the two arms, using relevant parameters that include:

1. *H. pylori* testing and eradication
2. Episodes of ulcer bleeding (trial primary endpoint)
3. Attributable long-term conditions such as gastric cancer and gastric lymphoma, gastric bleed, gastric mortality, stroke, AMI and combined APTC endpoints
4. Prescribing of PPIs, and episodes of drug related complications
5. Adverse events attributable to trial treatment and aspirin

Costs will be considered from an NHS perspective. Unit costs will be taken from NHS Reference Costs [41] (matching HES data to HRG codes), BNF prices [42] for drugs (for which we will know doses) and PSSRU Unit Costs of Health and Social Care [43]. Unit costs will be multiplied by units of resource to estimate total costs. Inputs include *H. pylori* testing and

eradication, aspirin use, PPI use, clopidogrel use, GP surgery attendance and inpatient/outpatient attendance adjudicated to be relevant. Key cost drivers for gastric bleed management (length of hospital stay, surgical intervention, number of days spent on intensive care and the management of re-bleeds within the same admission) will be recorded. Activity data will be collected from HES data, GP records and patient questionnaire, and will be collected by the research team.

The economic analysis will be via Markov decision analysis models: first decision/probability nodes will capture testing and identification (controlling for test sensitivity and specificity), treatment and treatment outcome. Following this, a Markov model will be used to extrapolate control and treatment experiences over the lifetime of the patient, capturing longer-term outcomes (dyspepsia, gastric bleed, gastric mortality, stroke and CVD). The model will be run on the life-time of the patient using 12-month cycles: mortality risk will be taken from Office of National Statistics (ONS) life-tables, adjusted for age, sex and relevant co-morbid conditions, and the model will be run until all patients are absorbed. Markov parameters will be collected within the trial where feasible; others will be found through literature searches. Analysis will be via fully-flexible Monte Carlo microsimulation in TreeAge, in which all parameters will be included with their sampling distributions. Age-at-entry, while initially reflecting the trial patients, will be subject to one-way sensitivity analysis. We will conduct probabilistic sensitivity analyses via fully flexible Monte Carlo microsimulation, with at least $n = 10,000$ simulations, so that our results include bootstrapped estimates that incorporate all known uncertainty within the model and the trial data.

For the modelling of incremental cost per QALY, results will be reported using incremental net benefit (INB) with a range of willingness to pay thresholds, also via fully flexible Monte Carlo microsimulation. Results will also be illustrated using cost-effectiveness acceptability curves (CEACs), which highlight the probabilistic likelihood that a given unit of QALYs gained is cost-effective, for a given willingness-to-pay per QALY and given the strength of the data.

We will also conduct several sets of univariate sensitivity analysis, principally focusing upon “what if” scenarios surrounding adherence, as well as changes to prescribing behaviour that may occur in response to a positive trial outcome. This is to reflect the fact that *H. pylori* eradication is predicted to have not only a direct impact on patient outcomes but to improve prescribing of aspirin to currently at-risk patients. This could include any range from no extra patients being prescribed aspirin to all patients in the future being prescribed aspirin. We will test these boundaries to substantially improve bounded estimates of plausible costs and cost-savings to the NHS of *H. pylori* eradication.

Finally, all future costs and benefits (including life-years) will be discounted: in the first instance at 3.5% p.a., however other discount rates for non-monetary costs and benefits (e.g. QALYs) will be explored also, in order to determine the sensitivity of the final results to the level of discounting.

7. ADVERSE EVENTS

7.1 DEFINITIONS

7.1.1 Adverse event (AE)

Any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

- i. exacerbation of a pre-existing illness.
- ii. increase in frequency or intensity of a pre-existing episodic event or condition.
- iii. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
- iv. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

- i. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
- ii. pre-existing disease or conditions present or detected at the start of the study that did not worsen.
- iii. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
- iv. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
- v. overdose of concurrent medication without any signs or symptoms.

Well-recognised adverse effects of *H. pylori* eradication medication that do not need to be reported are: nausea & vomiting; diarrhoea; dyspepsia; flatulence; abdominal pain or discomfort; constipation; unpleasant (metallic) taste in mouth / tongue discoloration; furred tongue / dry mouth or throat; oral mucositis / thrush; darkening of urine; headache; dizziness; transient visual disorders; tiredness; ataxia; urticaria / skin rash / itching; flushing.

Because the trial treatment is given for only one week and because existing data show that nearly all adverse reactions are experienced within four weeks of treatment [44], we have set a four week window for the assessment and reporting of suspected treatment-related adverse events. Treatment-related adverse events will not be reported after this time, unless the CI thinks there are compelling reasons to implicate treatment in an event detected during subsequent interrogation of GP records.

7.1.2 Serious Adverse Event (SAE)

Any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

- i. Death
- ii. A life-threatening adverse event
- iii. Inpatient hospitalisation or prolongation of existing hospitalisation
- iv. A disability / incapacity
- v. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalisations and deaths will be collected for the trial analysis, detected during annual GP record interrogation, or via patient self-reporting forms.

In line with restricted drug-SAE reporting, those AEs collected according to 7.1.1., but which also meet the criteria for seriousness defined here, will be assessed. All adverse events will be assessed for seriousness, expectedness and causality.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

7.1.3 Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation. This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

7.2 REPORTING OF ADVERSE EVENTS

7.2.1 Type A trial adaption

In accordance with the MHRA recommendation that “for medicines where there is already a significant amount of safety data available, such as many marketed medicines it is possible to state in the protocol that certain adverse events do not need to be reported by the investigator to the sponsor in the normal way”.

The process for categorising and reporting adverse events will be as described above. It is highly unlikely that any deaths, life threatening adverse events, hospitalisation or prolongation of hospitalisation, disability or incapacity or congenital anomaly will occur as a consequence of trial treatment outside of the four-week reporting window defined in this trial, but GPs will be instructed to inform the Regional Centre or Central Trial Coordinating Office of any such events that may bear a relationship to study drug treatment.

In addition, any patient reported events that could be a serious adverse reaction to the trial treatment will be treated likewise. Beyond this, there will be no other systematic adverse event reporting. However, the trial will collect data on hospitalisation and the relationship to treatment will be analysed as part of the trial’s primary statistical analysis.

7.2.2 Reporting methods

Participants will be asked to contact their Regional Centre following any SAE (i.e. hospitalisation) using an event form and pre-paid envelope, email, text or phone message. They will also carry a trial participant ID card (posted with the treatment) which asks admitting hospitals to inform the Regional Centre of admissions. We will contact patients on an annual basis to ask them for information regarding any hospitalisations they have experienced in the previous year.

GP records will be interrogated annually (more frequently as the trial nears completion) by searching for relevant read codes to identify any hospital admissions, as well as current health and prescribing information. The outcome measures used constitute, by definition, serious adverse events and will be recorded as such. All SAEs will be assessed as to whether they constitute a SUSAR.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

7.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as SUSAR and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise. The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- i. Assess the event for seriousness, expectedness and relatedness to the study IMP
- ii. Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- iii. If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- iv. Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- v. Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- vi. Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

7.4 PARTICIPANT REMOVAL FROM THE STUDY DUE TO ADVERSE EVENTS

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

8. ETHICAL AND REGULATORY ASPECTS

8.1 ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

8.2 INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, GCP and any other regulatory requirements that might be introduced.

Patients will receive all relevant information at the time of the GP's initial approach. They will give informed consent when they attend for their trial visit. By this time, they will have had several days or probably weeks to consider whether to enter the trial. Our Participant Information Sheet is short because of a study we performed showing that long information sheets reduce understanding and impair the ability of participants to understand risks and benefits [46]. Patients will have an opportunity to discuss risks and benefits further both on the telephone call made prior to the trial visit and at the time of the screening visit.

The patient's decision regarding participation in the study is entirely voluntary. The Investigator or their nominee (research nurse) shall emphasise to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be conducted before informed consent has been obtained.

The Investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the informed consent form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended informed consent form by the REC and use of the amended form (including for ongoing participants).

8.3 RECORDS

8.3.1 Case Report Forms

Each participant will be assigned a screening number, and a trial randomisation number, allocated at randomisation, for use on trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The Investigator will make a separate confidential record of the participant's name, date of birth, NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using a black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

8.3.2 Source documents

Source documents shall mostly consist of the patient's electronic GP record, and their hospital records. In addition to this, a source data worksheet will be completed at the patient's consent visit by the research nurse, which will record basic demographic information about the patient, along with confirmation of inclusion / exclusion criteria. This will be filed in the Trial Master File held at each of the four main centres, along with a copy being stored in the site file at each trial practice (which can be scanned and uploaded to the patient's electronic GP record if desired).

8.3.3 Direct access to source data / documents

The eCRF and all source documents shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g., MHRA).

8.4 DATA PROTECTION

All trial staff and Investigators will endeavour to protect the rights of the trial participants to privacy and informed consent, and will adhere to the Data Protection Act 1998. The CRF will only collect the minimum required information for the purposes of the trial. Access to the information will be limited to the trial staff and Investigators and relevant regulatory authorities. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server (within the N3 NHS Private Data Network). Access will be restricted by user identifiers and passwords (encrypted using AES-25S encryption). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours in encrypted format.

9. QUALITY ASSURANCE & AUDIT

9.1 INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

9.2 TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); AE recording and reporting; drug accountability. The Trial

Manager, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the TSC.

9.3 TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, and validation of data manipulation. The regional centre team, or where required, a nominated designee of the Sponsor (Nottingham CTU), shall carry out monitoring of trial data as an ongoing activity.

Entries on the trial database will be verified by inspection against the source data. A sample of CRFs (those patients experiencing an adjudicated endpoint) will be checked for verification of all entries made. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

9.4 RECORD RETENTION AND ARCHIVING

In adherence with the ICH-GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years from the end of the study, or for longer if required. If the responsible Investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

9.5 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

9.6 STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

10. PUBLICATION AND DISSEMINATION POLICY

The study results will be presented at scientific meetings and will be the subject of peer-reviewed publications. Trial participants will not be identified in any publications.

Patients will be informed of the results of the trial once they have been published.

Regional conferences will be arranged during the British Society of Gastroenterology's scientific meetings for patients to discuss HEAT and the broader issues surrounding aspirin, as well as publicity via the Society's recently established public Friends of CORE electronic network (5000 subscribers and growing).

11. USER AND PUBLIC INVOLVEMENT

There will be a lay advisor on the Trial Management Group. Their role will be to advise on strategies for recruitment and follow up of participants, comment on study documents and advise on dissemination. There will also be an independent lay advisor on the Trial Steering Committee to give strategic input from a patient cardiovascular perspective. Lay members will be drawn from the Nottinghamshire County PCT research advisors group (or similar in other regions) and from charity groups (such as the Core Friends Group, and the British Heart Foundation).

In addition the next British Society of Gastroenterology Patient Symposium at Digestive Diseases Week 2012 will coincidentally be on clinical research at which existing trials will be discussed and patients invited to make suggestions for others. HEAT will feature at that meeting.

During the set up of the trial, we have involved the Patient and Public Involvement group that has been established in partnership with the Nottingham Digestive Diseases Centre Biomedical Research Unit. This group was formed over a year ago and has experience in reviewing trial documents. The group were asked to review documents and make comments based on:

Readability (Patient Information Sheet): Does the document make sense in the manner in which it is written?

Acceptable: Does the research seem like a good idea and would it be valuable project to do?

Reasonable: Do you think what the patient is being asked to do for the trial is reasonable to expect?

Suitable: Do you think that patients would be keen to take part?

As mentioned previously, all the participants of the pilot study were asked their view on whether they would take part in a randomised trial. In our pilot study, 73% of patients stated they would still enter the trial, even if there was a possibility of being randomised to the non-eradication arm. Many of the remaining participants were unsure because they had not been able to consider the issue beforehand, so we think this will not be a deterrent.

The lay member on the TMG will have influence over the design of the trial and study documents and will be consulted at all stages of the research project.

12. STUDY FINANCES

12.1 FUNDING SOURCE

This study is funded by a grant from the National Institute of Health Research Health Technology programme.

12.2 PARTICIPANT STIPENDS AND PAYMENTS

Participants will not be paid to participate in the trial. Travel expenses will be offered.

13. SIGNATURE PAGE

SIGNATORIES TO PROTOCOL

Chief Investigator: Prof Chris Hawkey

Signature: _____

Date: _____

Principal Investigators: Prof Richard Hobbs

Signature: _____

Date: _____

Prof Michael Moore

Signature: _____

Date: _____

Prof Greg Rubin

Signature: _____

Date: _____

Prof Margaret Cupples

Signature: _____

Date: _____

Dr John Haughney

Signature: _____

Date: _____

Co-Investigators: Prof Tony Avery
Signature: _____

Date: _____

Prof Denise Kendrick

Signature: _____

Date: _____

Trial Statistician: Dr Carol Coupland
Signature: _____

Date: _____

Yana Vinogradova

Signature: _____

Date: _____

Trial Health Economist: Dr Murray Smith
Signature: _____

Date: _____

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APPENDIX 1: DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT

Eradication of *H. pylori* will be carried out using Lansoprazole (30mg), Clarithromycin (500mg) and Metronidazole (400mg) taken twice daily for seven days. This is one of the authorised recommended regimens for *H. pylori* eradication in adults.

Lansoprazole (CAS: 103577-45-3); 30mg capsules.

Clarithromycin (CAS: 81103-11-9); 500mg tablets.

Metronidazole (CAS: 99616-64-5) 400mg tablets.

See Summary of Product Characteristics document for full chemical and pharmacological properties.

KNOWN SIDE EFFECTS

Lansoprazole: General side effects of H₂-receptor antagonists include diarrhoea and other gastrointestinal disturbances, altered liver function tests, headache, dizziness, rash and tiredness. Rare side-effects include acute pancreatitis, bradycardia, AV block, confusion, depression and hallucinations particularly in the elderly or very ill, hypersensitivity reactions, blood disorders and skin reactions. Occasional reports of gynaecomastia and impotence. Side effects specific to Lansoprazole are glossitis, pancreatitis, anorexia, restlessness, tremor, impotence, petechiae and purpura. Very rarely it may cause colitis, raised serum cholesterol or triglycerides.

Drug Interactions: Absorption of lansoprazole may be reduced by antacids and by sucralfate. Plasma concentration may be increased by fluvoxamine. Lansoprazole may increase plasma concentration of cilostazol, avoid concomitant use.

PPIs reduce absorption of itraconazole and ketoconazole. They reduce the plasma concentration of atazanavir and may increase plasma concentration of raltegravir. They may possibly increase plasma concentration of digoxin slightly. PPIs may reduce antiplatelet effect of clopidogrel. They also may reduce absorption of lapatinib and other similar cytotoxics.

Clarithromycin: Nausea, vomiting, abdominal discomfort, diarrhoea, dyspepsia, tooth and tongue discoloration, smell and taste disturbances, stomatitis, glossitis and headache. Less frequently urticaria, rashes and other allergic reactions, reversible hearing loss reported after large doses, cholestatic jaundice, cardiac effects, myasthenia-like symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported, hepatitis, arthralgia and myalgia. Rarely tinnitus. Very rarely pancreatitis, dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, leucopenia, and thrombocytopenia.

Drug Interactions: Clarithromycin may (or does) increase plasma concentration of disopyramide (increased risk of toxicity); rifabutin (increased risk of uveitis); carbamazepine and phenytoin; itraconazole; fesoterodine (antimuscarinic); quetiapine (antipsychotic); mizolastine (avoid concomitant use); etravirine (clarithromycin concentration reduced); maraviroc; midazolam; aprepitant; verapamil; digoxin; cyclosporine; cilostazol; methylprednisolone; eplerenone

(diuretic), avoid concomitant use; dopaminergics; ergot alkaloids; 5HT₁ agonists; ivabradine; statins; ranolazine; sildenafil; sirolimus; tacrolimus; tadalafil; theophylline.

Plasma concentration of both drugs is increased when clarithromycin is given with atazanavir or tipranavir (antivirals). Plasma concentration of clarithromycin is reduced by rifamycins but is increased by ritonavir. Clarithromycin enhances anticoagulant effect of coumarins and effects of repaglinide (antidiabetic); increased risk of rash with efavirenz; reduces absorption of zidovudine; increased risk of colchicine toxicity; increased risk of ventricular arrhythmias when given with pimozide or sertindole, avoid concomitant use; inactivates oral typhoid vaccine.

Avoidance of macrolides advised by the manufacturers of reboxetine (antidepressant); artemether / lumefantrine (antimalarials); tolterodine (antimuscarinic); droperidol (antipsychotic); nilotinib (cytotoxic).

Metronidazole: GI disturbances including nausea and vomiting, taste disturbances, furred tongue, oral mucositis, anorexia, diarrhoea.

Very rarely hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, ataxia, psychotic disorders, darkening of urine, thrombocytopenia, pancytopenia, myalgia, arthralgia, visual disturbances, rash, pruritis, and erythema multiforme.

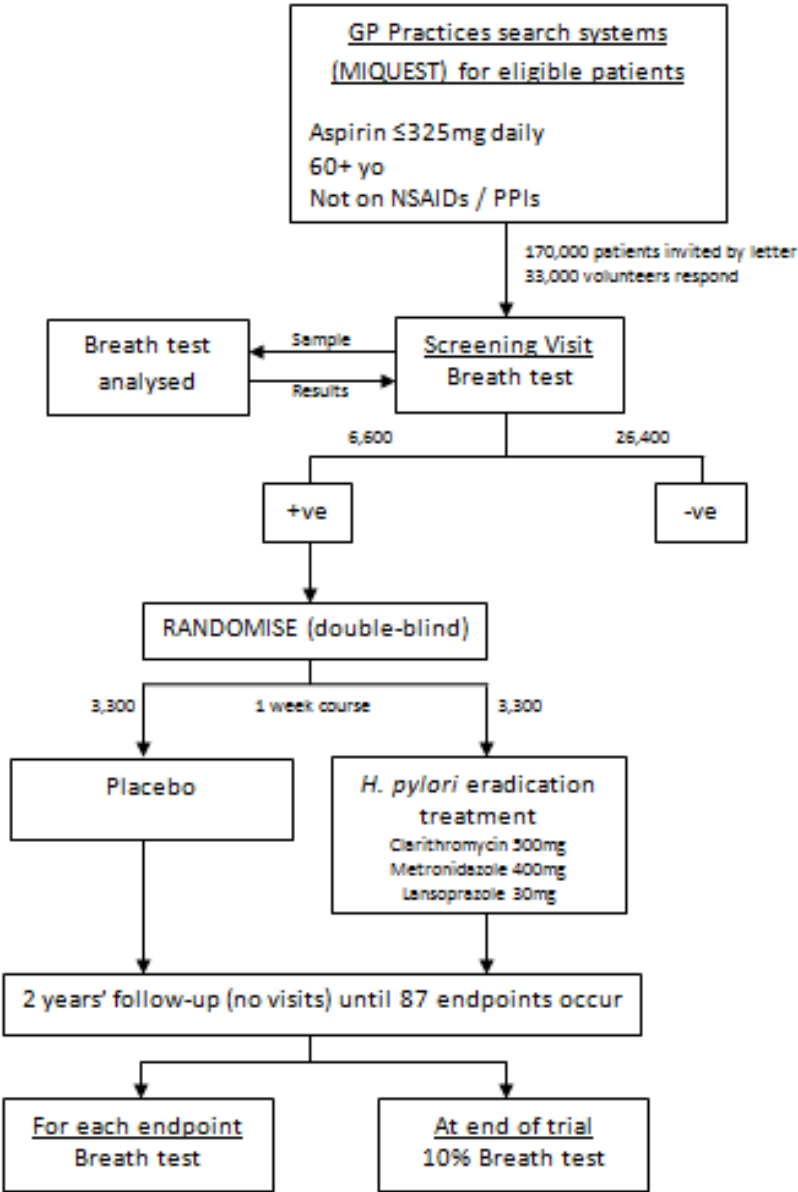
Prolonged and intensive therapy; peripheral neuropathy, transient epileptiform seizures, leucopenia.

Drug Interactions: Psychotic reaction with disulfiram, disulfiram-like reaction with alcohol; enhances anticoagulant effect of coumarins; increases risk of lithium toxicity; reduces bioavailability of mycophenolate; inactivates oral typhoid vaccine.

Metronidazole increases the plasma concentration of phenytoin (metronidazole concentration reduced); busulfan and fluorouracil (cytotoxic).

Metronidazole plasma concentration is reduced by barbiturates and phenytoin but increased by cimetidine.

APPENDIX 2: TRIAL FLOW-DIAGRAM



This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorisation from the University of Nottingham.

APPENDIX 3: CONTRAINDICATED MEDICATIONS

H₂-receptor antagonists

Cimetidine (Tagamet)	Famotidine (Pepcid)
Nizatidine (Axid)	Ranitidine (Zantac)

Proton Pump Inhibitors (PPIs)

Esomeprazole (Nexium)	Lansoprazole (Zoton)
Omeprazole (Losec)	Pantoprazole (Protium)
Rabeprazole Sodium (Pariet)	

Oral Non-Selective NSAIDS

Acelefenac (Preservex)	Acemetacin (Emflex)
Azapropazone (Rheumox)	Dexibuprofen (Seractil)
Dexketoprofen (Keral)	Diclofenac (Voltarol, Arthrotec)
Diflunisal	Fenbufen (Lederfen)
Fenoprofen (Fenopron)	Flurbiprofen (Froben)
Ibuprofen (Brufen, Fenbid)	Indometacin (Indocid PDA)
Ketoprofen (Orudis, Oruvail)	Mefenamic acid (Ponstan)
Meloxicam (Mobic)	Nabumetone (Relifex)
Naproxen (Naprosyn, Synflex, Napratec)	Piroxicam (Brexidol, Fendene)
Sulindac (Clinoril)	Tenoxicam (Mobiflex)
Tiaprofenic acid (Surgam)	

SIGNIFICANT INTERACTION WITH ERADICATION TREATMENT

Alcohol	
Anagrelide	Artemether with Lumefantrine
Atazanavir	Cisapride
Colchicine (in hepatic or renal impairment)	Disopyramide
Dronedarone	Droperidol
Eletriptan	Eplerenone
Ergotamine and Methysergide	Erlotinib
Everolimus	Ivabradine
Lithium	Midazolam
Mizolastine	Nilotinib
Pazopanib	Pimozide
Posaconazole	Quinidine
Raltegravir	Ranolazine
Reboxetine	Saquinavir
Sirolimus	Tolterodine
Ulipristal	

Patient should be advised to stop these drugs whilst they take eradication treatment. If they cannot they should be excluded:

Statins	Terfenadine (Telfast)
Astemizole	