AspECT

Full title: AspECT: A PHASE III, RANDOMISED STUDY OF ASPIRIN AND ESOMEPRAZOLE CHEMOPREVENTION IN BARRETT'S METAPLASIA

Short title: AspECT

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Trial Office, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

General contact information

Chief Investigator
Professor Janusz Jankowski
Consultant Physician and Honorary Professor
University Hospitals Coventry & Warwickshire NHS Trust
Warwick Medical School
University of Warwick
Warwick CV2 2DX
Tel +44 (0)24 7696 8609
Fax +44 (0)24 7696 8653
Email: Janusz.Jankowski@uhcw.nhs.uk

Trial Office (OCTO)
AspECT Trial Office
Oncology Clinical Trials Office (OCTO)
Department of Oncology, The University of Oxford
Old Road Campus Research Building
Oxford OX3 7DQ
Tel: 01865 617011
Email: aspect@octo-oxford.org.uk
Website:http://www.octo-oxford.org.uk

Clinical Trial Coordinator
Adelyn Wise
Tel.: 01865 617011
Fax: 01865 617010
Email: octo-aspect@oncology.ox.ac.uk

Sponsor
The University of Oxford
Ms Heather House
Clinical Trials and Research Governance
Joint Research Office, Block 60
Churchill Hospital
Oxford OX3 7LE
Tel: +44 (0)1865 572224
Fax: +44 (0)1865 572228
E-mail: ctrg@admin.ox.ac.uk

Statistician
Ms Sharon Love
Senior Medical Statistician
Oxford Clinical Trials Research Unit (OCTRU)
Centre for Statistics in Medicine, The University of Oxford
Botnar Research Centre
Windmill Road
Oxford, OX3 7LD
Tel : 01865 223441
Email: sharon.love@csm.ox.ac.uk

Trial Laboratory
Mr Sean James
ChOPIN/AspECT Office
3rd Floor PRI suite- opposite ward 32
University Hospitals Coventry & Warwickshire NHS Trust
Coventry
CV2 2DX
Office Tel: 02476 967587
Tissue Bank Tel: 02456 967033
Email: AspECTLab@uhcw.nhs.uk

Other key contacts

AspECT Trial Management Group	Professor Janusz Jankowski Dr John De Caestecker (Chair) Professor Hugh Barr (Deputy Chair) Professor Paul Moayyedi Dr Rebecca Harrison Professor Stephen Attwood Dr Peter Watson Dr Pradeep Bhandari Dr Yeng Ang Ms Sharon Love Dr Scott Sanders Mrs Adelyn Wise
TMG Advisory non-executive members	Dr Mark Anderson, City Hospital, Birmingham Dr Cathryn Edwards, Torbay Hospital, Torbay Dr Danielle Morris, QEII Welwyn Garden City Dr Colin Rodgers, Antrim, NI Dr Michael Gibbons, Craigavon, NI Dr Krish Ragunath, Nottingham Other observers at the invitation of the CI
Data and Safety Monitoring Committee	Dr Barrie Rathbone, Leicester Royal Infirmary, Leicester (Chair) Prof Julia Brown, Clinical Trial Research Unit, Leeds (Statistical Advisor) Prof David Ferry, New Cross Hospital, Wolverhampton
Non-Independent Members	Prof Janusz Jankowski (CI) Sharon Love (Trial Statistician) Adelyn Wise(Trial Coordinator)
Trial Steering Committee Independent Members	Prof John Primrose, Southampton University Hospital, Southampton (Chair) Ms Sally Stenning, MRC Clinical Trials Unit, London (Statistical Advisor) Prof Nick Talley, Newcastle, Australia Mrs Gwen Harlow (Patient Representative)
Trial Steering Committee Non-Independent Members	Prof Janusz Jankowski (CI) Dr John de Caestecker (TMG Chair) Sharon Love (Trial Statistician) Adelyn Wise(Trial Coordinator)
Trial Steering Committee Observers	Representative from Cancer Research UK Peter Nagy, AstraZeneca Heather House, University of Oxford (Sponsor)
Independent Pharmaceutical Advisor	Dr Emma Roffe

Clinical queries and emergency contact details

During office hours: Clinical Queries should be directed to the AspECT Trial Office and contact the Clinical Trial Coordinator. The call will be passed on to the Chief Investigator or to the Clinical Coordinator (medically qualified) or an appropriate member of the Trial Management Group.

Out of office hours: call the John Radcliffe Hospital switchboard on Tel: 01865 741166 and ask to call the AspECT Clinical Coordinator.

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PROTOCOL SYNOPSIS

Full Title of study:	AspECT: A Phase III, Randomised Study of Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia	
Short Title:	AspECT	
Trial Acronym:	AspECT	
Objectives:	Primary Objectives • To assess whether intervention with aspirin results in a decreased rate of all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia • To assess whether high dose PPI therapy results in a decreased rate of all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia	Secondary Objectives • To assess whether intervention with aspirin results in decreased high-grade dysplasia, in decreased all-cause mortality, in decreased oesophageal cancer incidence and in decreased cause-specific mortality when each is considered separately • To assess whether intervention with high dose PPI results in decreased high-grade dysplasia, in decreased all cause mortality, in decreased oesophageal cancer incidence and in decreased cause-specific mortality when each is considered separately • To assess whether there are clinical and molecular risk factors which can be identified in BM for the development of BA • To assess the cost effectiveness of aspirin and/or PPI treatment in the prevention of BA • To assess whether intervention with PPI and/or aspirin induces changes in the expression of molecular markers for BA. To assess the genomics of aspirin sensitivity (efficacy and side effects) • To assess how quality of life is affected by the different treatments • To assess what the biological risk factors are for cardiac disease and aspirin resistance • To assess gender differences in outcomes
Exploratory Objectives:	• To assess aspirin's role on the development of colorectal adenomas and cancer • To collect and bank samples for use in future ethically approved studies	
Scientific rationale:	The role of aspirin in the prevention of not only colorectal cancer but also oesophageal adenocarcinoma is already accepted in epidemiological studies (19 - 22). Although aspirin is already being used prophylactically in premalignant colorectal lesions, a study of its application to BM is urgently needed. PPIs are used widely but their efficacy in chemoprevention is unclear and if there is an effect the most cost-effective dose is not known. Esomeprazole is arguably the leading agent in its class.	
Clinical rationale:	Conventional clinical risk factors for BA have not been proven in randomised controlled studies, although males have an excess risk of oesophageal adenocarcinoma compared with females at a ratio of 3 to 1 (6 - 16). In the absence of proven stratification, surveillance of all cases of BM is required; this is neither feasible nor cost effective (17). Primary prevention strategies should be aimed at reducing the initiation and malignant degeneration of BM by pharmaceutical manipulation of the oesophageal environment.	

	Potent acid suppressing drugs and aspirin for chemoprotection have the greatest applicability.	
Primary Endpoint:	A composite primary endpoint of all-cause mortality and conversion to adenocarcinoma and conversion to high grade dysplasia.	
Secondary Endpoints:	• All-cause mortality • Conversion to oesophageal adenocarcinoma • Conversion to high grade dysplasia • Death from oesophageal cancer • Cost/oesophageal adenocarcinoma prevented • Cost/life year saved • Molecular markers to be identified at the end of the trial and used during analyses of collected blood and/or tissue samples • Cost/quality adjusted life saved • Formation of new tumours • Composite endpoint of all-cause mortality and conversion to adenocarcinoma and conversion to high grade dysplasia according to gender	
Study Design:	This is a pragmatic, national, multicentre, phase III, randomised 2x2 factorial controlled trial of low or high dose esomeprazole with or without low dose aspirin for 8-10 years	
Patient Numbers:	2513	
Target Population:	Patients with circumferential Barrett's metaplasia of at least 1cm in length (≥C1M1) or a tongue of Barrett's metaplasia of at least 2cm in length (≥C0M2)	
Inclusion and exclusion criteria	Inclusion Criteria A patient is eligible for inclusion in this study if all of the following criteria apply. 1. Aged ≥18 years. 2. Circumferential Barrett's metaplasia of at least 1cm in length (≥C1M1) or a tongue of Barrett's metaplasia of at least 2cm in length (≥C0M2) (irrespective of the presence now or historically of histologically proven intestinal metaplasia). 3. Able to give written informed consent. 4. WHO performance status of 0 or 1 i.e. fully active and self-caring.	Exclusion Criteria A patient is not be eligible for the trial if any of the following apply: 1. High grade dysplasia or carcinoma at enrolment. 2. Medical conditions which would make completing endoscopies or completing the trial difficult, including: a) Frequent transient ischaemic attacks (3 or more) or severe cerebral vascular accident in the previous 6 months*. b) Severe respiratory disease with arterial oxygen saturation of less than 90% at rest c) Severe ischaemic heart disease (exercise tolerance less than 100 yards or life expectancy < 4 years) or myocardial infarction in the previous 3 months. d) Severe inflammatory bowel disease requiring at least one hospital admission of 5 days in the last year or bowels open > 6 times/day. * Patients answering yes to criteria (a) were eligible for the PPI-only (non-aspirin) arms of the trial. 3. Patients with absolute contraindications to PPIs, aspirin or their excipients i.e. allergies, ulcers,

		renal impairment or use of oral anticoagulants. 4. Pregnant or lactating women will not undergo endoscopy and may be given dispensation to stop drug therapy for a year. This should be discussed with the Trial Office.
Trial dose and administration:	Patients receive either continuous PPI 20mg/day or continuous PPI 80mg/day (40mg BD) with or without aspirin 300mg/day.	
Duration on study:	Participants will be in the study for approximately 8 years or 10 years (if they re-consented to extend) from randomisation to last protocol visit. Follow up will end when the participant either reaches their 8th (or 10th if they re-consented) anniversary on trial, choose to withdraw consent, end treatment or on 28th February 2017 (+3 months for appointment slippage); whichever is soonest.	
Study Procedures and frequency: (Procedures For Remainder of Study)	<u>Follow Up</u> Patients will be asked questions and their medical notes checked to determine disease, survival and osteoporosis status. Any unreported SAEs, concomitant medications taken and use of other medications/interventions to treat Barrett's will also be determined and noted. Frequency: Annually whilst on study. <u>Endoscopy & Biopsy</u> Endoscopy will be performed on patients to assess their Barrett's status. Biopsy samples will also be taken for local pathology assessment and the Trial Laboratory. Frequency: Year 6, 8 and 10 (if patients re-consented) <u>Blood Samples</u> Blood samples will be taken for the Trial Laboratory to assess for cancer and cardiovascular risk factors. Frequency: Between year 4 and 6 (once), 8 and 10 (if patients re-consented).	
Patient care post-trial:	Following the end of study visit patients will receive standard care.	
Pharmacokinetic assays:	N/A	
Pharmacodynamic assays:	N/A	
No. of Study Site(s)	85 Centres in the UK	
End of study	Last Patient Last Visit Date is 28th February 2017 (we will allow +3 months for appointment slippage). Patients should be on the study for a maximum of 123 months.	
Publication policy	The results of this study will be published in a peer-reviewed scientific journal and other academic research purposes as agreed by the Investigators.	

SUMMARY SCHEDULE OF EVENTS

Date Due at OCTO (time after randomisation)	CRFs Due	Samples Due
5 years	5 year Follow-up	
Between 4 and 6 years		Blood sample
6 years (+/- 3 months)	6 year Follow-up Endoscopy and Pathology Biopsy Sampling	Endoscopy Biopsy samples
7 years	7 year Follow-up	
8 years (+/- 3 months)	8 year Follow-up Endoscopy and Pathology Biopsy Sampling End of Treatment (if not re-consented to 10 years follow up)	Endoscopy Biopsy samples Blood sample
9 years (only if patient consented for 10 years follow up)	9 year Follow-up	
10 years (+/- 3 months) (only if patient consented for 10 years follow up)	10 year Follow-up Endoscopy and Pathology Biopsy Sampling End of Treatment	Endoscopy Biopsy samples Blood sample
Unscheduled	Serious Adverse Event Death (when no causal relationship with trial medication is suspected) End of Treatment (for patients who withdraw from treatment early) Consent Withdrawal Notification (for patients who withdraw from all parts of the study) Change of Treatment Additional Data (for any other information you feel necessary to report or if you need more space to continue on from another CRF) Endpoint Sampling (for patients with low or high grade dysplasia or oesophageal adenocarcinoma) Pregnancy Notification Bowel Screening Clopidogrel	

ABBREVIATIONS

ALT	Alanine Aminotransferase (blood test to detect liver injury)
AST	Aspartate Aminotransferase (blood test to detect liver injury)
AE	Adverse Event
AUC	Area Under Curve
BA	Barrett's Adenocarcinoma
BM	Barrett's Metaplasia
BUN	Blood Urea Nitrogen (measurement of renal function)
CI	Chief Investigator
COX	Cyclo-oxygenase
CRF	Case Report Form
CVA	Cerebral Vascular Accident (stroke)
DNA	Deoxyribonucleic Acid
DSMC	Data and Safety Monitoring Committee
DSUR	Development Safety Update Report
EA	Esophageal Adenocarcinoma (see also OA)
ER	Endoscopic Resection
GAL	Grant Award Letter
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase (blood test to detect liver injury)
GI	Gastrointestinal
GORD	Gastro-Oesophageal Reflux Disease
HGD	High Grade Dysplasia
HSCIC	Health and Social Care Information Centre
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IHD	Ischaemic Heart Disease
IM	Intestinal Metaplasia
IMP	Investigational Medicinal Product
INR	International Normalized Ratio (measure of blood clotting time)
LGD	Low Grade Dysplasia
LPLV	Last Patient Last Visit
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
MRC	Medical Research Council
MRIS	Medical Research Information Service
NSAID	Non-Steroidal Anti Inflammatory Drug
OA	Oesophageal Adenocarcinoma (see also EA)
PBMC	Peripheral Blood Mononuclear Cell
PGE2	Prostaglandin E2
PI	Principal Investigator
PPI	Proton Pump Inhibitor
PUB	Peptic Ulcer Bleeding
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SNP	Single Nucleotide Polymorphism
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organisation

1 INTRODUCTION

1.1 Background

Erosive oesophagitis secondary to gastro-oesophageal reflux disease (GORD) is arguably the most common medical condition in Western countries affecting 10% of adults (1, 2). 10% of patients with erosive oesophagitis will progress to Barrett's metaplasia (BM), which is pre-malignant columnar epithelium that lines the distal oesophagus (1, 2). While dysplasia in BM is still the gold standard for assessing the premalignant potential, many individuals develop their adenocarcinoma without having dysplasia detected.

Barrett's adenocarcinoma (BA) is characterised by a poor prognosis, with a median survival time, following diagnosis, of less than one year and fewer than 10% surviving for more than five years. Detection is needed at an earlier stage where intervention can dramatically improve survival.

1.2 Investigational medicinal product(s) used in the study

Acid and bile are the predominant injurious agents in gastro-oesophageal reflux disease. Proton pump inhibitors (PPIs) are widely used in the treatment. They are highly effective and safe in minimising symptoms and healing of oesophagitis, but there is no clear evidence that they inhibit the evolution of cancer. There are no clinical studies that address this issue adequately. Proof of concept for the notion that PPIs can reduce cancer risk comes from observations that partial regression of metaplastic mucosa may be induced by suppression of acid (and bile) reflux with PPIs (23, 24). Whether this translates into a subsequent decrease in neoplastic change is unclear. Intermediate markers from patients with BM in whom intraoesophageal pH had been normalised on PPI therapy showed decreased cell proliferation and improved differentiation. Conversely, incomplete acid suppression that allows short pulses of acid led to epithelial changes, selecting poorly differentiated cells with increased proliferative potential (23). These data indicate that gastro-oesophageal reflux is implicated in the pathogenesis of BM and there is preliminary evidence to show that its attenuation reverses the surrogate markers in the short term and perhaps the cancer risk in the longer term.

The counter argument is that PPIs may not be protective against oesophageal cancer. Epidemiological studies suggest that since the widespread introduction of acid suppressing drugs (H2 antagonists and PPIs) BA has increased dramatically (1). In animal models of duodenogastric reflux there is an enhanced cancer risk when gastric acid blockade by omeprazole is employed (25). Bile acids may be more cytotoxic at a neutral pH, and it is therefore possible that PPI therapy could promote oesophageal cancer. It is likely that any cytotoxic effects of PPIs either directly or indirectly, are determined by the extent and/or pattern of acid suppression i.e. total acid suppression by high dose PPI or incomplete/partial acid suppression by low dose PPI.

Because BM is relatively insensitive to acid (24, 25, 26), symptom control is easier to achieve than complete normalisation of intra-oesophageal pH (26, 27, 28). Therefore, symptoms are an unreliable indicator of the adequacy of treatment. Most patients' reflux symptoms are controlled with a once daily standard dose of PPI (esomeprazole 20mg) and normalisation of intra-oesophageal pH is achieved in about 65% (29). Patients with Barrett's oesophagus may have substantially greater degrees of reflux and may require higher doses of PPI to achieve normalisation of the oesophageal pH. Evidence indicates that the latest PPI esomeprazole is more effective than other PPIs at both suppressing acid (43) and at treating more severe reflux disease including Barrett's (29, 30). Although 20mg/day will be sufficient for symptomatic relief in the majority of reflux patients, the level of acid suppression achieved is not optimal (only 53% of 24hour period has gastric acid at pH > 4) and normalisation of oesophageal pH is even worse (acid reflux in the oesophagus reduced to 'current accepted physiological levels'). However, a recent study has demonstrated that twice daily dosing with esomeprazole 40mg produces a profound level of acid suppression that is superior to that demonstrated by any other PPIs. In this regard, 40mg esomeprazole twice daily usually achieves a 96% of 24 hour period with pH > 4 (44) compared with < 50% on 20mg/day esomeprazole or equivalent (31).

BM does not regress once the external stimulus for its initiation is removed. In epidemiological studies aspirin has been shown to be associated with a dramatically decreased incidence of both oesophageal and gastric adenocarcinoma. Its anticancer effects are thought to be mediated in part by its ability to inhibit the enzyme cyclo-oxygenase (COX). Aspirin inhibits PGE2 thereby inhibiting prostaglandin formation by COX-1 and the inducible COX-2 enzymes, as well as the inhibitor of apoptosis protein (c-IAP)-2. Aspirin also dampens down β-catenin signalling and NFκB transcription (33, 34). This makes aspirin a potentially more effective cancer chemopreventative agent than Non-Steroidal Anti Inflammatory Drugs (NSAIDs).

A meta-analysis of aspirin in eight upper GI cancer prevention cohorts has estimated cancer reduction by about 50% when compared with NSAIDs (35). In addition, combined aspirin and PPI therapy was shown in a recent model to be more effective and cheaper than any other intervention including surveillance. Early pilot data also indicates that low dose aspirin is also more effective in decreasing PGE2 levels in Barrett's patients than 25mg of rofecoxib, a selective COX-2 inhibitor (personal communication Prof George Triadofilopoulos, USA). In a model of cancer prevention a selective COX-2 inhibitor was not as effective as a non-selective NSAID (36).

There is some controversy surrounding the potential for cardiovascular side effects of some of the COX-2 selective inhibitors in susceptible patients. Aspirin is unique in its drug group because it irreversibly inhibits platelet activity at low doses. This property explains the well-established cardioprotective properties of aspirin in at-risk individuals. Patients with BM have an increased risk of cardiovascular events. Therefore use of aspirin may be useful for secondary prevention and perhaps even primary prevention in certain at-risk groups (37). The peak incidence of Ischaemic Heart Disease (IHD) is about 10 years before the development of adenocarcinoma in Barrett's and therefore in order to both chemoprevent and cardioprotect, aspirin should be commenced in the early 50s for maximum benefit. Any NSAID drug (including the COX-2 selectives) other than aspirin would carry risks of cardiovascular complication. For this reason, together with the fact that aspirin is the best-studied anti-cancer COX inhibitor, aspirin is the drug of choice for this trial.

There is undoubted risk with aspirin (and without PPI) of gastrointestinal haemorrhagic complications (1-2%). But this is decreased 10 fold with PPI therapy as the damage is acid related (38, 39, 40), and still further with helicobacter pylori (HP) eradication. Indeed, aspirin may sensitise the organism to eradication therapy (41). Also, to a lesser extent, haemorrhagic stroke has also been reported. However, several reports have indicated that aspirin's advantages far outweigh any adverse effects, with major complications occurring in 0.002% and death from major complications in 0.00005% (35). While the optimal dose of aspirin for cardiac protection is probably 75mg/day, the ideal dose for chemoprevention is currently unknown and lies between 75-300mg/day.

Anti-reflux surgery has been advocated for patients with BM but it is not first line therapy due to issues of fitness for surgery and peri-operative mortality rate for surgery. It is also clear that anti-reflux surgery has at most a modest effect on cancer prevention (2). Other forms of surgical intervention including endoscopic mucosal resection and laser therapy are at present carried out in too few centres and by too few people to be able to be exploited reproducibly in a national study in the near future.

The majority of adenocarcinomas in the oesophagus in the community are not diagnosed in surveillance programs. The average life expectancy in the UK for males is 73 years and for females 77 years. At these ages the commonest cause of death is ischaemic heart disease and cerebrovascular or peripheral vascular disease (42). The average age of presentation of patients with BA is 69 years. Therefore chemoprevention aims to prolong survival or delay onset of the cancer by 4 years in males and 8 years in females to allow other 'morbid diseases' to intervene naturally.

AspECT is a chemoprevention trial of acid suppression and aspirin in patients with Barrett's oesophagus. This study will allow the validation of several surrogates including biomarkers and clinical parameters. Aspirin is an effective chemoprotective agent in a number of cancers of the gastrointestinal tract. Continuous acid suppression therapy is well tolerated, has extremely low morbidity and mortality, and is available readily in every centre in the UK. These two treatments are unlikely to 'neutralise' the real benefits of each other in the majority of patients as the drugs act independently and their effects will be additive and possibly complementary. In addition, the use of these two drugs together may help decrease the side effects of aspirin intervention alone, especially in men. PPIs will be required for symptom control of reflux and aspirin may have additional benefits in reducing colorectal cancer and cardiovascular events. While the main study concentrates on males we will assess a smaller cohort of females in the integrated women's AspECT study (WASP). By doing so we will be able to address genetic and environmental reasons why males develop more oesophageal adenocarcinoma than females.

1.3 Pharmacokinetics of aspirin

Absorption

Absorption of non-ionised aspirin occurs in the stomach and intestine.

Metabolism

Some aspirin is hydrolysed to salicylate in the gut wall. After absorption, aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma.

Aspirin is bound to plasma proteins and is widely distributed. Plasma aspirin concentrations decline rapidly (half life 15-20 minutes) as plasma salicylate concentrations increase.

Hepatic Insufficiency
Salicylate is mainly eliminated by hepatic metabolism – the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Aspirin should be avoided in patients with severe hepatic impairment (ALT > 150 or bilirubin over 100).

Renal Insufficiency
Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption. Aspirin may cause salt and water retention and renal failure, especially in patients with pre-existing renal impairment. Aspirin should be avoided in patients with severe renal impairment (Urea > 30 and/or Creatinine > 300).

Indications relevant to Barrett's Metaplasia
None

1.4 Pharmacokinetics of esomeprazole

Absorption
Esomeprazole is acid labile and is administered orally as enteric coated granules. In vivo conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40mg and increases to 89% after repeated once-daily administration. For 20mg esomeprazole, the corresponding values are 50% and 68% respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose- dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Hepatic insufficiency
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction is similar to that in patients with symptomatic Gastro Oesophageal Reflux Disease (GORD) with normal liver function. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum dose of 20mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal insufficiency
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Indications relevant to Barrett's Metaplasia
Esomeprazole tablets are indicated for:

- Gastro-oesophageal Reflux Disease (GORD)
- Treatment of erosive reflux oesophagitis
- Long-term management of patients with healed oesophagitis to prevent relapse
- Symptomatic treatment of gastro-oesophageal reflux disease

1.5 Rationale for the study

The rationale for medical intervention before the development of dysplasia or indeed neoplasia currently lacks an evidence base. The UK has one of the highest worldwide prevalence of BM (0.5-2% of adults) (3). The resulting incidence of Barrett's adenocarcinoma (BA) is 3-4 times that seen in either Europe or North America (4). In addition the conversion rate to BA of individuals with BM in surveillance programmes is twice as common in the UK compared with the USA (5).

Oesophageal adenocarcinoma causes over 7,500 deaths in the UK each year and the incidence is increasing at a rate greater than that of any other cancer in the western world. The study of aspirin is timely in relation to popular expectation and now is the time to do this trial. Prevention by using simple, cheap and commonly used medications is much more likely to be an effective way to reduce these deaths than the current attempts of treating established disease. In this regard, the role of aspirin in the prevention of not only colorectal cancer but also oesophageal adenocarcinoma is already accepted in epidemiological studies (19 - 22). Although aspirin is already being used prophylactically in premalignant colorectal lesions, a study of its application to BM is urgently needed. PPIs are used widely but their efficacy in chemoprevention is unclear and if there is an effect the most cost-effective dose is not known. Esomeprazole has been introduced into the clinical arena and is arguably the leading agent in its class.

Conventional clinical risk factors for BA have not been proven in randomised controlled studies, although males have an excess risk of oesophageal adenocarcinoma compared with females at a ratio of 3 to 1 (6 - 16). In the absence of proven stratification, surveillance of all cases of BM is required; this is neither feasible nor cost effective (17). Primary prevention strategies should be aimed at reducing the initiation and malignant degeneration of BM by pharmaceutical manipulation of the oesophageal environment. Potent acid suppressing drugs and aspirin for chemoprotection have the greatest applicability. Detecting additional risk factors (including aneuploidy, p16, p53 mutations, altered catenin biology and cyclinD1 expression), which more accurately predict the subgroups that will progress to malignancy, may help to prove the hypothesis that cancer can be prevented (18).

2 TRIAL DESIGN

This is a pragmatic, national, multicentre, phase III, randomised 2x2 factorial controlled trial of low or high dose esomeprazole with or without aspirin for at least 8 years. Recruitment closed at the end of February 2009. 2012 male patients and 501 female patients were recruited. A subset of patients re-consented to extend their trial participation to 10 years or until the 28th February 2017 (whichever will be sooner).

ARM A: 20mg PPI = symptomatic treatment only standard therapy control arm	**Arm B: 80mg PPI strong acid suppression arm**	**No Aspirin (A&B)**
Arm C: 20mg PPI symptomatic treatment and aspirin arm	**ARM D: 80mg PPI strong acid suppression and aspirin arm**	**Aspirin (C&D)**
Low dose PPI (A&C)	**High dose PPI (B&D)**	

Patients are followed up annually by a trial nurse via phone call or clinic visit and by endoscopy at approximately 2 yearly intervals from the date of randomisation (+/- 3 months either side). Once patients come out of the trial endoscopy schedule due to clinical need/patient choice, the endoscopy for trial can be performed every 2 years from

that date (+/- 3months) and not have to revert back to trial schedule. In 2010 BSG guidance recommended a 2 year surveillance interval. Thereafter patients should be endoscoped at 2 yearly intervals unless they develop dysplasia, in which case they should be managed according to local procedure.

Although current guidelines, including the recent British Society of Gastroenterology guidelines (Fitzgerald et al, GUT 2014), suggest 3 year instead of 2 year surveillance intervals, these are purely empirical. The BoB CAT (Benign Barrett's and CAncer Taskforce) group provides a more comprehensive systematic review, has a larger consensus group and is badged by over 10 international organisations including NICE (Bennett et al, Am J Gastro 2015). The group has indicated the need for more evidence in this area.

AspECT patients should remain on the 2 year surveillance interval. At the end of the trial this will help AspECT to contribute to the discussion on different surveillance intervals.

3 OBJECTIVES AND ENDPOINTS

Primary Objectives	**Endpoints/ Outcome measures**	**Timepoint(s) of evaluation of this end point**
• To assess whether intervention with aspirin results in a decreased rate of all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia • To assess whether high dose PPI therapy results in a decreased rate of all causes of mortality or conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia	• A composite primary endpoint of all-cause mortality and conversion to adenocarcinoma and conversion to high grade dysplasia	2 yearly
Secondary Objectives	**Endpoints/ Outcome measures**	
To assess whether intervention with aspirin results in decreased high-grade dysplasia, in decreased all-cause mortality, in decreased oesophageal cancer incidence and in decreased cause-specific mortality when each is considered separately	• All-cause mortality • Conversion to oesophageal adenocarcinoma • Conversion to high grade dysplasia • Death from oesophageal cancer	2 yearly
To assess whether intervention with high dose PPI results in decreased high-grade dysplasia, in decreased all-cause mortality, in decreased oesophageal cancer incidence and in decreased cause-specific mortality when each is considered separately	• All-cause mortality • Conversion to oesophageal adenocarcinoma • Conversion to high grade dysplasia • Death from oesophageal cancer	2 yearly
To assess whether there are clinical and molecular risk factors which can be identified in BM for the development of BA	• Conversion to oesophageal adenocarcinoma	2 yearly
To assess the cost effectiveness of aspirin and/or PPI treatment in the prevention of BA	• Cost/oesophageal adenocarcinoma prevented • Cost/life year saved	End of trial
To assess whether intervention with PPI and/or aspirin induces changes in the expression of molecular markers for BA. To assess the genomics of aspirin sensitivity (efficacy and side effects)	• Molecular markers to be identified at the end of the trial and used during analyses of collected blood and/or tissue samples	End of trial

To assess how quality of life is affected by the different treatments	• Cost/quality adjusted life saved	End of trial
To assess what the biological risk factors are for cardiac disease and aspirin resistance	• Molecular markers to be identified at the end of the trial and used during analyses of collected blood and/or tissue samples	End of trial
To assess gender differences in outcomes	• A composite endpoint of all-cause mortality and conversion to adenocarcinoma and conversion to high grade dysplasia • All-cause mortality • Conversion to oesophageal adenocarcinoma • Conversion to high grade dysplasia • Death from oesophageal cancer	End of trial
Tertiary/Exploratory Objectives	**Endpoints**	
To assess aspirin's role on the development of colorectal adenomas and cancer	New tumour	End of trial
To collect and bank samples for use in future ethically approved studies	Not applicable	Not applicable

4 PATIENT SELECTION

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria:

4.1 Eligibility criteria for entry into the study

Inclusion criteria:

A patient is eligible for inclusion in this study if all of the following criteria apply.

1. Aged ≥18 years.
2. Circumferential Barrett's metaplasia of at least 1cm in length (≥C1M1) or a tongue of Barrett's metaplasia of at least 2cm in length (≥C0M2) (irrespective of the presence now or historically of histologically proven intestinal metaplasia).
3. Able to give written informed consent.
4. WHO performance status of 0 or 1 i.e. fully active and self-caring.

4.2 Exclusion criteria:

A patient is not be eligible for the trial if any of the following apply:

1. High grade dysplasia or carcinoma at enrolment.
2. Medical conditions which would make completing endoscopies or completing the trial difficult, including:
    a. Frequent transient ischaemic attacks (3 or more) or severe cerebral vascular accident in the previous 6 months*
    b. Severe respiratory disease with arterial oxygen saturation of less than 90% at rest
    c. Severe ischaemic heart disease (exercise tolerance less than 100 yards or life expectancy < 4 years) or myocardial infarction in the previous 3 months
    d. Severe inflammatory bowel disease requiring at least one hospital admission of 5 days in the last year or bowels open > 6 times/day

    * Patients answering yes to criterion a. were eligible for the PPI-only (non-aspirin) arms of the trial
3. Patients with absolute contraindications to PPIs, aspirin or their excipients i.e. allergies, ulcers, renal impairment or use of oral anticoagulants.
4. Pregnant or lactating women will not undergo endoscopy and may be given dispensation to stop drug therapy for a year. This should be discussed with the Trial Office.

If a patient was suitable for inclusion but later becomes unsuitable, this should be discussed with the Trial Office before they are withdrawn. Only in exceptional circumstances should patients not be followed up i.e. complete

withdrawal of consent or current life threatening disease with poor outcome and therefore unable to tolerate endoscopy. In these circumstances patients should be followed up in outpatient clinics.

4.3 Protocol deviations

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety reasons.

Investigators should not deviate from the protocol for the management of enrolled subjects deliberately unless essential to protect the rights or safety of the individual. Examples might include the addition or deletion of tests, dosing, duration of treatment, etc. It may be necessary to withdraw the patient from further study. All waivers and deviations should be fully documented/ justified and reported to the Trial Office without delay.

5 TRIAL ASSESSMENTS AND PROCEDURES

Please refer to the Schedule of Investigations given at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the patient's medical record for extraction onto the CRF.

5.1 Evaluations during the study

All patients will be followed-up annually after study entry, and an annual Follow-Up Form completed. The patients should be asked about their disease and osteoporosis status and this should be recorded on the form. The Follow-Up Site staff are reminded to:

a) Ask patients at each follow-up visit/call about any hospital admissions or event.

AND

b) Check patient medical records for any hospital admissions or events which should be reported as a Serious Adverse Event.

Treatment or intervention for Barrett's since the previous follow-up should also be determined and recorded along with any concomitant medication that the patient may have taken.

The Patients may be followed up by telephone or in person at year 1, 3, 5, 7 and 9 (if patients re-consented) post randomisation. A Follow-Up Form must be completed on all occasions.

At year 2, 4, 6, 8 and 10 (if patients re-consented) post randomisation (+/- 3 months either side) patients will have an endoscopy to assess their Barrett's. The following forms must be completed at these time points:
Biopsy Sampling Form
Endoscopy and Pathology Form
Follow-up Form

If the final endoscopic procedure is performed later than 8 years + 3 months (for those patients that did not re-consent to additional follow up) or later than 10 years + 3 months (for those patients who did re-consent to additional follow up), or later than 28th February 2017 (the date of LPLV) + 3 months, then provided that the patient has agreed, trial biopsy samples and trial endoscopy & pathology data will be collected.
Patients whose trial medication dose changes or is temporarily suspended (see section 8.5) should be reported using the Change of Treatment Form.

Patients who are prescribed clopidogrel should be reported using the clopidogrel CRF.

Patients who become pregnant should be reported using the Pregnancy Notification Form. Pregnant or lactating women will not undergo endoscopy and may be given dispensation to stop drug therapy for a year. This should be discussed with the Trial Office. During the first trimester only Gaviscon should be taken, after this it is advised that Omeprazole is prescribed if required. Patients may re-start esomeprazole after a break of 1 year.

Patients who undergo colonoscopy or flexible sigmoidoscopy during the trial should be reported using the Bowel Screening Form.

Patients will also be flagged with the NHS Health and Social Care Information Centre (HSCIC, previously called MRIS) in the UK if the patient agreed during the consent process. This should be done so that endpoint data can be subsequently gathered from those lost to follow-up.

Patients who are not already members of the patient support group called FORT (Fight Oesophageal Reflux Together) may be invited to join.

5.2 Duration of patient participation

Participants will be in the study for approximately 8 years or 10 years (if they re-consented to extend) from randomisation to last protocol visit. Follow up will end when the participant either reaches their 8th (or 10th if they re-consented) anniversary on trial, choose to withdraw consent completely, end treatment or on 28th February 2017 (+ 3 months); whichever is soonest.

5.3 Post-trial care and follow-up

Following the end of study visit, patients will receive standard care. Patients they should discuss this with their GP. Regular endoscopic follow up should continue as per local standard of care. This may not be every 2 years as it was on the study. The endoscopist should advise the patient's GP as to the recommended treatment for normal clinical practice.

6 EARLY PATIENT WITHDRAWAL

6.1 Withdrawal from treatment

At any time during the course of the trial, a patient may withdraw early from treatment. The Investigator also has the right to withdraw patients from the study or study treatments if he/she feels that it is in the best interests of the patient. This may happen for a number of reasons, including:

- Unacceptable toxicity
- AE/SAEs requiring discontinuation
- Clinical decision
- Patient decision

When the patient stops treatment early, an 'End of Treatment' Form must be completed along with any other relevant forms, e.g. SAE Form or Consent Withdrawal Notification Form if the patient has withdrawn consent from the whole study. In this case a Consent Withdrawal Form should be offered to the patient to sign (see section 6.3. below). The reason for withdrawing from treatment early should be clearly documented on the End of Treatment form. The patient should continue to be followed-up as per protocol.

At the end of trial participation, all patients must have an End of Treatment Form completed, recording whether they complete treatment as per protocol or withdrew from treatment early.

6.2 Withdrawal from endoscopy

If a patient absolutely cannot tolerate endoscopy every 2 years, or is removed by clinical decision from routine endoscopic screening, the patient may remain on trial medication (if clinically indicated) and remain on trial follow up as "withdrawn from endoscopic follow up". The Trial Office should be notified when a patient withdraws from endoscopic follow up and a File Note be created. The patient should still be seen by the local PI every 2 years even if not endoscoped.

6.3 Consent withdrawal

Consent withdrawal means that a patient has expressed a wish to withdraw from the study in its entirety. Under these circumstances, the site needs to document all relevant discussions in the patient notes and offer the patient the current Consent Withdrawal Form to sign. It is not compulsory for a patient to sign the Consent Withdrawal Form in order to withdraw from the trial, but in this case the patient's intentions must be clearly documented in their notes.

Sites must notify the Trial Office of the patient's wishes using the Consent Withdrawal Notification form.

If the patient withdraws from any or all parts of the study, investigators are still responsible for following up any SAEs until resolution.

6.4 Reaching a trial endpoint

Low Grade dysplasia

Low grade dysplasia is NOT a strict AspECT trial endpoint however the AspECT laboratory need to receive a tissue sample in formalin (and if possible fresh tissue in RNA later) from the diseased area in order to address endpoints related to translational studies. Please complete an Endpoint Sampling form and send to the Trial Office. Patients must stay on trial medication and be followed up according to protocol. BSG guidelines suggest 6-12 monthly endoscopy – this is at the discretion of the local investigator. Once patients come out of the trial endoscopy schedule due to clinical need/patient choice, the endoscopy can be continued to be repeated for trial every 2 years from that date (+/- 3months) and not have to revert back to trial schedule.

High Grade dysplasia

When a patient is diagnosed with high grade disease, they should be withdrawn from trial medication and transferred to standard care as per local procedure. An End of Treatment form should be completed. Both formalin and fresh tissue (RNA later) from the diseased area should be collected for the trial and sent to the AspECT laboratory. An Endpoint Sampling form should be completed and sent to the Trial Office. Patients should be treated and followed up as per BSG and MDT guidance but for the purpose of the trial they should additionally continue to be followed up (off trial medication) as per trial protocol (annual follow-up, 2 yearly endoscopies and biopsy collection). The subsequent management of the HGD should be notified to the Trial Office on the annual Follow-up Form (e.g. continued surveillance, endoscopic mucosal resection, radio frequency ablation, argon plasma coagulation, laser therapy, minimal access surgery, oesophagectomy or other and any combinations).

Oesophageal adenocarcinoma

When a patient is diagnosed with OA, they should be withdrawn from trial medication and transferred to standard care as per local procedure. An End of Treatment form should be completed. Both formalin and fresh tissue (RNA later) from the diseased area should be collected for the trial and sent in formalin to the AspECT laboratory. An Endpoint Sampling form should be completed and sent to the Trial Office. Patients should be treated and followed up as per BSG and MDT guidance but for the purpose of the trial they should additionally continue to be followed up (off trial medication) as per trial protocol (annual follow-up, 2 yearly endoscopies and biopsy collection). The subsequent management of the OA should be notified to the Trial Office on the annual Follow-up Form (e.g. continued surveillance, endoscopic mucosal resection, radio frequency ablation, argon plasma coagulation, laser therapy, minimal access surgery, oesophagectomy or other and any combinations).

6.5 Death

If a patient dies, an End of Treatment Form and a Death Form should be completed and sent to the Trial Office immediately. Deaths resulting from SAEs must be reported on the trial SAE report form instead of the Death Form.

7 SAMPLES FOR LABORATORY ANALYSIS

7.1 Samples to be analysed in local Trust's laboratories

Pathology

Biopsy samples are collected from patients participating in the trial. Patients were endoscoped at baseline (the endoscopy prior to randomisation is defined as the baseline visit for patients recruited retrospectively) and thereafter, will be endoscoped at approximately 2 yearly intervals from the date of randomisation (+/- 3 months either side). At each endoscopy any macroscopic abnormality of the Barrett's metaplasia will be biopsied for formalin fixation and histological assessment for dysplasia.

The routine diagnostic pathology samples taken at endoscopy will be labelled, processed and reported according to local hospital protocols.

7.2 Samples to be sent to and analysed in a Trial Laboratory

All samples sent to the Trial Laboratory should be labelled with the trial code, trial patient number, and date taken. Should the laboratory receive any samples carrying unique patient identifiers, the recipient must immediately obliterate this information and re-label. The study site will be informed of the error. In order to create a unique tissue

bank, extra samples must be collected for submission to the tissue bank in addition to the usual diagnostic samples collected during the endoscopy. The new tissue bank will be the Arden Biobank based at the University Hospitals of Coventry and Warwick.

7.2.1 Research biopsies in formalin

Oesophageal biopsies for the AspECT trial must be performed in the following manner every 2 years or when a patient is diagnosed with low grade dysplasia, high grade dysplasia or oesophageal adenocarcinoma:

Research biopsies (1 each for formalin, 3 in total) must be taken from:

a. The unaffected squamous oesophagus.
b. Just below the squamo-columnar junction.
c. Below the gastro-oesophageal junction.

The research biopsies should be submitted to the Trial Laboratory in formalin solution as per the SOPs provided by the laboratory. In addition for longer segments of Barrett's oesophagus, extra discretionary biopsies for metaplastic segments are encouraged to achieve adequate sampling.

7.2.2 Formalin fixed paraffin embedded tissue blocks

Formalin fixed paraffin embedded (FFPE) tissue blocks were requested from the local pathology lab for patients who were recruited retrospectively and therefore did not have trial biopsy samples collected at baseline, or for patients for whom biopsy samples for the Trial Laboratory were not collected during a follow-up endoscopy. These should be sent to the Trial Laboratory. FFPE blocks will be returned at the end of the trial unless they are required sooner in which case they will be returned on request. These tissues will be anonymised.

7.2.3 Fresh specimens in RNA later solution

All sites which have recruited 25 or more patients should additionally provide fresh tissue specimens from the normal oesophagus, Barrett's oesophagus, and fundus (3 in total), using RNA Later solution which will be supplied by the Trial Laboratory and should be submitted to the laboratory as per the SOPs provided. This is compulsory for sites which have recruited 25 or more patients as these tissues are required for secondary endpoints and these larger sites contribute 80% of the patients. DNA and RNA will be extracted from additional samples in RNA later (although in occasional circumstances paraffin embedded material may be used when the former isn't available) for SNP analysis and micro array analysis.

7.2.4 Blood samples

Blood samples are collected from all patients at baseline, between 4 and 6 years post randomisation, plus at 8 and 10 (if patients re-consented) years post randomisation to assess cancer and cardiovascular risk factors. The remainder will be stored for analysis of circulating genetic mutations as and when reliable assays become available. Patients who did not provide a blood sample at any of these visits or whose sample was collected but found to be clinically unsuitable will be asked to provide a blood sample at the next follow-up visit. The blood tubes and packaging to post samples to the Trial Laboratory are provided by the laboratory. The procedure for taking blood is provided with the supplies. Samples should not be taken from patients who are known to be HIV, HBV or HCV positive. Samples which may contain any other infectious material should not be submitted.

7.3 Helicobacter testing

Helicobacter testing can be completed in two ways; either a blood or biopsy sample (preferred) maybe taken for diagnosis at local pathology lab or a Clo test may be taken on a biopsy sample during the endoscopy. In the case of the latter, the result this should be recorded in the relevant section of the Endoscopy and Pathology CRF. If the initial biopsy test is positive then patients should be tested post treatment with a breath test. If the Clo test is the initial test and it is negative it is preferable that serum testing is done in these individuals at some point during the study. This may be done from the donated serum. All patients should have their Helicobacter Pylori status checked at least once during the study. At the end of the trial all patients should have Helicobacter Pylori status noted even if eradicated (as eradication can be unsuccessful in 10% of cases).

7.4 Clinical reporting of exploratory research assay results

The results of the AspECT trial research assays are exploratory and are not intended to influence the individual patient's medical care. Findings will not be reported routinely to the responsible clinician except in the unlikely event that the result might be beneficial to the patient's clinical management.

7.5 Trial sample retention at end of study

Trial samples collected from AspECT patients will fall under the custodianship of the ChOPIN trial which runs under its own separate approval, REC Ref: 06/Q1603/07 (East London Research Ethics Committee 1). The CI for ChOPIN is also Prof Jankowski. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigator on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study, any surplus samples may be retained for use in other projects that have received ethical approval. Hence, any surplus study samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

7.6 Withdrawal of consent for sample collection and/or retention

A patient may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in their medical record and will inform the Trial Office accordingly. The investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymised, it would not be possible to destroy such samples.

8 INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

8.1 Name of IMPs

Esomeprazole (Nexium)
Aspirin

8.2 Treatment dose

Patients receive either continuous PPI 20mg/day or continuous PPI 80mg/day with or without aspirin 300mg/day. No washout period was required for individuals already on aspirin or PPI to allow baseline blood tests and biopsy to be assessed easily.

If patients are on low dose aspirin for medical reasons (i.e. previous IHD or CVA rather than self-prescribed) they were randomised to either continuous PPI 20mg/day or continuous PPI 80mg/day arms. They are allowed to continue to take their aspirin therapy.

Patients are allowed to default from the prescribed drugs or doses for up to six months at one time or for a total of 12 months during the length of the trial. A drug holiday longer than this time period will be deemed a protocol violation but the patient should still be kept on follow-up.

8.3 Duration of treatment

Patients should remain on trial medication for the duration of follow-up period of 8 years or 10 years (if the patients re-consented) unless they withdraw or are withdrawn from treatment or withdraw consent.

8.4 Special precautions

Aspirin

Aspirin - Gastro-intestinal
The risk of significant gastro-intestinal complications associated with NSAIDs is not completely eliminated by low dose aspirin. Ulcers and upper GI perforations, ulcers or bleeds (PUBs) did occur in osteoarthritis patients treated with aspirin.

Aspirin - Hepatic
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated and treatment should be discontinued if persistently abnormal tests are detected (bilirubin > 100, ALT > 150 and caution used when any enzymes are 3x upper limit of normal).

Aspirin - Effects on ability to drive and operate machinery
Patients who experience dizziness or somnolence whilst taking aspirin should refrain from driving or operating machinery.

Esomeprazole
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Esomeprazole - Hepatic insufficiency
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction is similar to that in patients with symptomatic Gastro Oesophageal Reflux Disease (GORD) with normal liver function. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum dose of 20mg should not be exceeded in patients with severe dysfunction i.e. advanced liver failure with a combination of ascites, encephalopathy and varices and other biochemical or haematological features. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Esomeprazole - Renal Insufficiency
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Other special precautions
Asthma: Patients with asthma or other respiratory disease were entered into the trial provided that there was no history of side effects or complications when taking aspirin. If a patient with asthma was randomised to one of the aspirin arms of the trial, then monitoring of their condition may have been indicated. If the patient's asthma worsens due to the aspirin, then the aspirin should be ceased.

Hepatic and renal function: If hepatic and renal function tests are indicated, and the result is above normal limits for any test, then the patient should not have been entered into the trial if the local investigator feels it is appropriate. Please note, hepatic and renal function tests are not mandatory. If done, we consider ALT, GGT and bilirubin should not be over x3 the upper end of the normal range. In that case we would recommend cessation of aspirin especially if the platelets are less than 60 and the INR is prolonged greater than 1.6. If further advice is required, please contact the Trial Office on 01865 617011.

Osteoporosis: The potential risk of osteoporosis/osteoporotic fracture including hip fracture, in relation to PPI (including esomeprazole) exposure has been discussed in the published literature but no causal link has been established. However, patients with suspected osteoporosis will be investigated by bone scan. If the results of the bone scan indicate a requirement for therapy according to local guidelines, they may be prescribed calcium and vitamin D or indeed biphosphonates according to local practice and this must be noted in the CRFs.

Cardiac Disease: There is caution required for those on clopidogrel as esomeprazole may decrease bioavailability. Patients should be advised by their local investigator. In the management of these patients the SmPC of clopidogrel should be considered: http://www.medicines.org.uk/emc/medicine/24206. Trial staff are asked to document patients who are prescribed clopidogrel using the clopidogrel CRF.

Witholding drugs prior to endoscopy
There is no need to withhold esomeprazole therapy prior to endoscopy. Aspirin, as with all antiplatelet drugs, can aggravate bleeding in an unpredictable way. BSG guidelines regarding suspension of aspirin prior to endoscopy should be followed. The decision lies with the local PI.

Investigators should ask specifically about these special precautions on each return visit and record this on the Follow-Up CRFs.

8.5 Dose modification

Aspirin dose reduction:
Dyspepsia is a risk factor for NSAID GI bleeding (Aalycke, 1999). If the patient has dyspepsia and it is thought this might be due to aspirin therapy the patient may decrease from 300mg/day to 150mg/day at the decision of the local PI. If symptoms still persist after 3-7 days the patient can be decreased to 75mg/day. If the symptoms have not resolved after a further 3-7 days the patient may take aspirin 75mg twice a week (every 3 days or on specified days

e.g. Thursday and Sunday). Further symptoms or a frank GI bleed (malaena or vomiting of blood) should be clinically reviewed and may lead to immediate cessation of aspirin.

Esomeprazole dose changes:
If the patient is receiving 80mg/day of esomeprazole and expresses a wish to take a lower dose, the dose can be changed to 40mg/day indefinitely at the decision of the local PI. This should be prescribed as 20mg BD.

Alternatively if the patient is on 20mg/day of esomeprazole and still has reflux symptoms, the dose can be increased to 40mg/day indefinitely. This should be prescribed as 20mg BD.

Patients are allowed 6 months of another treatment option or a break from treatment for any 6 month period or 12 months in total over the entire trial length of up to 10 years.

All dose changes or breaks in treatment must be documented on a Change of Treatment Form.

8.6 Compliance

Compliance should be checked by asking patients to bring all their unused/remaining trial medicines (empty, opened or unopened) with them when they visit the hospital pharmacy to pick up their new drug supply.

8.7 Management of overdose

Aspirin

Symptoms of overdose include dizziness, tinnitus, sweating, nausea, vomiting, hyperventilation, fever and restlessness. Treatment includes gastric lavage or emesis, rehydration and forced alkaline diuresis. Serum electrolytes, particularly potassium and acid base balance should be treated accordingly. Haemo or peritoneal dialysis may be necessary in the case of severe overdose.

Esomeprazole

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280mg were gastrointestinal symptoms and weakness. Single doses of 80mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

8.8 Concomitant medication and non-drug therapies

Concomitant medication may be given as medically indicated. At every annual follow-up, all patients are asked to provide a complete list of prescription and over-the-counter medications that have been taken for more than 2 weeks during the last 12 months. Details (including indication, doses, frequency and start / stop dates) of concomitant medication taken during the trial until the completion of the off-study visit must be recorded in the medical record and the appropriate CRF.

8.9 (Potential) Drug Interactions

Aspirin
Alcohol and corticosteroids may enhance the effects of aspirin on the gastrointestinal tract. Aspirin may enhance the effects of coumarin anticoagulants and oral hypoglycaemics of the sulphonylurea type. The toxicity of methotrexate may be enhanced by concomitant use of aspirin. Aspirin diminishes the action of uricosurics. Post marketing reports have suggested that the plasma concentration of lithium could be increased whilst taking aspirin [25]. Stop aspirin if there is a chance of bleeding, such as INR > 1.6 or platelets < 60. If INR is between 1.3 and 1.6 the local clinician can judge the collective risk/benefit of aspirin use or if in doubt ask the Trial Office. If the patient is also on other anticoagulants such as warfarin, aspirin should only be used if necessary for other conditions such as CVA prophylaxis or post-coronary stent insertion as prescribed by the physician caring for this problem.

Esomeprazole
The decreased intragastric acidity during treatment with esomeprazole might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of the other inhibitors of acid secretion or antacids, the absorption of ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects)

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy. Concomitant administration of 30mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Concomitant administration of 40mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Concomitant administration of 40mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However a few isolated cases of elevated INR of clinical significance have been reported post marketing, during concomitant treatment. Monitoring is recommended when initiating and ending concomitant treatment.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxycillin or quinidine.

There is no firm evidence suggesting a required change to the way esomeprazole or clopidogrel are prescribed but the MHRA suggests the concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged unless considered essential.
See Nexium IB and Summary of Product Characteristics as well as
http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON076501 for further information. Any important updates may be provided by newsletters.

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid) resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

For further information please refer to the Investigator Brochure (IB) and Summary of Product Characteristics (SmPC) provided. Copies are available from the Trial Office.

9 DRUG MANAGEMENT

9.1 Drug supplies

Commercial esomeprazole (Nexium) tablets are supplied by AstraZeneca free of charge for a period of 8 or 10 years (if the patients re-consented) from the date of each patient's randomisation or until 28th February 2017 (we will allow +3 months for appointment slippage). The last delivery of study drug will be on or around 31st August 2016. Esomeprazole is supplied in blister packs of 2 x 28 tablets.
Aspirin should be supplied by the local hospital pharmacy. There is no specification on the brand of aspirin, although soluble aspirin should be supplied wherever possible.

Patients are requested to come to the hospital pharmacy every 6 months to return unused medication and pick up a new 6-month supply. In some cases where this is not possible, special dispensation by the local research team may allow the medication to be posted as per local procedures. However, there is no central funding available to cover postage costs.

9.2 Drug ordering

The Trial Office will calculate the quantity of 20mg and 40mg esomeprazole required for the year based on the number of patients taking each dose (20mg/40mg/80mg). The Trial Office will order the IMP and Astra Zeneca will deliver the IMP to the hospital on a 6-monthly basis until 31st August 2016. Ad hoc drug orders are not possible.

9.3 IMP Receipt

Upon receipt of trial medication, a fax-back confirmation form (included in the delivery) included in the delivery, must be signed and faxed from the hospital pharmacy to the Trial Office Fax: 01865 617010

If supplies are damaged on arrival, contact the Trial Office. Damaged supplies should be destroyed on site and a Drug Destruction Form completed and a copy forwarded to the Trial Office by Fax or email.

9.4 Handling and storage

Esomeprazole should not be stored above 30°C. There is no minimum storage temperature specified, although Astra Zeneca have confirmed that the drug remains stable at sub-zero temperatures. Store in the original package (blister). Esomeprazole has a shelf life of 3 years. Aspirin should be stored in a dry place below 25°C. Aspirin has a shelf life of 3 years.

9.5 Labelling

The responsible Pharmacy will ensure that IMP supplies dispensed for trial use are appropriately labelled in accordance with all applicable regulatory requirements.

Labelling of trial esomeprazole is to be carried out by the site pharmacies. MHRA approved labels for esomeprazole for clinical trial use will be supplied by the Trial Office.

MHRA approved labels for aspirin for clinical trial use are not required and labels for aspirin will not be supplied by the Trial Office. Aspirin must be labelled as per normal dispensing requirements.

9.6 Dosing dispensing

Both esomeprazole and aspirin should be dispensed from the participating hospital's pharmacy every six months (from date of first trial prescription).

9.7 Drug accountability

Participating pharmacies must maintain a Dispensing and Returns Log to document all aspirin and esomeprazole dispensed to trial participants. This Log must be available for inspection by AspECT staff and the MHRA if required. Each Dispensing and Returns Log must be copied and the original returned to the Trial Office once the patient has completed their treatment. The photocopy must be retained in the Pharmacy File.

9.8 Drug returns from patients

Patients must return unused tablets to their local trial pharmacy for accountability and compliance checks.

9.9 Drug destruction

Unused drugs must be destroyed on site as per local practice and a Drug Destruction Form completed. The Drug Destruction Form must be faxed to the Trial Office Fax: 01865 617010

10 ASSESSMENT OF SAFETY

The Investigator must monitor each patient for clinical and laboratory evidence of adverse events at each contact with the participant throughout the study. During the course of the annual Follow Up, all patients should be asked directly if they have had any hospital admissions or events which should be reported as a SAE (see definition in Section 10.1). Their patient notes should also be checked for such occurrences. All SAEs should be reported to the Trial Office as described in Section 10.4.

Adverse event monitoring starts from the time the patient commences study medication until they complete the trial. An SAE which occurs more than 30 days after a patient has stopped taking trial medication is not required to be reported, unless the event is related to a trial procedure (e.g. biopsy or blood collection). All SAEs will be followed to a satisfactory conclusion. Any SAEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated.

All SAEs reported to the Trial Office will be processed according to internal SOPs. The Trial Office may request additional information for any SAE as judged necessary.

10.1 Adverse event definitions

An Adverse Event or experience (AE) is any untoward medical occurrence in a study subject temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product, whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and /or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

Results in death	
Is life-threatening	This 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 in-patient hospitalisation or prolongs existing inpatient hospitalisation	In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
Results in persistent or significant incapacity or disability	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption.
Is a congenital anomaly or birth defect	
Is any other medically other medically important event	Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above.

An Adverse Drug Reaction (ADR) is an AE which is considered to be causally related to any dose of the IMP. This means that a causal relationship between the IMP and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An Unexpected Drug Reaction is an adverse drug reaction, the nature or severity of which, is not consistent with applicable product information (referring to information in the SmPC or IB).

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or SmPC for an approved product).

10.2 Determining adverse event causality

The Investigator will assess and classify the relationship of an AE to the trial IMP as follows:

Classification	Relationship	Definition

Drug-related (reasonable possibility)	**Definitely Related**	• Starts within a time related to the study drug administration *and* • No obvious alternative medical explanation.
	Probably Related	• Starts within a time related to the study drug administration *and* • Cannot be reasonably explained by known characteristics of the patient's clinical state.
	Possibly Related	• Starts within a time related to the study drug administration *and* • A causal relationship between the study drug and the adverse event is at least a reasonable possibility.
No reasonable possibility of being drug related	**Probably Not Related**	• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
	Definitely Not Related	• The AE is definitely not associated with the study drug administered.

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event (i.e. relation to study drug, other illness, progressive malignancy etc.) and give their opinion of the causal relationship between each AE and study drug. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

10.3 Expected adverse events

Section 4.8 of the SmPC for aspirin lists all the expected side effects associated with the use of aspirin. A copy of this document must be held in the Site File for reference.

Section 4.8 of the SmPC for 20mg and 40mg esomeprazole lists all the expected side effects associated with the use of 20mg and 40mg esomeprazole. A copy of this document must be held in the Site File for reference.

For patients receiving the 80mg esomeprazole dose, Section 4.8 of the IB lists all the expected side effects associated with the use of esomeprazole. A copy of this document must be held in the Site File for reference.

A list of the most noteworthy expected side effects known at the time of writing is given below for ease of reference.

Aspirin
Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), 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) and not known (cannot be estimated from the available data).

Aspirin: Undesirable Effects

Blood and lymphatic system disorders	*Common:* Increased bleeding tendencies. *Rare:* Thrombocytopenia, agranulocytosis, aplastic anaemia. *Not known:*

	Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses). anaemia, haemolytic anaemia, hypoprothrombinaemia, pancytopenia, occult blood loss, elevated transaminase levels
Immune system disorders	*Rare:* Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.
Metabolism and digestive system disorders	*Not known:* Hyperuricemia.
Nervous system disorders	*Rare:* Intracranial haemorrhage *Not known:* Headache, vertigo.
Ear and labyrinth disorders	*Not known:* Reduced hearing ability; tinnitus.
Vascular disorders	*Rare:* Haemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	*Uncommon:* Rhinitis, dyspnoea. *Rare:* Bronchospasm, asthma attacks.
Reproductive system and mammary disorders	*Rare:* Menorrhagia
Gastrointestinal disorders	*Common:* Dyspepsia. *Rare:* Severe gastrointestinal haemorrhage, nausea, vomiting. *Not known:* Gastric or duodenal ulcers and perforation which can occasionally be major (may develop bloody or black tarry stools, severe stomach pain and vomiting blood), gastrointestinal irritation (mild stomach pain), erosions, heartburn, Fatalities have occurred.
Hepatobiliary disorders	*Not known:* Hepatic insufficiency, hepatitis (particularly in patients with SLE or connective tissue disease)
Skin and subcutaneous tissue disorders	*Uncommon:* Urticaria. *Rare:* Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.
Renal and urinary tract disorders	*Not known:* Impaired renal function
Body as a whole – general disorders	*Not known:* Salicylism – (mild chronic salicylate intoxication may occur after repeated administration of large doses, symptoms include dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and mental confusion, and may be controlled by reducing the dose)

Children

Aspirin may be associated with the development of Reye's Syndrome (encephalopathy and hepatic failure) in children presenting with an acute febrile illness.

Esomeprazole: Undesirable Effects

	Common (≥1/100)	**Uncommon (≥1/1000 and <1/100)**	**Rare (≥1/10000 and <1/1000)**	**Very rare <1/10000**
Blood and lymphatic system disorders			Leukopenia, thrombocytopenia	Agranulocytosis, pancytopenia
Immune system disorders			Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock	
Metabolism and nutrition disorders		Peripheral oedema	Hyponatraemia	Hypomagnesaemia; severe hypomagnesaemia may also result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia.
Psychiatric disorders		Insomnia	Agitation, confusion, depression	Aggression, hallucination
Nervous system disorders	Headache	Dizziness*, paraesthesia, somnolence	Taste disturbance	
Eye disorders			Blurred vision*	
Ear and labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation	Dry mouth	Stomatitis, gastrointestinal candidiasis	Microscopic colitis
Hepatobiliary disorders		Increased liver enzymes	Hepatitis with or without jaundice	Hepatic failure, hepatic encephalopathy
Skin and subcutaneous tissue disorders		Dermatitis, pruritus, urticaria, rash	Alopecia, photosensitivity	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Muscoloskeletal, connective tissue and bone disorders			Arthralgia, myalgia	Muscular weakness

	Common (≥1/100)	Uncommon (≥1/1000 and <1/100)	Rare (≥1/10000 and <1/1000)	Very rare <1/10000
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders				Gynaecomastia
General disorders and administration site conditions			Malaise, hyperhidrosis	

*The SmPC for esomeprazole has been updated with the following: “Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (rare) has been reported. If affected patients should not drive or use machines.”

10.4 Reporting of SAEs

In the case of a Serious Adverse Event, an SAE Form must be completed as soon as possible and faxed to 01865 227038. This should be done within 24 hours of becoming aware of the event. If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Form.

Each separate SAE episode must be recorded. For example, if an SAE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate SAE. For SAEs to be considered intermittent, the events must be of similar nature and severity.

SAEs for which there is no reasonable possibility of being drug related to one or both of the IMPs should be reported by completing sections 1-5 **and** the Reporting Information in section 10 of the SAE Form. Sites must provide data that is minimal for the assessment of the SAE, including: reason for seriousness, causality, event term and a narrative of the event.

All other SAEs (where there is at least reasonable possibility of it being related to trial medication) i.e. SARs - should be reported by completing all sections of the SAE Form.

On receipt of the SAE Form, the Trial Office staff will check the SAE Form for minimal criteria, then log the SAE and allocate it an identifying number. The Trial Office will confirm receipt of the SAE by sending a copy of the SAE log to the site within 24 hours of receipt. If the site have not received notification of receipt within 24 hours, it is the responsibility of site staff to confirm that the Trial Office have received the SAE form. For SARs the Trial Office will send the SAE Form to a clinical review panel who will give their opinion on the Site Investigator's classification of the SAR with respect to seriousness, causality and expectedness.

10.5 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or SmPC for an approved product). SUSARS therefore are suspected to be at least possibly related to the study agent, fulfil the definition of a SAE, but the nature and severity of which are not consistent with the applicable product information.

All SUSARS must be reported to the responsible Authority and main REC by the Trial Office within the required timelines:

- Fatal or life threatening SUSARs will be reported within 7 days of the Trial Office receiving the initial report. Any additional information will be reported within eight days of sending the first report.
- All other SUSARs will be reported within 15 days of the Trial Office receiving the initial report.

The Trial Office will report SUSARs according to their SOPs. In addition, other safety issues may qualify for expedited reporting where they might materially alter the current risk assessment of an IMP or be sufficient to change IMP administration or the overall conduct of the trial.

10.6 Follow-up of Serious Adverse Events

If new or amended information on a reported SAE becomes available, the Investigator should update the existing form, without obscuring any initial information. All new data must be initialled and dated so that all changes are clearly identified.

Follow-up will continue until all the necessary safety data for the event has been gathered. Any SAE that is ongoing when a subject completes his/her participation in the trial must be followed until any of the following occurs:

- The event resolves or stabilizes;
- The event returns to baseline condition or value (if a baseline value is available);
- The event is attributed to other agent(s) or to factors unrelated to study conduct.

10.7 Reporting Adverse Events on the CRF

Adverse events (non-serious) need only be recorded if the event leads to the patient withdrawing from study medication. Details must be recorded on the End of Treatment Form.

Terms and Grading of Events

The NCI CTCAE Version 4.0 (currently up to Version 4.03) must be used to report AEs and where possible use the Lowest Level Terms provided. Where indicated on the form, provide the severity grade for each AE/SAE.

10.8 Events exempt from being reported as AE/ SAEs

Progression of underlying disease

Trial endpoints will be reported on Follow-Up CRFs and are not be required to be reported as an SAE.

Death on study

Provided it is not as a result of an SAE, then a death during the course of the study should be recorded on the Death CRF. Deaths arising from SAEs should be reported using the SAE Form.

10.9 Informing Investigators of new safety information

The Trial Office or the Chief Investigator will ensure that all investigators are kept informed in a timely manner as new safety profile information becomes available. Investigators are responsible for briefing their study team and onward transmission to R&D office as appropriate.

11 PREGNANCY

Pregnancies (in a participant or partner) occurring within 30 days of the last IMP dose require expedited reporting. A Pregnancy Notification Form should be completed and faxed to the Trial Office within the same timelines as an SAE. Women who become pregnant should be withdrawn from the interventions at the earliest opportunity. All reported pregnancies should be followed and the outcome reported using the same form. If the outcome of the pregnancy meets any of the criteria for seriousness, it must also be reported as an SAE. Examples of pregnancy outcomes that are SAEs:

- Reports of congenital anomalies or developmental delay, in the foetus or the child.
- Reports of foetal death and spontaneous abortion.
- Reports of suspected adverse reactions in the neonate that are classified as serious.

12 DEFINING THE END OF TRIAL

For this study the end of the trial is defined as “The last visit of the last patient after a minimum of 8 years follow-up in the trial (LPLV)”.

The Sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants’ best interests.

13 STATISTICAL CONSIDERATIONS

13.1 Primary and Secondary Endpoints

PRIMARY: Time from randomisation to the first of the following:

- conversion from Barrett’s oesophagus to adenocarcinoma of the oesophagus (event)
- high grade dysplasia (event)
- death by all causes (event)
- last known follow-up (no event)

SECONDARY: Time from randomisation to:

- adenocarcinoma of the oesophagus
- high grade dysplasia
- all-cause mortality
- cause-specific mortality

Also safety, quality of life, health economics, new tumours and molecular markers.

13.2 Sample size and power

Original sample size statement

The event rate in the UK is 0.98% (95% CI = 0.67 to 1.39%) (This is higher in the UK than the USA) however to be cautious we have agreed on 0.76%/year (approximately half way between the UK and USA).

Aspirin has a hazard ratio of 1.5 (33.3% effective) in preventing the colorectal cancer rate. Evidence from epidemiological studies suggests that aspirin may decrease BA rates with a hazard ratio of 1.6 to 10 (40-90%) (35-37). While we believe that current evidence indicates that aspirin is at least equally effective in the prevention of oesophageal adenocarcinoma as colorectal cancer, the role of PPI is more difficult to estimate for the reasons given previously. Therefore we have chosen a hazard ratio of 1.4 (28% effective) to assess weaker therapeutic effects.

Compliance to repeated endoscopy is excellent with over 90% of patients coping well with repeated examinations. Compliance to the therapy indicates that 90% manage well with no serious side effects to PPIs or low dose aspirin according to drug data sheet based on over 1 million patients for PPI and millions of people with over 50 years' experience for aspirin therapy. In addition evidence from other chemoprevention trials using 300mg of aspirin suggests that it is well tolerated over several years (< 5% side effects) UKcap study. Therefore a 20% non-compliance rate will be included in our calculations over and above losses calculated for loss to follow-up. Patients will be returning unused drugs to their local pharmacy every 6 months. The annual follow-up will be used to remind patients about the importance of compliance.

A total of 5000 patients (1250 in each intervention group) will allow us to detect a difference in conversion rates of 0.22% per year between the PPI and aspirin intervention. The sample size required was calculated using nQuery Advisor® Release 4.0 based on the following:

- Patients will be recruited over 2 years and followed up for a further 8 years.
- Exponential time to conversion with a constant event rate of at least 0.76% per year
- Conversion hazard ratio (drug response) of control to treatment is 1.4
- Power = 80% (2-sided test at 5% level of significance).
- No interaction between the effects of aspirin and PPI interventions.
- A 10% loss to follow-up from NHS HSCIC flagging
- A 20% non-compliance with medication
- Calculations adjusted for competing causes of mortality. A further proportion may take their medication but be lost to follow-up as they do not return their questionnaire and/or attend for surveillance endoscopy. This will not affect the primary outcome as all-cause mortality and conversion to BA will be assessed by the Office of National Statistics, which has almost complete follow-up of registered subjects (we have conservatively assumed a 90% follow-up rate).

Exploratory sample size statement October 2008

Due to protocol amendments and an expected restriction on the number of patients to be recruited, an exploratory sample size is presented at the request of the Funders. Since the trial recruited until the end of February 2009 in the UK rather than to the number calculated in the original sample size, this calculation should be considered as a guide to the power and treatment effect size the trial should achieve.

This exploratory sample size is calculated as per the original sample size, but with

- Annual rate of conversion of 1% (allowing for the composite primary endpoint of all-cause mortality and conversion to adenocarcinoma and conversion to high grade dysplasia.)

Justification: Using the National Statistics figures for 2005 based on the age and gender structure of the first 2046 patients recruited to AspECT gives a mortality rate in a year of 1.16%.

Using the UK Barrett's conversion rate to adenocarcinoma of at least 0.98% per year without treatment for 60% of the sample and 40% with a lower conversion rate of 0.66% (due to being female, have tongues of Barrett's metaplasia or only 1cm of Barrett's, or being <45 years old). Differing rates are not published for these patients so a rate of two thirds the UK conversion rate has been used) i.e. 0.85% conversion rate without treatment over the whole sample.

No good estimates of rates for conversion to high grade dysplasia for the UK could be found.

In this population, it is unlikely that the event rate for the composite primary endpoint in the control arm will be less than 1%.

- Hazard ratio as in colorectal cancer
- No adjustment for compliance
- the follow-up increased to 10 years (subject to available funding)

Apart from limited recruitment and checking the event rate using the age/sex structure, no information or estimates from the current trial are used.

A total of 2224 patients (approximately 556 in each intervention group) will allow us to detect a difference in conversion rates of 0.34% per year between low dose and high dose PPI and aspirin or no aspirin. This sample size was calculated using ARTMENU in STATA release 10.0 based on the following:

- Patients will be recruited over 3 years and followed up for a further 10 years (subject to available funding)
- Exponential time to conversion with a constant event rate of at least 1% per year without treatment
- Conversion hazard ratio (drug response) of control to treatment is 1.5 (1 year conversion rate 1% no or standard treatment vs 0.66% in the treated patients)
- Power = 80% (2-sided test at 5% level of significance)
- No interaction between the effects of aspirin and PPI interventions
- A 10% loss to follow-up from NHS HSCIC flagging

13.3 Randomisation – Stratification and Standardisation

Randomisation was by minimization with a random element. The variables were:

Length of Barrett's – tongue, <2cm, ≥2cm and ≤3cm, >3cm and ≤8cm, >8cm
Age - 18-49, 50-59, 60-69, ≥70
Intestinal metaplasia – yes, no

These may be risk factors for the development of dysplasia and adenocarcinoma. Through using minimization with the same variables, women and men are randomised separately, as are those only taking part in the PPI randomisation.

14 STATISTICAL ANALYSIS PLAN

All analyses will be on an intention-to-treat basis. This means that patients will be analysed as they are randomised irrespective of the treatment actually received. The intention-to-treat population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomisation number. All participants who receive one dose of IMP will be evaluable for the safety analysis.

It is therefore important that every effort is made to encourage patients, including those patients who do not receive/complete their allocated treatment, to attend for follow-up clinic visits and complete the questionnaires to avoid bias in the analysis of the results.

Analyses will be carried out at the 5% level of significance. The main analysis will be a comparison of A+B v C+D (aspirin v no aspirin) and A+C v B+D (high v low dose PPI) assuming no treatment interaction. Logrank analysis will be used to compare the time from randomisation to primary outcome (high grade dysplasia, adenocarcinoma of the oesophagus or death from all causes) for the different treatment comparisons. An Accelerated Failure Time (AFT) model will be constructed to adjust the treatment comparisons for length of Barrett's metaplasia, age and occurrence of intestinal metaplasia (as used in the minimisation procedure). This will be repeated with Cox regression model for comparison with other research. Interim analyses of the primary aim were planned at 2 and 4 years after the end of recruitment.
A number of patients will be randomised to the PPI comparison only; hence they will only be included in the analysis of the effect of high vs low dose PPI.
Sensitivity analysis will use the per protocol sample and the possibility of interaction between the two treatments will be investigated.

Health economics: An economic analysis will be undertaken, which compares the mean per patient cost of the alternative trial arms using resource use data collected in the trial and appropriate UK unit costs. Differential costs could then be related to conversion to BA. To increase the value to decision makers, the economic data collected in the trial could be synthesised with other evidence by relating long-term (lifetime) health service costs to long-term quality-adjusted life expectancy. The analysis would be based on a state transition model, which would characterise how patients progress from BM to dysplasia and to BA competing risk of death. The annual cost and health-related quality of life associated with each stage of the disease will be estimated using trial data collected and literature. In addition, some limited data collection in appropriate non-trial patients would be undertaken. Assessments will be completed at baseline and every two years at the time of endoscopy.

14.1 Final analysis

This trial completed recruitment within 4 years of opening to recruitment. The DSMC will decide the time point for the final analysis. Final analysis is planned 8 years after the end of patient recruitment and will be guided by the fulfilment of the sample size calculation to be when there are at least 200 events and a median of at least 5 years follow up.

15 TRIAL COMMITTEES

15.1 Trial Management Group (TMG)

The Chief Investigator will chair a TMG responsible for overseeing the successful conduct and publication of the trial. The TMG will provide regular progress reports to the Trial Steering Committee.

15.2 Data and Safety Monitoring (DSMC)

An independent Data and Safety Monitoring Committee (DSMC) is established for this trial. This committee meet to assess the trial data; frequency will depend on event rates, and may be increased upon request by the committee. The DSMC will monitor protocol compliance as well as toxicity and serious adverse events taking into account relevant worldwide information. The main outcomes will be analysed as stated above and in the analysis plan. The DSMC will run in accordance with its charter.

15.3 Trial Steering Committee (TSC)

The TSC (at least 3 members including an independent chair) provide overall supervision of the safe and effective conduct of the trial according to its terms of reference. It reviews trial progress against agreed milestones, adherence to protocol, patient safety and consider new information. The TSC has the authority to recommend study closure where appropriate. The TSC will run in accordance with its charter.

16 DATA MANAGEMENT

16.1 Database considerations

Data management will be performed by the Trial Office via a bespoke trial database.

16.2 Case reports forms (CRFs)

AspECT collects data on paper CRFs. The Investigator and study site staff (as noted on the Site Contact and Responsibility Sheet) should ensure that data collected on each subject is recorded in the CRF as accurately and completely as possible. Please ensure that:

- The relevant CRFs are completed legibly, accurately and as thoroughly as possible.
- All CRF data are verifiable in the source documentation or the discrepancies must be explained.
- CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.
- Data queries are resolved and documented by authorised study staff, giving a reason for the change or correction where appropriate.

Any errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not clear why the change has been made, an explanation should be written next to the change.
The above considerations also apply to patients who are withdrawn early from treatment. If a patient withdraws from the study, the reason must be noted on the appropriate form and the patient must be followed-up as per protocol.

CRFs must be photocopied and a copy kept on site. The original (wet-ink) is to be sent to the Trial Office using the address on page 2 (OCTO).

16.3 Accounting for missing, unused, or spurious data.

Missing data will be chased up and supplemented where possible after consultation with the Investigator. The control of the correctness of the data is performed with ranking tests, validity tests and consistency checks. Unused data will be retained as for used data.

17 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represent the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The clinical study report will be based on the final data listings. The locked trial data may then be used for analysis and publication.

18 STUDY SITE MANAGEMENT

18.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the Staff Contact Responsibility Sheet provided, prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

18.2 Study documentation

The Trial Office has provided an Investigator File and Pharmacy File to each investigational site containing the documents needed to conduct the study. The Trial Office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

19 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor and Investigators should ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations[1], the Principles of Good Clinical Practice (GCP)[2] and the applicable policies of the Sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

19.1 Ethical conduct of the trial and ethics approval

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC). Principal Investigators will be approved by the REC.

19.2 Regulatory Authority approval

This study is conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). Approval to conduct the study has been obtained from the Responsible Authority prior to initiating the study.

19.3 NHS Research Governance

Investigators are responsible for ensuring they obtain local Trust management agreement to conduct the trial in accordance with local arrangements and policies.

19.4 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the Responsible Authority application, the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.
2 GCP Directive 2005/28/EC .

- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

All amendments will be generated and managed according to the Trial Office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients.

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

19.5 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the Trial Office IMMEDIATELY if the study site initiates an urgent safety measure.**
The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the Trial Office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out.
The Trial Office will follow written procedures to implement the changes accordingly.

19.6 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The Trial Office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

19.7 Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial"

Investigators must notify the Trial Office at once if any serious breach of GCP is suspected. The Trial Office will review the event and, if appropriate a report will be submitted to the REC, Regulatory Authority and the NHS (host) organisation within 7 days of the Trial Office becoming aware of the breach as per Trials Office SOPs.

19.8 REPORTS: Progress, Safety and End of Study Reports

This protocol will comply with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor requirements for the provision of periodic study safety and progress reports. Any additional reports will be provided on request. Reporting will be managed by the Trial Office according to internal SOPs. Sites will be urged to return as much data as possible before each database lock point.

The Trial Office will determine which reports need to be circulated Principal Investigators and other interested parties according to internal SOPs. Study sites are responsible for forwarding trial reports they receive to their local Trust as required.

20 EXPENSES AND BENEFITS

There are no intended payments or any other benefits to sites or participants.

21 QUALITY ASSURANCE

21.1 Risk assessment

A risk assessment and a monitoring plan have been prepared. The risk assessment will be repeated if necessary in the light of changes while the study is ongoing or in response to monitoring reports. Monitoring plans will be amended as appropriate.

21.2 Central monitoring

Regular central monitoring is performed according to the central monitoring plan. Data is evaluated for compliance with the protocol and accuracy in relation to source documents.

Study sites are monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. All changes to data that could influence the outcome will be queried with and approved by the study site in a timely manner. For all other data, where there is no doubt about the source of any errors, clear changes to data will be made internally by OCTO staff without referring back to the study site. Study staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and deal with any queries that they may have including those arising from queries raised by the Trial Office. In the event of site visits, reports will be sent to the site in a timely fashion and sites are expected to action any points highlighted in the report.

In sites where concern has arisen, including those arising from queries raised by the Trial Office and in consultation with the TMG, audit teams may be sent by or on behalf of the Sponsor to inspect the site according to appropriate SOPs. The Trial Office will inform the relevant committees e.g. TMG, DSMC and TSC of issues arising in a timely manner. The DSMC will monitor data and may recommend to the Sponsor inspection of sites where concern arises.

21.3 Quality Monitoring Committees

There are specific central Quality Monitoring Committees (QMCs) for endoscopy (coordinator Prof H Barr), pathology (coordinators S Sanders/R Harrison), physiology (coordinator Dr J de Caestecker), molecular biology (coordinator Prof J Jankowski) and health economics (coordinator P Moayyedi).

Endoscopy QMC: During the trial, visits will be undertaken by the trial and endoscopy coordinator (or their deputies) to sites where concerns about endoscopy rise.

Pathology QMC: this group will jointly assess the suitability of the local pathology resources. A proportion of all normal cases (approximately 10%) will have their slides reviewed centrally. In addition, all dysplastic and neoplastic specimens will also be reviewed centrally by one of two panels of five expert pathologists, who will return a consensus score. They will ensure that all criteria for the histological diagnosis for metaplasia, dysplasia and cancer are met. Any normal cases found to be dysplastic or neoplastic on review will be put into the abnormal panel review process. All cases will have 'research paraffin tissue blocks' as well as fresh tissue where available. The central pathology panels will report compliance to the TMG. The pathology coordinator will submit the final pathology review results to the local site PI.

Molecular biology QMC: this group will assess the suitability of the local resources for collecting additional blocks for pathology as well as tissue storage. All patients had blood samples collected at baseline and 4-6 years after randomisation. They will have blood sample taken 8 years after randomisation. In addition, all patients will have at

least one histological block from each case sent to the Trial Laboratory. Furthermore, where available, fresh tissue samples can be stored locally and sent in batches to the AspECT Trial Laboratory. The co-ordinators will ensure that all assays are carried out to standard operating procedures. The conversion to cancer will be assessed from baseline to the end of the study. All individuals will be assessed for trial inclusion/exclusion criteria and after informed consent they will have a baseline blood sample for helicobacter serology, PBMC isolation, storage of blood DNA for genetic assessment and baseline biochemistry.

Physiology QMC: this group may assess the local resources prior to activation of each site in the physiology sub study. A sub-group of up to 400 patients will have 24hour pH, oesophageal manometry and/or impedance and bile acid studies as outlined in physiology sub study protocol.

Cardiovascular and nutritional QMC: The data may be assessed by a random check of 10-20% of the case notes.

21.4 Audit and regulatory Inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the Trial Office without delay.

22 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure, the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request, for the minimum period required by national legislation, or for longer if needed. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the host institution policy.

Retention and storage of laboratory records for clinical trial samples must also follow these guidelines.
Retention and storage of Trial Laboratory records supporting PK or PD endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is the University of Oxford's policy to store data for a minimum of 5 years. Investigators may not archive or destroy study essential documents or samples without written instruction from the Trial Office.

23 PATIENT CONFIDENTIALITY

Personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only their initials and date of birth will be recorded on the CRFs. The patient's name and NHS number (where available) will be collected once to allow flagging with the NHS HSCIC, only if the site will allow and the patient has completed the relevant section of the Consent Form.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

24 STUDY FUNDING

Cancer Research UK approved the study in 2003 for a 10 year period to run from 1st January 2005 to 31st December 2014 - CRUK reference number CRUK/05/006. Funding is renewable annually and is dependent on a satisfactory review by an independent committee. An application submitted in March 2014 for a 44 month funding extension starting from 1st January 2015 has been approved by CRUK (GAL reference no. A4584).

25 SPONSORSHIP AND INDEMNITY

25.1 Sponsorship

The Sponsor has provided written confirmation of Sponsorship and authorised the trial commencement once it was satisfied that all arrangements and approvals for the proper conduct of the trial were in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor were also put into place between the parties.

25.2 Indemnity

Compensation for Harm

Arrangements for NEGLIGENT harm

Indemnity and/or compensation for negligent harm arising specifically from accidental injury for which the University is legally liable (as the Research Sponsor) is covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Arrangements for NON-NEGLIGENT harm

Indemnity and/or compensation for harm arising specifically from an accidental injury and occurring as a consequence of the research subjects' participation in the trial for which the University is the research Sponsor may be covered by the University of Oxford.

25.3 Contracts/Agreements

This trial has been subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) was placed between the Sponsor and participating NHS Trust(s) prior to site activation. The Sponsor has also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

26 PUBLICATION POLICY

The Sponsor retains ownership of all data arising from the trial, however the trial team have unfettered access to the data for follow-up studies and cross tabulation of genomics and other data from the ChOPIN study using the same patient cohort.

The intention is to publish this research in a specialist peer reviewed scientific journal on completion of the study. The results may also be presented at scientific meetings and/or used for a thesis. The AspECT Chief Investigator and Trial Management Group will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Individuals wishing to present or publish material arising from AspECT must not do so without the written approval of the Chief Investigator and Trial Management Group.

The TMG are responsible for deciding which investigators and scientists are added to the paper. Local investigators qualified for authorship for the main paper by recruiting a minimum of 25 patients and having a data return rate of 95% or greater or for all clinical papers including translational studies related to AspECT by recruiting 50 patients and having a data return rate of 95% or greater.

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