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Barrett's Oesophagus two yearly Surveillance versus endoscopy at need: a randomised controlled trial to estimate effectiveness and cost-effectiveness Study (BOSS)

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CONTENTS

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1.0 BACKGROUND

1.1. Rationale for the study

Oesophageal adenocarcinoma is the fastest rising cancer in the developed world[1]. Thirty years ago it was a rare malignancy and now there are over 5,000 cases each year in the UK. The relentless rise in this malignancy is likely to continue unless the underlying causes are delineated and appropriate prevention strategies are evaluated.

The most accepted sequence of events is that longstanding gastro-oesophageal reflux induces a metaplastic change in the distal oesophageal mucosal lining in susceptible individuals[2]. The metaplasia from squamous to columnar mucosa is termed Barrett's oesophagus (BO) and the length of oesophageal mucosa affected changes little over time. We have conducted a systematic review that identified 46 papers evaluating 11,056 Barrett's patients with 42,880 patient years follow-up. There were 255 cases of oesophageal adenocarcinoma in this systematic review with a cancer conversion incidence rate of 0.76% (95% CI = 0.56% to 1.0%) per year[3]. Unlike earlier reports there was no evidence of funnel plot asymmetry, suggesting these data are not due to publication bias. Furthermore meta-analysis of papers from the UK[4] suggest the cancer conversion rate is about 1% per year (95% CI = 0.67 to 1.39%) again without any statistical evidence of publication bias. This is consistent with the UK having the highest incidence of oesophageal adenocarcinoma worldwide. The prognosis for advanced oesophageal adenocarcinoma is poor with a median survival of one year and a 10% five-year survival[5]. This has promoted the development of surveillance programs and guidelines recommend that patients with Barrett's oesophagus have upper gastrointestinal endoscopy every 2-3 years to detect oesophageal adenocarcinoma early when the prognosis is much more favourable[6].

These guidelines acknowledge that the data to support endoscopy surveillance in patients with Barrett's oesophagus are relatively weak[7] and the value of surveillance is still subject to considerable debate[8, 9]. The most appropriate method of evaluating whether surveillance reduces oesophageal adenocarcinoma mortality is through randomised controlled trials. There are, however, no trials published or being conducted in this area. There are some observational data to suggest that patients enrolled in surveillance programmes have oesophageal cancer detected at an earlier stage than non surveillance detected cancers and have a better actuarial survival[10,11]. These are very weak data in epidemiological terms, however, as patients attending surveillance programmes are very different from patients presenting with advanced oesophageal adenocarcinoma and the positive results could be due to any one of a number of different forms of bias[12]. A better method is to directly compare patients with prospectively identified Barrett's oesophagus that attend and do not attend surveillance. There is only one paper that has reported this design and this did not find any benefit of surveillance in 409 BO patients[13]. One of our groups reviewed the patients enrolled in this study from Leicester. Many did not in fact have Barrett's oesophagus but a large hiatal hernia. This type of cohort study reduces the number of possible biases but does not eliminate the problem and in particular there are concerns about healthy volunteer, lead and length time bias[14]. There is therefore good reason to be sceptical of this type of data and demand randomised controlled trial evidence before advocating Barrett's surveillance particularly as studies suggest that BO patients have either a normal life expectancy[15] or if it is reduced this is attributable to other diseases and not mortality from oesophageal adenocarcinoma[16,17].

Modern medicine is expensive and resources are limited so it is important to determine whether surveillance of Barrett's oesophagus is cost-effective as well as efficacious. The weak observational data available have been modelled to provide an incremental cost-effectiveness ratio of Barrett's surveillance under ideal assumptions. Decision analytic models have suggested that BO surveillance every two years costs less than £25,000/ life-year saved[18-20] however, the recent model completed by PenTAG following their review found that surveillance was not cost-effective (with a cost/QALY of approximately £125,000). All of the models found that cost-effectiveness was very sensitive to the risk of oesophageal adenocarcinoma developing and the efficacy of surveillance. A randomised trial would provide robust evidence for the cancer risk in Barrett's patients and the efficacy of surveillance in reducing

oesophageal adenocarcinoma mortality. Data on the costs of the program from a health service and societal perspective would be collected prospectively to provide input to determine the cost-effectiveness of the program.

It is essential to use hard endpoints for the trial since surrogate biomarker endpoints have not been validated for Barrett's oesophagus[21, 22].

Surveillance by endoscopy for Barrett's oesophagus is expensive, commonly causes minor adverse events (1-10%) and 10% of patients reported that it is inconvenient. It causes anxiety and very rarely can result in complications of oesophageal perforation or death (0.03% and 0.001% respectively[23]). It is important to establish the efficacy of such an intervention before routinely offering it to patients. Proponents of Barrett's surveillance suggest that randomised controlled trials evaluating the cost-effectiveness of surveillance are not possible, are expensive and possibly unacceptable to patients and professionals. On the other hand there is strong support among both patients and clinicians to enter randomised clinical trials for surveillance of Barrett's Oesophagus [24] in particular support has been expressed by the British Society of Gastroenterology (BSG), National Cancer research Network (NCRN) – Upper Gastrointestinal Clinical studies group, Welsh Association of Gastroenterology and Endoscopy (WAGE) and the Fight Oesophageal Reflux Together (FORT) patient group.

1.2. Assessment of the feasibility of the trial

One hundred and sixty seven patients from 3 centres (Leicester, Belfast and 3 Counties Cancer Network) were asked the hypothetical question "would you accept the offer of a study that would randomise you into surveillance of your Barrett's oesophagus by an endoscopy every 2 years or no endoscopy at all"… 60% of patients found the idea acceptable.

1.3. Service user involvement

The feasibility data for BOSS was collected in consultation with the Three Counties Cancer Research Network Consumer/Patient Panel. This has been set up under the auspices of the National Cancer Research Network Consumer Liaison team. Mr Charles Brownhill, a patient with Barrett's oesophagus is a member of the trial steering committee and former Chairman of FORT. He has provided advice to NICE and discussed his personal experience at the Royal Society of Medicine. He has

advocated a true surveillance trial in order to obtain clarity for Barrett's Patients. He is chairman of FORT which has a membership of over 500 patients with Barrett's oesophagus.

2.0 STUDY OBJECTIVES and DESIGN

2.1. Aim

To establish whether the benefits of two-yearly endoscopic surveillance[25] in Barrett's oesophagus patients outweigh the risks compared with endoscopy at need only.

2.2. Primary objective

The primary objective of the trial is to establish whether two-yearly endoscopic surveillance or endoscopy at need only is superior in terms of overall survival and, if neither is superior, whether endoscopy at need only is non-inferior to two-yearly surveillance.

A stepwise testing procedure will be used testing first for superiority of either treatment and, if this cannot be concluded, then testing for non-inferiority of non-surveillance. The non-inferiority margin is set at a 5% difference in 10-year overall survival, and 1-sided 97.5% confidence interval will be used. No adjustment for multiple testing is required for this strategy (CPMP/EWP/482/99)[26]

2.3. Secondary objectives

2.3.1. To estimate cost-effectiveness of two-yearly endoscopic surveillance policy as compared to endoscopy at need only

2.3.2. To establish whether there is a significant difference between two-yearly endoscopic surveillance or endoscopy at need only in terms of:

a. 1. Oesophageal Cancer
   2. Gastric or Oesophageal Cancer
   3. All Cancers
b. Time to diagnosis of oesophageal adenocarcinoma
c. Stage of oesophageal adenocarcinoma at diagnosis using TNM staging.
d. Morbidity and mortality related to endoscopy, oesophageal surgery, and other endoscopy-related interventions (e.g. ablation)
e. Frequency of endoscopy

2.4. Justification for trial design

A randomised controlled trial is the most rigorous method of assessing the efficacy of endoscopy surveillance in reducing oesophageal adenocarcinoma mortality. However, due to the nature of the intervention this study cannot be blinded since patients and their clinicians will be aware of the intervention that has been allocated. A number of studies have informed the approach [27, 28, 29, 30] indicating the most acceptable method of trial conduct for patients.

2.5. Participants

2.5.1. Inclusion Criteria

a. Patients over the age of 18 years

b(i). With histologically definite, consistent with or corroborative of circumferential Barrett's metaplasia, at least 1cm from the gastro-oesophageal junction. A length of 1cm has been chosen as studies [31, 32, 33] have shown that endoscopists are inaccurate at measuring the length of Barrett's of less than 1cm. Inclusion of shorter segments of Barrett's is therefore likely to include patients that have no Barrett's epithelium and simply have specialised intestinal metaplasia at the gastro-oesophageal junction. This group has an uncertain oesophageal adenocarcinoma risk and it is not appropriate to include them in this trial.

OR

b(ii). Patients with at least a 2cm non circumferential tongue/island(s) of Barrett's supported by the following histological definitions: definite, consistent with or corroborative.

c. Endoscopy within the last 2 years to confirm Barrett's metaplasia and exclude high grade dysplasia and carcinoma.

d. Patients with low grade dysplasia can be entered at clinician's discretion.

e. Able to give written consent.

f. Fit for endoscopy.

g. Patients must have been informed of the risk of Barrett's oesophagus developing into oesophageal cancer, either at the visit when the invitation letter is issued, or on a documented previous occasion.

2.5.2. Exclusion criteria

a. Previous upper Gastro-Intestinal (GI) cancer.

b. Previous non-upper GI cancer where the investigator considers the research to be an added burden to the participant.
c. Histologically confirmed high grade dysplasia or carcinoma of the oesophagus at enrolment.
d. Patients who are currently in follow up as part of the AspECT trial.
e. Medical conditions which would make endoscopy difficult or hazardous.
f. Those non-resident in the UK as they will be unlikely to be followed up either by endoscopy or NHS flagging (see section 2.7).

2.6. Planned interventions

a. The experimental intervention will be surveillance endoscopy every two years with quadrantic biopsies taken every 2 cm. An endoscopy carried out within three months either way from the due date, and not prompted by symptoms, will be deemed as a scheduled endoscopy. The final scheduled endoscopy will not be later than the 10th anniversary of recruitment into the trial.
b. The control intervention will be endoscopy at need rather than routinely.
c. All patients (including those in the endoscopy at need arm) will be offered urgent endoscopy if they develop dysphagia, unexplained weight loss of > 7lb, iron deficiency anaemia, recurrent vomiting, or worsening upper gastrointestinal symptoms. The Data & Safety Monitoring Committee (DSMC) will be apprised of the number of endoscopies actually received by each intervention group. An endoscopy prompted by symptoms rather than time will be classed as unscheduled.
    i. All other care for patients should be as standard practice for the treating hospital. This includes decisions about treatment of, and endoscopy frequency following, oesophageal changes.
    ii. Patients who develop low grade dysplasia whilst participating in the study should remain in the study. Following each subsequent endoscopy a BOSS Endoscopy & Pathology Form should also be encouraged to complete a QoL Questionnaire, with the exception of those who have completed one in the last 3 months.

2.7 Flagging of Participants

The trial team will register participants with the Medical Research Information Service (MRIS) or Information Service Division (ISD for Scotland) to obtain details of cancer registrations / dates and cause of death.

Those patients, who withdraw their consent from the study, will be asked if they are happy for the trial team to continue to obtain this data.

2.8 Proposed Sample Size

For the superiority analysis of the primary aim of overall survival, a total of 3,400 Barrett's patients will allow us to detect a hazard ratio of 1.3 at 93% power (2 sided test at the 5% significance level). This assumes all cause mortality has an exponential time to conversion with a constant all cause mortality rate of at least 1.25% per year, recruitment for 2 years, follow-up for 10 years and a 10% loss to follow-up from national flagging.

For the non-inferiority analysis of the primary aim of overall survival with 3,400 patients there is 87% power to conclude non-inferiority of non-surveillance if there is no underlying difference between the arms, assuming a non-inferiority margin of 5% absolute difference in 10 year survival rate. This non-inferiority margin is equivalent to a hazard ratio for overall survival of 1.37.

3.0 RECRUITMENT, CONSENT and RANDOMISATION

3.1. Recruitment and consent

Patients will be identified at local centres through normal endoscopy clinics and surveillance lists. There will be two routes of identification and recruitment, described below:

3.1.1. Recruitment of newly diagnosed participants with Barrett's oesophagus

Local clinicians will identify participants undergoing endoscopy who have a potential diagnosis of Barrett's oesophagus following the procedure. These participants (who have a provisional diagnosis of Barrett's oesophagus following their endoscopy) will be given an information sheet and some verbal information about the study. They will be recruited at their next follow-up clinic appointment, following histological confirmation of Barrett's oesophagus, where informed consent will be obtained. They will then be randomised to the study.

3.1.2. Recruitment of participants with an existing diagnosis of Barrett's oesophagus

Participants who have an existing diagnosis of Barrett's oesophagus will be sent the information having been identified from disease registers. They will be identified and sent a letter, signed by their consulting clinician. Participants will be recruited at their next follow-up clinic appointment where informed consent will be obtained or at specially arranged appointment with the local study nurse. They will then be randomised to the study.

3.1.3. Recruitment of participants to be randomised via postal consent

It is appreciated that for some recruiting hospitals their catchment area may be geographically large making repeated visits by patients to discuss entry into the BOSS trial difficult and costly. Where this happens the BOSS trial team will accept postal consents to be carried out. This would require strict annotation in the medical notes and patient CRF packs detailing dates of the conversation with the patient, date the information sheet and consent form was posted to the patient and the date received by the recruiting hospital. The trials nurse should sign and date the consent on the date they receive it from the patient. Please ensure that a maximum of 4 weeks do not lapse between the date the consent was sent to the patient, the date it was signed by the patient and the date it was signed by the trials nurse. Hospitals that need to obtain consent in this way should contact the BOSS trial office to discuss this.

Recruiting centres can contact non respondents to the Introduction Letter, when used but only once.

3.2. Recruitment of Data Collection Only Participants (Demographic)

Both existing and newly diagnosed patients who do not wish to take part in the study will be asked to the time of initial study consultation for their consent to provide anonymised demographic and disease profile information (completion of the Initial History Sheet only with the exception of the patient identifiable data). This will enable comparisons to be made between those who choose to take part and those who do not.

The recruiting centre will fax the participant's 3 page Initial History Sheet *(see section 4.1)* along with a copy of the hospital pathology and gastroscopy results with trial number inserted and date of endoscopy / histology intact, to the BOSS Trial Office in Gloucester.

3.3. Method of Randomisation

The trials office will supply each site with a list of trial numbers which they will allocate to their patients upon consent. Randomisation codes will be generated by the Centre for Statistics in Medicine and administered by the Gloucestershire trials office. The randomisation will be block randomisation using varying block size, stratified on 3 factors:

- Age at date of diagnosis (<65, ≥ 65 years)
- Length of BM segment including tongues/island(s) (<2cm, ≥2cm and ≤3cm, >3 and ≤8cm, >8cm)
- Barrett's newly diagnosed (yes / no), where "newly diagnosed" means the date of endoscopy confirming Barrett's metaplasia was less than four months before the date the patient consented to trial entry.

Randomisation will take place after the patient has consented. Patients will only be randomised once the diagnosis is histologically definite, consistent with or corroborative with Barrett's Oesophagus.

The recruiting centre will fax the participant's, completed consent form, 3 page Initial History Sheet *(see section 4.1)* and a copy of the hospital pathology and gastroscopy results with trial number inserted and date of endoscopy / histology intact to the BOSS Trial Office in Gloucester and the details of the allocated group will be sent by secure fax to the Principal Investigator or designee. The allocated group will be notified to the participant and their GP, by letter, from the recruiting site.

4.0 CONDUCT OF THE STUDY

4.1. Ongoing diagnosis of High grade / Low grade dysplasia and Oesophageal Cancer

Where a current trial patient develops either High grade / Low grade dysplasia or Oesophageal Cancer the local hospital should carry out all necessary treatment for that patient. The BOSS protocol does not contain any procedures for these events. The Chief Investigator, Professor Hugh Barr, is available should advice be sought on any aspect of ongoing care.

From a BOSS trial point of view we would encourage sites to discuss ongoing data collection for the trial with the patient *(see section 4.2.8 below).* This would be basic data only, for example completion by the trials nurse, of the BOSS Endoscopy and Pathology CRF along with copies of the trust gastroscopy and histology reports and the completed QoL Questionnaire.

4.2 Case Report Forms (CRFs) completion

Data collected on each patient will be recorded by the Investigator, or his/her designee (as noted on the Site Delegation Log), as accurately and completely as possible. The Investigator will be responsible for the promptness, completeness, legibility and accuracy of the CRF and he/she will retain a copy of each completed form. The Investigator will allow study staff access to any required background data from such records (source data e.g. medical records) on request.

CRFs should be completed according to the following specifications in a timely fashion, where possible.

- Always use a black ink ballpoint pen.

- Ensure data entry is as complete as possible without omissions. It is not possible for BOSS personnel to interpret blank spaces. If data is unavailable write, for example; ND: not done, NA: not applicable, NK: not known and then this should be initialled and dated. Avoid using the ambiguous phrase, 'not available'.

- Ensure all entries are accurate, legible and verifiable with the source data in the medical record.

- Never over-write an entry. Corrections should be made as follows:
  - Score through the incorrect entry with a single line so that the incorrect entry remains legible. Never use correction fluid or obliterate entries made on the CRF.
  - Enter the correct data.
  - Initial and date the correction.
  - If it is not clear why the change has been made, an explanation should be written next to the change

- Any discrepancies with source data should be explained and the significance noted in the CRF and/or patients medical records. For values outside the reference range or some other range agreed with the study Sponsor, or if a value shows significant variation from one assessment to the next, this should be commented on and the significance noted in the CRF and/or patients medical records.

- The CRF must be signed where indicated, by the Principal Investigator or designee *(as appropriate)* to assert that he/she believes they are complete and correct.

- CRFs should be kept in a secure location during the course of the study as agreed by Local Trust R&D approval. When CRFs have been completed they should be filed in a secure location with a file note in the site file to say where they are stored. At the end of the study the CRFs should be archived.

- Each patient enrolled into the study must have the correct CRFs completed and signed by the Investigator (or designee). This applies to those patients who fail to complete the study.

- CRFs must be photocopied and a copy kept on site, either within the site file or within the patient pack and also the patient's medical notes (QoL questionnaires should not be placed in medical notes due to possible number of QoLs completed). The original is to be sent to the BOSS Trial Office using the following address:

  BOSS Trial Team
  c/o Gloucestershire Research & Development Support Unit
  Leadon House
  Gloucestershire Royal Hospital
  Great Western Road
  Gloucester GL1 3NN

4.2.1. Initial History Sheet

The Initial History Sheet should be completed at the time of consent as much as possible, using a black ball-point pen in capital letters. Dates should be written in the format shown unless otherwise indicated e.g. DD / MM / YYYY.

Numerical data should be entered from the right with “0’s” in the empty boxes and decimal points should be rounded up unless a box has been provided.

Please ensure that prior to submission of the Initial History Sheet that the form is fully completed and checked. For example within the spaces available for indicating the Length of Circumferential Columnar Lining and the Length of Tongues/Island(s) of Columnar Lining their shouldn’t be any blanks, therefore if the circumferential is 0cms and tongues/Island(s) 5cms the responses would be

Length of circumferential Columnar Lining **C** | **0** | **0** | . | **0** | cm

Length of Tongues/Island(s) of Columnar Lining (maximal extent - i.e. total length)

M | **0** | **5** | . | **0** | cm

NB: Minimal figure in Circumferential (C) can be 0, if Tongue/Island(s) (M) is >2, thus M is the maximal (i.e. total)

Once completed the Initial History Sheet along with the Hospital Pathology and Gastroscopy Results, signed Consent Form and Helicobacter Update Form (if necessary) should be faxed to the BOSS Trial Office on 08454 225469 *(unless alternative arrangements have been agreed).*

If the BOSS Trial Office have any queries with regards to the data provided within the form they will contact the named individual who completed the form for clarification, this may involve an alteration being made and the form being resent. Once the BOSS Trial Office are satisfied the patient will be randomised into the study.

4.2.2. QoL Questionnaire

QoL Questionnaire should be given to the participant at the time of consent, at which point could the PI or designee complete the top section, indicating the site, trial number and participants DOB and tick the baseline box which will indicate that this is the first QoL Questionnaire, they can either take this away or complete whilst in consultation, if the patient takes the questionnaire away they should also be provided with a pre-paid return envelope (as provided by the BOSS Trial Office). QoL Questionnaires should also be given to participants each time they attend for an endoscopy, unless they have completed one within the last three months. It would be appreciated if the PI or

designee could indicate the date of the Endoscopy to which the QoL corresponds to in the section provided, this will assist the BOSS Trial Office in matching the QoL with the appropriate Endoscopy and Pathology CRF Form.

For those participants within the endoscopy at need arm the QoL questionnaire will be sent directly from the BOSS Trial Office on a two yearly basis, the first being sent 2 years after the patient was randomised into the study and then two yearly thereafter unless they have an endoscopy in the meantime then the clock will be restarted from the date of their most recent endoscopy. The BOSS Trial Office will contact the patient once only if the QoL has not been returned to the Trial Office within 1 month of sending it out.

4.2.3. Endoscopy & Pathology Form

Each time the participant undergoes an endoscopy the BOSS Endoscopy & Pathology CRF Form must be completed, indicating whether this was a scheduled or unscheduled scope, whether the results were histologically, definite, consistent with, or corroborative and the type of endoscopy undertaken, and submitted along with copies of the Hospital gastroscopy and pathology results to the BOSS Trial Office.

For those patients who had been randomised into the 2 yearly surveillance arm of the study, following an endoscopy whether scheduled or unscheduled, the date of the participant's next endoscopy will be reset to 2 years from the date of that scope, not the date of the previously booked scheduled scope.

4.2.4. Helicobacter Update Form

Helicobacter test is not obligatory and completely at the discretion of the clinician but if performed we would request that the Helicobacter Update Form is completed and sent to the BOSS Trial Office.

If a helicobacter test has been ordered but its results are not yet available, the Initial History Form or Endoscopy and Pathology CRF Form should not be delayed, awaiting the result. Instead, the Initial History Form or Endoscopy and Pathology CRF Form should be completed with "Awaiting Result" for the helicobacter test, and a Helicobacter update form should be completed as soon as the result is known. Similarly, if a positive test result has been obtained but

the treatment is not yet given, a Helicobacter update form should be completed when the treatment is given.

4.2.5. Hospital Admission Form (not related to a BOSS procedure)

The Principal Investigator or designee should complete the Hospital Admission Form as soon as the episode is complete (discharge or death) or become aware of the event.

A day's admission to hospital will be calculated from the admission and discharge dates, there will be no need to enter times of admission and discharge. An important measurement within health economics for BOSS is length of stay in high cost areas such as CCU, HDU and / or ICU. Therefore when completing the Hospital admission form we would require the total number of days that each patient spent in those areas. So if the participant went to HDU on two separate occasions for a stay of 2 and 4 days respectively during their whole stay in hospital then we would require 6 days to be noted on the form.

The ICD 10 code identifies the International Classification of Disease, which can be obtained from your hospital coders, however this information does not need to be obtained at the time of completion and submission of this form but can be forwarded at a later date. The BOSS Data Officer will chase missing codes 4 months after receiving the Hospital Admission Form. The ICD 10 code will be used by the Health Economists to calculate the costs of a stay in hospital.

4.2.6. Serious Adverse Event Form

A serious adverse event will be any event that may be related to a trial procedure (including oesophageal or endoscopy related events) that results in hospital admission, prolongation of hospital stay or death within 30 days.

The Principal Investigator (PI) or designed will report any serious adverse events within one working day (24 hours) of the Investigator/designee becoming aware of the event, to the Chief Investigator (CI). As these must be reported to the Sponsor and the Research Ethics Committee, prompt reporting is essential.

A Serious Adverse Event form should be completed, marked “Initial Report” and faxed to 08454 225469. Once the stay is complete, the serious adverse event form should be completed again, with the remaining detail(s), marked “on Discharge/Death” and faxed with 24 hours of discharge or death.

The BOSS Trials Team will prepare the SAE reports and the CI will sign them off before being reported to the sponsor and to the main Research Ethics Committee.

Serious Adverse Event Forms, but not Hospital Admission forms, should be copied to the R&D Manager at the Investigators site.

For clarification on how a days admission into CCU, HDU and / or ICU will be calculated and the ICD 10 please see *section 4.2.5 (above).*

4.2.7. Participant Details update form

The Principal Investigator or designee should upon becoming aware of any change of name, address or contact number(s) of the participant following entry into the study, advise the BOSS Trial Office by completing this form and faxing it to 08454 225469.

4.2.8. Study Exit Form

The Principal Investigator or designee should upon becoming aware of any reason why the participant cannot continue to be followed up within the trial advise the Trials Office by completing this form and faxing it to 08454 225469.

Please note that participants who receive a cancer diagnosis do not thereby cease to be followed up, as their treatment and outcome are important trial endpoints.

Participants who wish to exit the trial should be asked whether they would be willing to provide data about their ongoing treatment but not remain within their allocated randomised arm of the study, if this is the case the Study Exit Form should indicate this request.

4.3 Timing of Interventions

This is a randomised controlled trial and those invited to participate will be patients with a diagnosis of Barrett's oesophagus. They will be randomised to surveillance endoscopy every two years or endoscopy at need. In the surveillance arm, endoscopy should be scheduled whenever the time since the previous endoscopy reaches two years, regardless of whether the previous endoscopy was scheduled, unscheduled or before trial entry.

Investigators should submit an endoscopy and pathology form (along with the Hospital Pathology and Endoscopy results) to the trial office following each subsequent endoscopy following recruitment for a trial participant, whether scheduled or unscheduled.

All patients will receive a questionnaire that includes a quality of life measure and questions about medication on entering the trial, and then at each endoscopy appointment, whether scheduled or unscheduled (unless the participant has completed a QoL Questionnaire in the last 3 months). This will be administered by the clinical staff at each site and returned to the trial's office. Questionnaire returns will be monitored against the completed endoscopy forms.

In addition, subjects in the Endoscopy at need arm of the study will receive the same questionnaire, by post, directly from the main trial office whenever the time from them last receiving a questionnaire reaches two years. (Note that the previous questionnaire may have followed an unscheduled endoscopy, therefore the 2 yearly clock would be recalculated to commence from the date of the unscheduled endoscopy) and / or receipt of QoL Questionnaire.

In addition, subjects in both arms of the study will receive the same questionnaire following key events, for example, following diagnosis of any cancer or high grade dysplasia.

5.0 STATISTICAL ANALYSIS

5.1. Survival endpoints

All statistical analysis will be led by the Centre for Statistics in Medicine in Oxford with data entry and data cleaning by the BOSS Trial Team at the Research and Development Support Unit, Gloucestershire Royal Hospital.

Analysis of survival outcomes will use the stratified log-rank test statistic to compare the two groups, stratified by the variables used in randomisation. A Cox regression model will be used to adjust the comparison for other prognostic variables in addition to the stratification variables. Consideration will be given to methods taking account of interval-censoring in assessing time to oesophageal adenocarcinoma diagnosis.

Analysis of stage will use a chi-square test for trend and ordinal logistic regression model adjusting for factors as in the survival models. Morbidity and mortality will be analysed using a chi-square test and presenting odds ratios from probit regression. Frequency of endoscopy will be modelled using Poisson regression.

All superiority analyses will be intention to treat, and will be performed at the two-sided 5% significance level. Non-inferiority analysis will use both per protocol and intention to treat populations, and uses a two-sided 95% confidence interval.

A statistical analysis plan is being prepared separate to the trial protocol. This will be finalised prior to data lock. The statistical analysis plan gives detailed description of the analyses to be carried out and results to be presented for this trial.

5.2. Economic analysis

All economic analysis will be led by a team from Glasgow University.

5.2.1. Cost-effectiveness will be expressed in terms of cost/life year saved and cost/quality adjusted life year saved from a health service perspective comparing surveillance with endoscopy at need. Data will be presented as the extra cost per extra health benefit of surveillance every two years compared to endoscopy at need and this is termed the incremental cost effectiveness ratio (ICER). This figure has a range of uncertainty due to the statistical uncertainty around the estimates of costs and effects. Bootstrap sampling techniques will be used to assess the uncertainty, which will be presented using confidence intervals for cost-effectiveness, where appropriate, and through cost-

effectiveness acceptability curves, that graphically displays the probability of a given ICER.

5.2.2. A Markov model will be constructed to extrapolate the data beyond the 10 years of the trial and to explore other issues such as variations in oesophageal adenocarcinoma incidence rates in different centres and the most cost-effective interval for endoscopic surveillance. Data will be synthesised from other sources as appropriate.

5.3. Plan for the cost-effectiveness analysis

The proposed cost-effectiveness analysis of BOSS will proceed by several stages, including data collection, within trial analysis, extrapolation to patient lifetimes and inclusion of evidence from sources external to the trial. It was clear from the models and estimates in the PenTAG HTA[35] commissioned report that surveillance was cost ineffective (approx £125,000 per QALY). Thus this is a very important part of the bid.

5.3.1. Perspective

The perspective of the economic analysis will be the UK health and personal social services, following the general guidance outlined by the National Institute for health and Clinical Excellence (NICE) for its appraisals[36].

5.3.2. Comparators

The BOSS trial offers a unique opportunity to answer the question of the efficacy and cost effectiveness of surveillance. In addition, by using the data gathered in the trial the final model will be able to assess the consequences for cost-effectiveness of altering the screening interval.

5.3.3. Data collection

In addition to the primary outcome of mortality, the economic analysis requires the collection of resource use information (which will be valued using standard NHS reference costs) and quality of life utilities. A particular focus of the analysis will be to attach costs and utilities to the key stages and events in the development of the condition.

5.3.4. Resource use data collection

Health Service resource use will be collected from healthcare records. We aim specifically to include additional data collection at key events, endoscopy, following diagnosis of carcinoma and after interventions for carcinoma. The biennial questionnaire will collect information about medications for Barrett's taken in the preceding 3 months.

5.3.5. Quality of life utilities

Quality of life data will be collected using the EQ-5D[37] instrument from the biennial questionnaires and following endoscopy events (scheduled and unplanned).This will give a good indication of the general quality of life experience of patients with Barrett's oesophagus and quality of life at important events (after endoscopy and pre and post oesophageal surgery). The PenTAG HTA review [34]of surveillance for Barrett's oesophagus identified the poor quality of utility data for these events as a particular area of concern. By encouraging patients to complete the EQ-5D questionnaire at these key stages of their treatment, this study offers the opportunity to generate robust quality of life estimates for the economic analysis.

A key feature of the calculation of costs and quality adjusted life years (QALYs) for the analysis will be to base the analysis on a balance sheet of events. Key events such as numbers of endoscopies, cancers detected and oesophageal procedures undertaken will be calculated for each arm, then the costs and quality of life implications of these events will be calculated for each arm in order to calculate the total costs and QALYs for each arm.

Statistical uncertainty will be captured through confidence intervals where appropriate, and through the use of cost-effectiveness acceptability curves and net-benefits when confidence intervals for the ICER are inappropriate.

5.3.6. Modelling & extrapolation

In order to project the cost-effectiveness of the surveillance to patient lifetimes a model will be developed. Consideration will be given to building on the existing structure developed by the PenTAG group. In any case, the model is likely to be a Markov Model with transition parameters estimated from the clinical trial data. The ten year follow-up of the trial will offer a major source of

data from which to robustly estimate the progression of this disease. Extrapolation will proceed by projecting forward the observed rates of disease progression. Consideration will be given to potential time dependencies in disease progression rates using standard survival analysis techniques. Parameter uncertainty will be handled through probabilistic sensitivity analysis supplemented by one-way sensitivity analysis for key structural assumptions relating to the modelling (such as the form of the baseline hazard function).

5.3.7. Evidence synthesis

The BOSS trial is expected to generate by far the most important randomised evidence on the value of surveillance for Barrett's oesophagus. Nevertheless, although existing data on the condition are sparse (as was noted in the PenTAG review[36]) it is likely that additional information will become available during the time that the trial is underway. Therefore, the economic modelling will involve maintaining and updating the review of key economic parameters undertaken by the PenTAG review. This external evidence could then be synthesised with the data generated from the trial in order to ascertain whether the inclusion of all relevant evidence into a 'comprehensive decision model' improves the robustness of the model compared to simply extrapolating data from this trial.

5.3.8. Modelling additional policy questions

The surveillance arm of the BOSS study is based upon two-yearly surveillance with endoscopy (current guidelines from British Society of Gastroenterology). However, one modelling study Provenzale[38] showed that the cost-effectiveness of any surveillance strategy was strongly related to the surveillance interval. Therefore, once a model of the lifetime cost-effectiveness analysis is built based on the existing trial, it will be possible to alter certain aspects of the surveillance strategy, such as the appropriate interval for surveillance endoscopy. It is worth noting that it will be much more robust to model the consequences of reducing the frequency of surveillance having observed disease progression rates based on more frequent surveillance than to model more frequent surveillance based on data obtained from a less frequent surveillance programme.

6.0 QUALITY ASSURANCE

6.1. Protocol Compliance

All study sites taking part in the study will be required to attend a start-up meeting or participate in a telephone call to ensure compliance with the protocol and allow training on study procedures and data collection methods. The Principal Investigator at each study site must apply for local R&D Approval, submit all amendments and changes to the protocol and provide any necessary documentation for their site before they can recruit into the study.

The BOSS Trial Office will monitor the compliance of study sites taking part in the study on an ongoing basis. The first site audit will take place once 10 patients have been recruited and at regular intervals thereafter.

Where non-compliance with the protocol or the standard procedures set out in the Trial Agreement is suspected, one of the Lead Investigators for the study will contact the study site to resolve any problems. If appropriate, the matter will be referred to the BOSS Trial Management Group at their next meeting or by correspondence with members if urgent. The BOSS Trial Management Group has the full authority to take appropriate corrective action, including temporary or permanent withdrawal of the study site from BOSS.

The information will be communicated with the site R&D Office.

6.2. Monitoring and Audit

6.2.1. Central Monitoring

Study sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. 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.

6.2.2. On-Site Monitoring

The BOSS Trial Team will conduct site visits as needed. The Principal Investigator will allow the BOSS Team access to source documents as requested. Investigators and site staff will be notified in advance about forthcoming monitoring visits

6.2.3. Inspection

If a site is notified of an inspection relating to BOSS by a regulatory or other official body, the site staff must notify the BOSS Trial Office immediately.

7.0 TRIAL ETHICS and GOVERNANCE

7.1. Ethical arrangements

Although this is not a trial of an investigational medicine, it will be conducted to the same standard as set out in the directive 2001/20/EC of the European Parliament. Written, informed consent will be obtained from all participants and subjects can withdraw from the trial at any stage without giving a reason or suffering any detriment as a result. NHS indemnity arrangements will apply. Participants will be given written information on the trial and be given a contact point where they may obtain further information if required. A favourable opinion from an NHS Research Ethics Committee will be needed, and approval from each host NHS organisation will be needed before commencing the trial at each site. Any protocol amendments after the trial has been approved will also be referred to the Ethics Committee.

7.2. Data Protection

Following publication of the results the trial documentation will be stored for 10 years in a secure environment that complies with the Data Protection Act (1998)

8.0 MANAGEMENT

8.1. Responsibilities

This trial will be conducted under the auspices of the Research and Development Support Unit at Gloucestershire Hospitals NHS Foundation Trust (GHNHSFT) in conjunction with the Centre for Statistics in Medicine, Oxford under its Director Professor Doug Altman.

Professor Hugh Barr (Chief Investigator) will take overall responsibility for the trial. Mr Attwood, Prof Moayyedi Prof Jankowski and Dr Watson (Clinical Leads) will provide clinical advice relevant to their areas of expertise. The Chief Investigator will lead a Trial Management Group (TMG), which will be responsible for implementing the decisions of the Trial steering committee. The overall management of the trial will be undertaken by Julie Hapeshi and Prof. Ian Russell from the University of Wales, Bangor, will act as mentor for the trial's management group.

8.2. Trial Management Group

The members of the TMG for this study are:
Professor Hugh Barr (Chief Investigator)
Elisabeth Fenwick (Health Economist)
Professor Andrew Briggs (Health Economist)
Professor Janusz Jankowski (Expert)
Mr Michael Lang (Patient Representative)
Sharon Love (Trial Statistician)
Milensu Shanyinde (Assistant Trial Statistician)
Julie Hapeshi (Trial Manager)
Chris Foy (Data Manager)
Clive Stokes (Trial Coordinator)
Sue Woods (Trial Administrator)
Zarah Famy (Data Officer)
Mandy Phelps (Assistant Director of Finance, Gloucestershire NHS Foundation Trust)
Emma Jackson, (Finance Officer)

8.3. Trial Steering Committee

The members of the TSC for this study are:
Professor Brendan Delaney - Independent member
Mr Simon Dwerryhouse - Independent member (Clinician)
Jacqueline Birks - Independent member (Statistician)
Mr Charles Brownhill - Independent member (Expert patient)
Joanne Lord (Health Economist)

In addition, the following members of the trial management group have the right to attend at least part of every TSC meeting:
Professor Hugh Barr (Chief Investigator/Clinician)
Clive Stokes (Trial Coordinator)
Sharon Love (Trial Statistician)
Other members of the TMG may attend meetings by invitation only.

8.4. The Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee (DSMC) will be established for this trial, to safeguard the interests of trial participants, potential participants and future

patients. It is intended that this committee will meet on a 6-monthly basis during recruitment and annually thereafter; the exact frequency will depend on accrual and event rates, and may be increased upon request by the Committee. The DSMC will monitor the overall conduct of the clinical trial including recruitment to the trial, protocol compliance and safety, taking into account relevant worldwide experience. An interim analysis of the primary aim for dissemination only to the trial statistician and the DSMC will be carried out 4 years after the last patient recruitment.

The DSMC members and the Chief Investigator work to an agreed charter, with the DSMC making recommendations to the TSC and TMG. This information will be used by the Chief Investigator to provide reports to the main Research Ethics Committee reviewing the trial and the trial funder.

The members of the DSMC for this study are:
Richard Robinson (Chair), Consultant Gastroenterologist University Hospital Leicester

Ed Juszczak, Head of Trials, National Perinatal Epidemiology Unit

Dr Cathy Bennett, Systematic Research Cochrane Collaboration Upper Gastrointestinal Group

9.0 DISSEMINATION

The findings of the study will be presented in a final report to the funders of the study and to each participating site. The results will be disseminated widely through conference presentations, publication in peer reviewed journals and by a summary to the participants.

10.0 LINKED STUDIES

In the future one or more linked studies may be offered to participants, for example: Chemoprevention of Premalignant Intestinal Neoplasia (ChOPIN) and the Sibling Pairs study subject to the agreement of the TSC.

11.0 TIMETABLE

YEAR 1												
Months	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Finalise protocol												
Prepare documentation for REC review												
Ethical review												
Recruit trial coordinator when study REC approved												
Agree trial management committees												
Trial coordinator in post												
Research governance approvals												
Activate centres as sites approved												
Start recruitment of subjects												
Trial management group meetings p.a.						1						
Trial steering group meetings p.a.						1						
YEAR 2-13												
Years	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Continued recruitment of subjects												
Continued site activation												
Follow-up questionnaires												
Collection of MRIS or ISD data												
Trial management group meetings p.a.	2	2	1	1	1	1	1	1	1	1	1	1
Trial steering group meetings p.a.	2	2	1	1	1	1	1	1	1	1	1	1
DSMC committee p.a.	2	2	1	1	1	1	1	1	1	2	2	1
Data management and quality assurance												
Data analysis												
Report writing – progress reports & final report												

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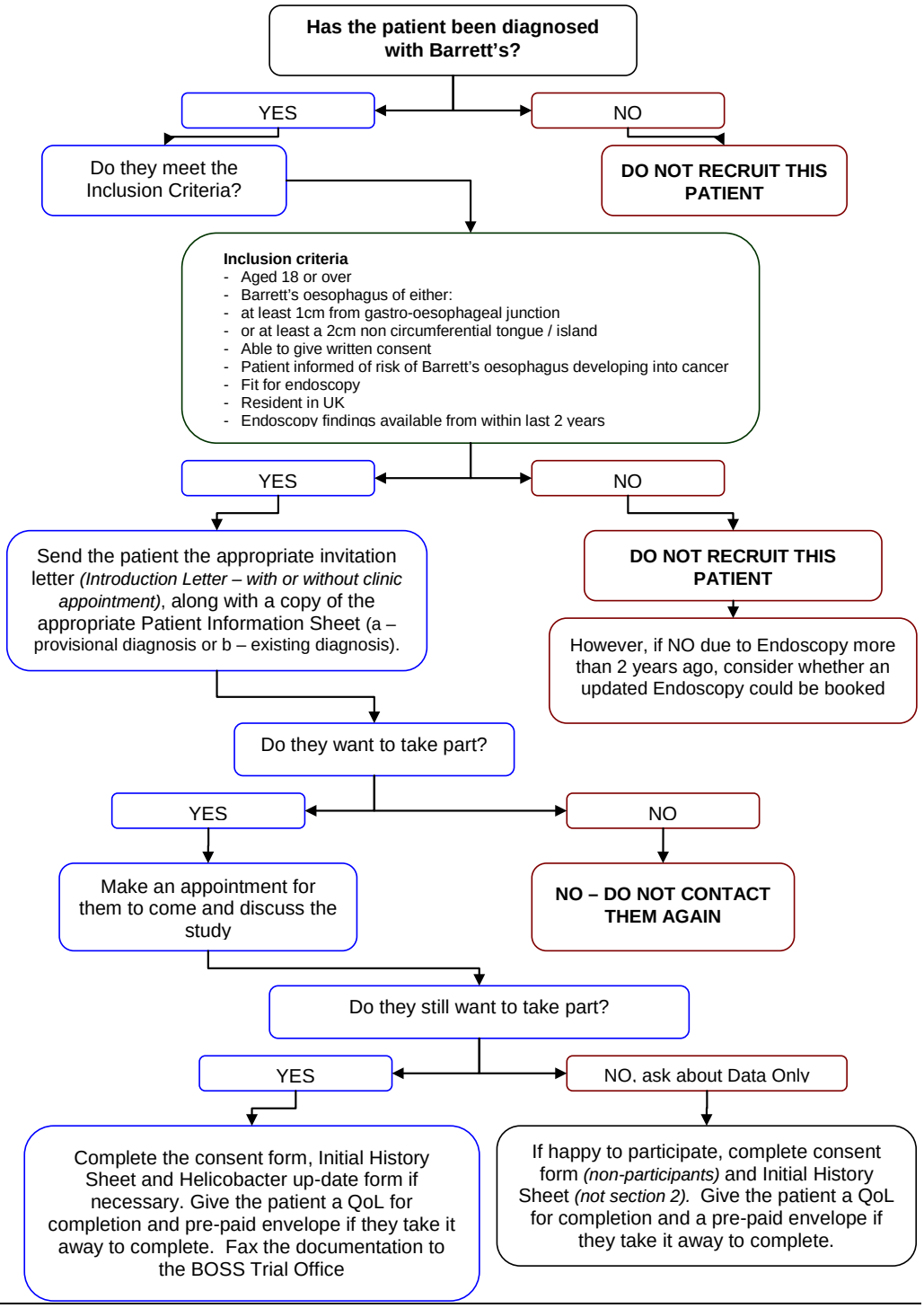
13.0 APPENDICES

APPENDIX 1

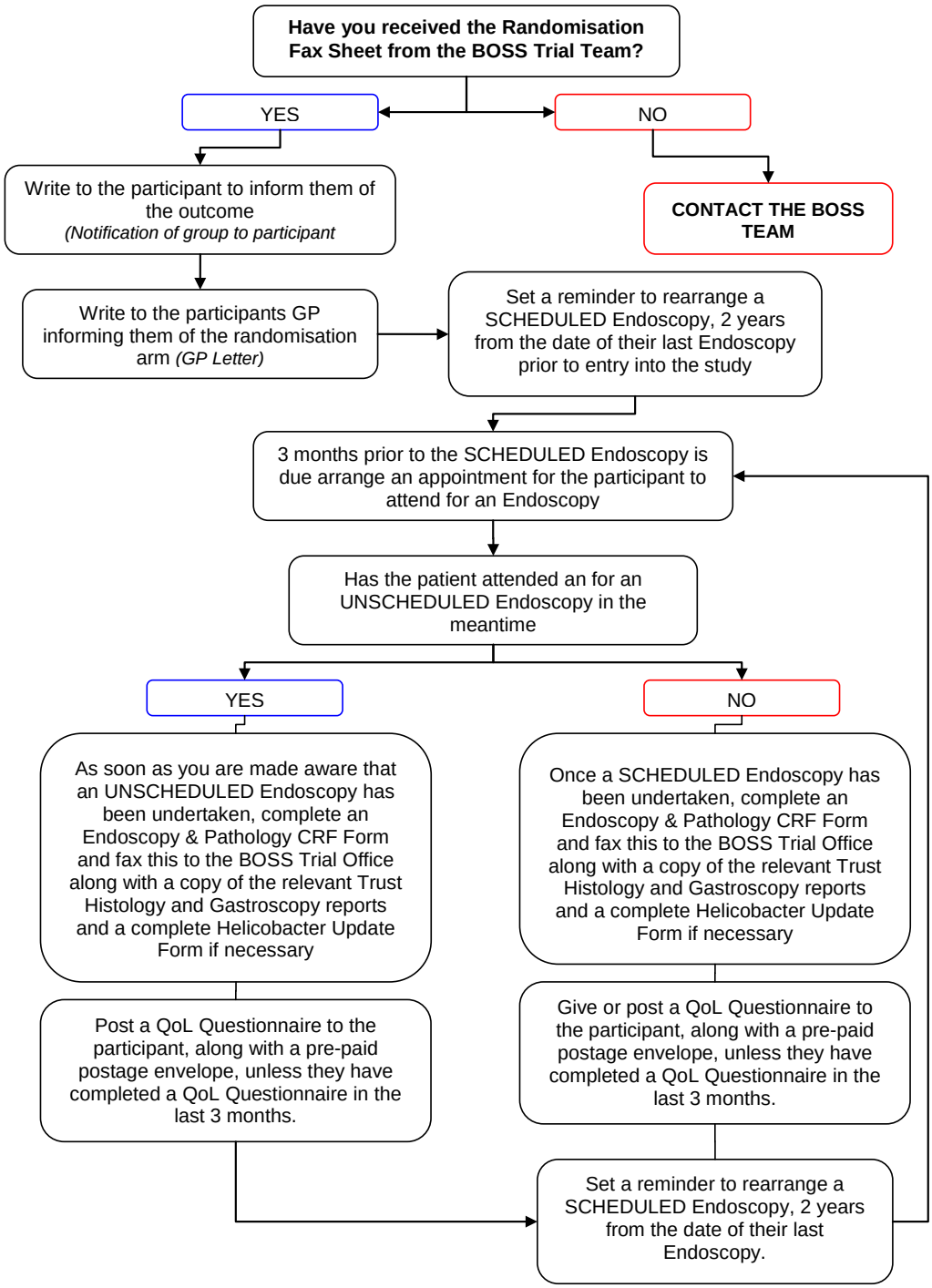
HOW DO I RECRUIT A PATIENT? IS THE PATIENT ELIGIBLE?



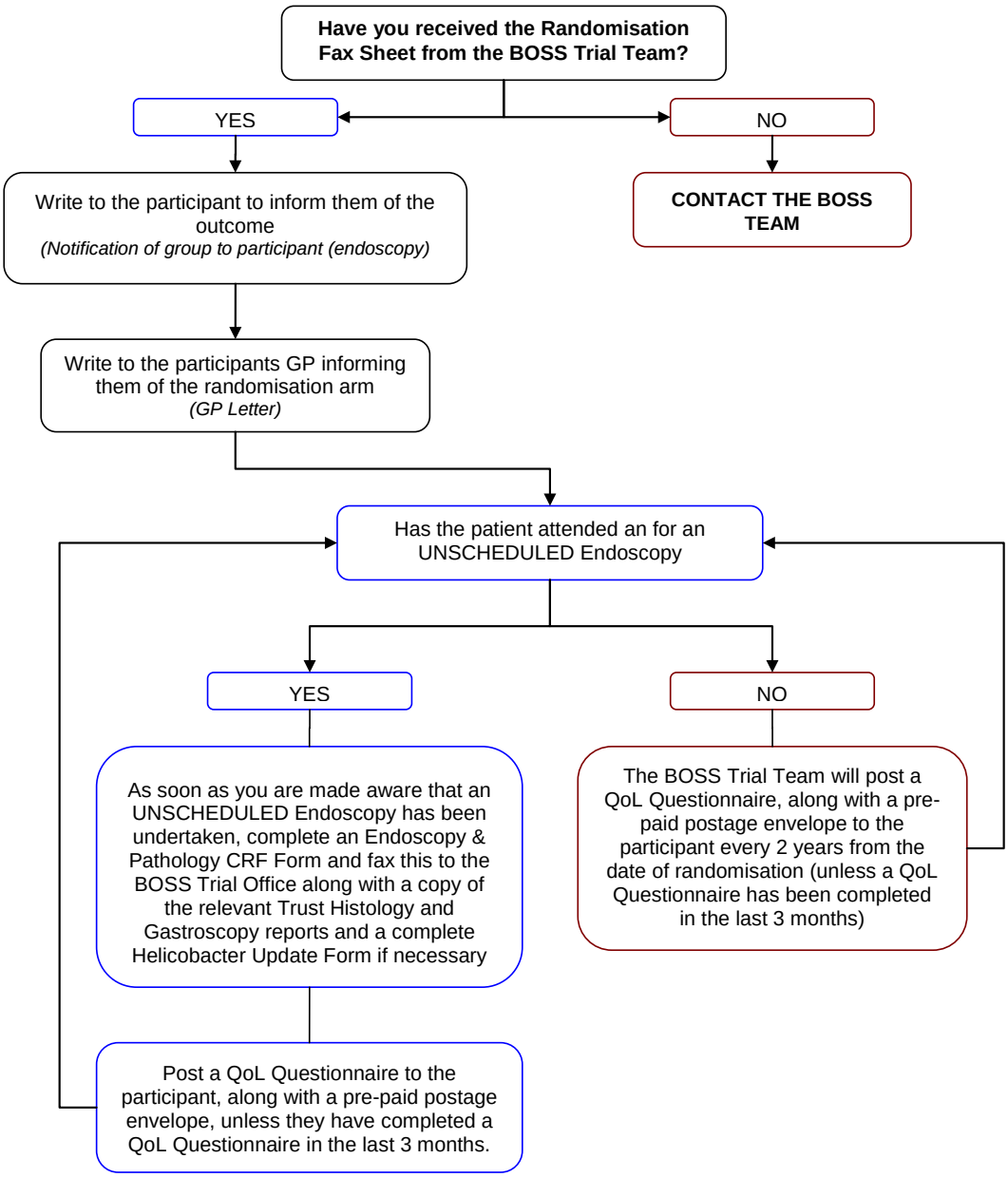
How do I recruit a patient – Flow Chart v1 27/07/ 2011

APPENDIX 2

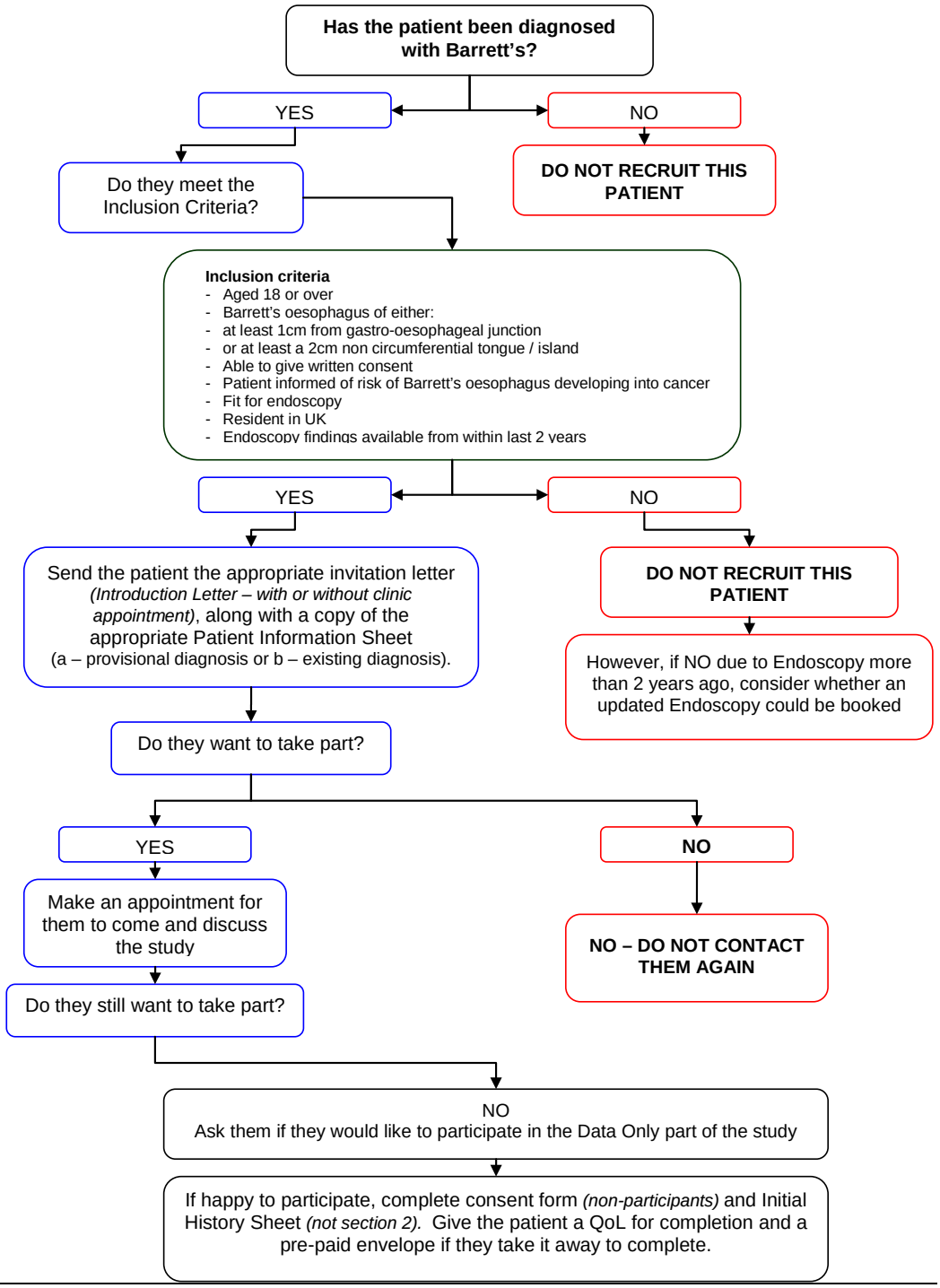
PATIENTS RANDOMISED INTO THE 2 YEARLY SURVEILLANCE ARM



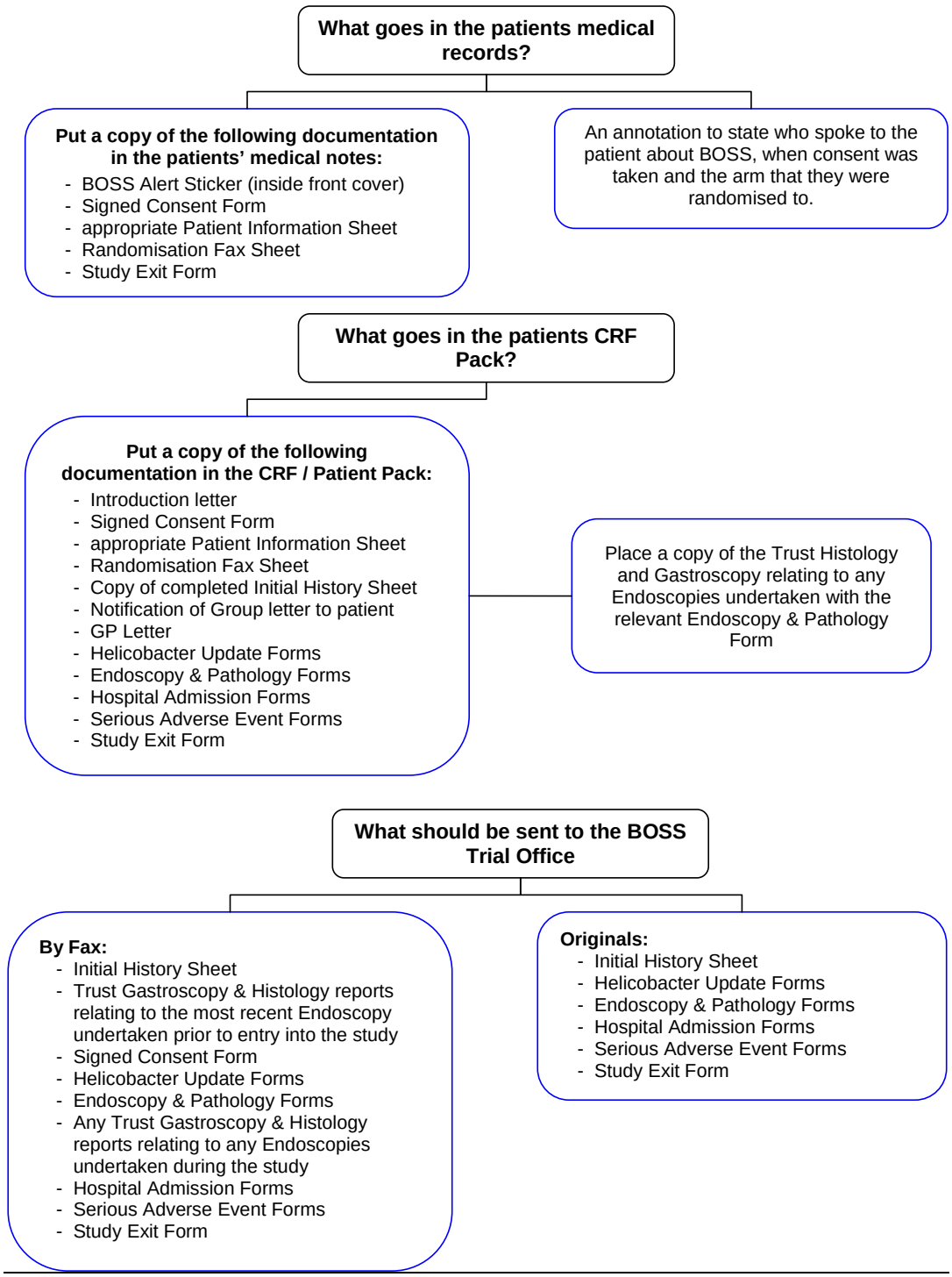
PATIENTS RANDOMISED INTO THE ENDOSCOPY AT NEED ARM



HOW DO I RECRUIT A DATA ONLY PARTICIPANT?



WHAT DOCUMENTATION GOES WHERE!

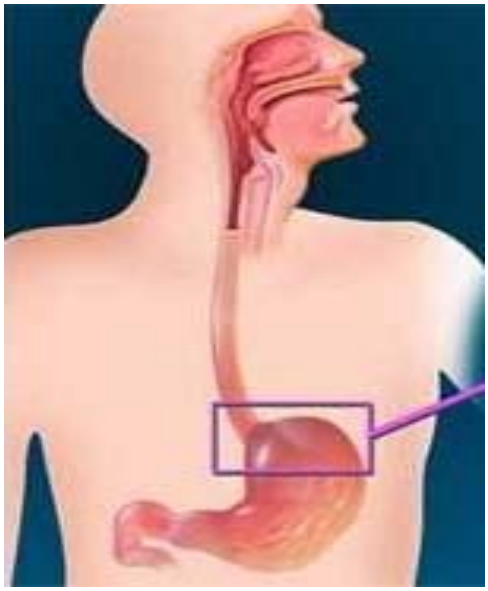


NIHR Health Technology Assessment programme funded project

BOSS
Barrett's Oesophagus Surveillance Study

NHS National Institute for Health Research

Have you been diagnosed with Barrett's Oesophagus? The BOSS trial could be for you



We are conducting the BOSS study because we are not sure whether regular endoscopy, is beneficial to patients with Barrett's oesophagus or whether using patients' symptoms could be just as good. It should be important to find out if regular endoscopy benefits patients before routinely offering it.

To see if the BOSS trial is right for you please ask your Hospital Doctor / Research Nurse for further information

or contact the BOSS Trial Team at:
Leadon House
Gloucestershire Royal Hospital
Great Western Road
Gloucester GLI 3NN
Telephone: 08454 225465

BOSS Poster v3, 27/07/2011

PATIENT SUMMARY SHEET

This is a trial funded by the National Institute for Health Research through the NIHR Health Technology Assessment Programme, and run by the Research and Development Support Unit based at Gloucestershire Hospitals NHS Foundation Trust. We are looking for patients from many areas of the UK.

The aim of the study is to see whether regular endoscopic surveillance is better than endoscopy at need for detecting any early signs of oesophageal cancer in patients diagnosed with Barrett's oesophagus.

Guidelines have been developed to check for early development of cancer using endoscopy. However these guidelines acknowledge that there is low confidence in the information available to support endoscopic surveillance in patients with Barrett's oesophagus, and the value of surveillance is still subject to considerable debate. The most appropriate method of evaluating whether surveillance is appropriate is through a randomised controlled trial.

The study randomises patients to receive a standard upper gastrointestinal endoscopy with biopsy every two years for 10 years or endoscopy at need. Those patients randomised to endoscopy at need will be free to request an endoscopy at any time if they have concerns. (This would also apply to those allocated 2 yearly endoscopy). All patients will receive a questionnaire every 2 years or after each endoscopy (which ever is sooner, to record their symptoms) and other health related data. (Those patients randomised to endoscopy at need will be sent theirs by the trial centre).

Rationale for the study
Barrett's oesophagus is a change in the lower gullet (oesophagus) brought about by the frequent reflux of gastric juice from the stomach into the oesophagus. The lining of the lower oesophagus changes to become like the lining of the small intestine. Barrett's oesophagus affects approximately 1% of the population.

A small number of patients with Barrett's oesophagus may go on to develop oesophageal cancer.

We are conducting the BOSS study because we are not sure whether regular endoscopy, is beneficial to patients with Barrett's oesophagus or whether using patients' symptoms could be just as good. It should be important to find out if regular endoscopy benefits patients before routinely offering it.

How many patients will be involved?
A total of 2,500 Barrett's patients (1,250 in each group) will be invited to join this trial over the next 2 years. You will then be followed up for a further 10 years.

How to register interest:
If you have Barrett's oesophagus and would like to take part in this trial please ask your hospital doctor / research nurse for further details. They will be happy to give you the full patient information sheet.

Alternatively please contact:
The BOSS Trial Team at Leadon House
Gloucestershire Royal Hospital
Great Western Road
Gloucester GL1 3NN
Telephone: 08454 225465

Taking part in this trial is purely voluntary

Summary Sheet, version 2, 27/07/2011

APPENDIX 8

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

Date

Patient Name
Address

Dear ***Patient Name***

I am writing to you as you will remember having had an endoscopy and being told that you have a condition called Barrett's oesophagus. This condition often goes along with troublesome symptoms such as indigestion and acid reflux. This hospital is taking part in a research study to see whether regular endoscopies (every 2 years) for patients with Barrett's oesophagus are a beneficial thing to do.

The current available information does not give us a clear answer, one-way or the other, as to whether regular endoscopies are a good way of spotting any changes in patients with Barrett's oesophagus that might signal the need for further treatment. It may be that the small risks that are associated with endoscopy outweigh any benefits that there might be in diagnosing changes in patients with Barrett's oesophagus at an earlier stage.

I would like you to invite you to consider taking part in this project and am sending you the information sheet to explain the study in more detail. I am sending this information ahead of your next clinic appointment when you can sign the consent form if you are happy to do so.

The BOSS Research Nurse, *Insert Name of Nurse*, will contact you in several days from the date from the date of this letter to discuss the study further and answer any questions that you may have prior to your clinical appointment.

Thank you for taking the time to read this information.

Yours sincerely

Name of Principal Investigator

APPENDIX 9

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

Date

Patient Name
Address

Dear ***Patient Name***

I am writing to you as you will remember having had an endoscopy and being told that you have a condition called Barrett's oesophagus. This condition often goes along with troublesome symptoms such as indigestion and acid reflux. This hospital is taking part in a research study to see whether regular endoscopies (every 2 years) for patients with Barrett's oesophagus are a beneficial thing to do.

The current available information does not give us a clear answer, one way or the other, as to whether regular endoscopies are a good way of spotting any changes in patients with Barrett's oesophagus that might signal the need for further treatment. It may be that the small risks that are associated with endoscopy outweigh any benefits that there might be in diagnosing changes in patients with Barrett's oesophagus at an earlier stage.

I would like you to invite you to consider taking part in this study and I am sending you the information sheet to explain the study in more detail. The BOSS Research Nurse, *Insert Name of Nurse,* will contact you in several days from the date of this letter to discuss the study further. At this time he/she will arrange an appointment for you to formally join the trial if you wish to do so.

Thank you for taking the time to read this information. If you think that this does not apply to you, please accept my apologies and contact the number at the head of this letter to inform them so that our records can be corrected.

Yours sincerely

Name of Principal Investigator

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

The BOSS study
(Barrett's Oesophagus Surveillance Study)
A randomised controlled trial of surveillance for patients with Barrett's oesophagus

You have just had an endoscopy that has provisionally diagnosed a condition called Barrett's oesophagus. Barrett's oesophagus is a change in the lower gullet (oesophagus) brought about by the frequent reflux of gastric juice from the stomach into the oesophagus. The lining of the lower oesophagus changes to become like the lining of the small intestine.

If this diagnosis is confirmed when the results of the biopsy samples have been tested then we would like to invite you take part in a research study. This will be discussed with you at your next hospital clinic appointment. In the meantime it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish, for example family and friends or your family doctor (GP). Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
For most people, Barrett's oesophagus it is not a life threatening condition but it can cause troublesome indigestion-like symptoms. It occurs in about 1% of the adult population and can lead to oesophageal cancer in some people. Once you have Barrett's oesophagus the life-time risk of it developing into cancer is about 5%.

The best method of detecting this cancer and early changes and thus preventing its progress is not clear. Some have recommended and developed guidelines that recommend that patients with Barrett's oesophagus have an endoscopy every 2-3 years to detect cancer. Others suggest that endoscopy should be in response to patient symptoms and performed at the time of need or change in the patient's condition after consultation with their physician.

The use of regular endoscopy to review the progress of Barrett's oesophagus commonly causes minor complications in between 1-10% of patients. These include discomfort, pain and/or breathing difficulties, which should settle down in a few days. Endoscopy is also inconvenient for patients and may causes anxiety for some patients and their families. On very rare occasions it can result in perforation of the oesophagus (1 in 3,000 endoscopies), or death (1 in 100,000 endoscopies).

Recent analysis acknowledges that the information to support endoscopy surveillance is relatively weak and the value of planned, regular endoscopy is still subject to considerable debate. A randomised trial is the best way of determining whether regular endoscopy allows for earlier detection and treatment of oesophageal cancer, leading to a better outcome. At the moment there are no other trials published or being conducted in this area.

We are conducting this study because we are not sure whether regular endoscopy, with the risks described, is beneficial to patients with Barrett's oesophagus or whether using patients' symptoms could be just as good. It should be important to find out if regular endoscopy benefits patients before routinely offering it.

Why have I been given this information sheet?
As a patient who has a likely diagnosis of Barrett's oesophagus you are being informed of a research project in this area. If your condition is confirmed as Barrett's oesophagus then you will be asked at your next clinic appointment whether you wish to take part in the study. A total of 3,400 patients with Barrett's oesophagus will be recruited from across the UK during a 3 year period and followed up for a further 10 years.

What will happen to me if I take part?
Since we do not know the best way of managing patients with Barrett's oesophagus we need to make comparisons. If you agree to go into the study you will be randomly allocated to one of two groups:

1. You will be invited for a planned endoscopy every two years or in between times if you need one

   OR

2. You will only be offered an endoscopy if you need one.

Regardless of which group you are in you can still be referred back to the hospital consultant for further tests and investigations if necessary.

The groups are selected by a computer, i.e. allocation is by chance, like tossing a coin. Patients in each group then have different management and these are compared. The Trial is much fairer if people are assigned to groups by chance, not by choice.

You will also be registered with the Medical Research Information Service (MRIS) or Information Service Division (ISD) to follow your health outcome in the longer term, even if you have moved away and we haven't got your address.

What do I have to do?
Everyone taking part in the study will receive a questionnaire every two years for up to ten years. The questionnaire will ask you about the medicines you currently take for your Barrett's oesophagus and your general well-being. If you are not in the group who are having regular endoscopies this will be sent to you by the BOSS study office. You will also be asked to complete a questionnaire after each endoscopy that you have during the period of the study.

Any additional information we might need about your condition will be provided by your local hospital doctor.

What are the possible benefits of taking part?
We cannot promise that taking part will benefit you. However, the information we get from this study may help us to treat future patients with Barrett's oesophagus more effectively and given the long term nature of the condition this might include you.

What if I don't want to take part?
Regardless of your diagnosis your hospital doctor will discuss the most appropriate way of monitoring your condition and treating the symptoms.

If you decide not to take part we would like to collect some information about you and your condition. This will help us to find out if the people who choose to take part in the study are any different than those who do not. This may be important information to consider at the end of the study. The information will not identify you. You do not have to agree to this.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about what is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.
Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?
If the project were to stop early then your care will return to the best available at that time. At the end of the project we will look at the findings and then make recommendations about what changes in care there should be.

What if something goes wrong?
We believe that this study is basically safe and do not expect you to suffer any harm or injury because of your participation in it. The NHS indemnity scheme will compensate you if you are harmed due to someone's negligence but there is no compensation scheme for harm that was not caused by negligence.

Will my taking part in this study be kept confidential?
If you decide to participate in BOSS, the information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored at the BOSS Trial Office at Gloucestershire Royal Hospital on paper and electronically, under the provisions of the 1998 Data Protection Act. Your name and address will also be given to dedicated staff at the BOSS Trial Office when you first enter the study, so that they can send Quality of Life questionnaires to your home address. This information will not be accessed by any other personnel. Any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. You will be allocated a study number, which will be used as a code to identify you on all study forms. Only the BOSS Trial Office and your hospital will be able to identify you from this number. With your permission, your GP and the other doctors involved in your clinical care will be kept informed, but otherwise all information about you and your treatment will remain confidential.

With your permission, your relevant medical records may be inspected by authorised individuals from the research team or the Gloucestershire Hospitals NHS Foundation Trust (the study Sponsor). They may also be looked at by the regulatory authorities. The purpose of this is to check that the study is being carried out correctly.

What will happen to the results of the research study?
The results of the research will be published in one or more papers in medical journals so that they are available to all doctors. At the end of the study you can request a copy of the results from your research doctor. No individual patients will be identified in any publication or report.

Who is organising and funding the research?
The trial has been organised by Prof. Hugh Barr, a surgeon specialising in Barrett's oesophagus at Gloucestershire Hospitals NHS Foundation Trust. The study is funded by the NHS Health Technology Assessment Programme. The doctor conducting the research is not paid for including patients in the study and for looking after them. These costs are borne by the NHS.

Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Once you have decided to take part you are still free to withdraw at any time and without giving a reason. Your decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What if I have any further questions?
Please contact the doctor who is conducting the study in your local hospital:

<insert name and contact details here>
Name of Consultant
Job Title
Address

Telephone Number

Thank you for reading this.

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

The BOSS study
(Barrett's Oesophagus Surveillance Study)
A randomised controlled trial of surveillance for patients with Barrett's oesophagus

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish, for example family and friends or your family doctor (GP). Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
Barrett's oesophagus is a change in the lower gullet (oesophagus) brought about by the frequent reflux of gastric juice from the stomach into the oesophagus. The lining of the lower oesophagus has changed to become like the lining of the small intestine.

You have had an endoscopy that has diagnosed Barrett's oesophagus and for most people it is not a life threatening condition but it can cause troublesome indigestion-like symptoms. It occurs in about 1% of the adult population and can lead to oesophageal cancer in some people. Once you have Barrett's oesophagus the life-time risk of it developing into cancer is about 5%.

The best method of detecting this cancer and early changes and thus preventing its progress is not clear. Some have recommended and developed guidelines that recommend that patients with Barrett's oesophagus have an endoscopy every 2-3 years to detect cancer. Others suggest that endoscopy should be in response to patient symptoms and performed at the time of need or change in the patient's condition after consultation with their physician.

The use of regular endoscopy to review the progress of Barrett's oesophagus commonly causes minor complications in between 1-10% of patients. These include discomfort, pain and/or breathing difficulties, which should settle down in a few days. Endoscopy is also inconvenient for patients and may causes anxiety for some patients and their families. On very rare occasions it can result in perforation of the oesophagus (1 in 3,000 endoscopies), or death (1 in 100,000 endoscopies).

Recent analysis acknowledges that the information to support endoscopy surveillance is relatively weak and the value of planned, regular endoscopy is still subject to considerable debate. A randomised trial is the best way of determining whether regular endoscopy allows for earlier detection and treatment of oesophageal cancer, leading to a better outcome. At the moment there are no other trials published or being conducted in this area.

We are conducting this study because we are not sure whether regular endoscopy, with the risks described, is beneficial to patients with Barrett's oesophagus or whether using patients'

symptoms could be just as good. It should be important to find out if regular endoscopy benefits patients before routinely offering it.

Why have I been invited?
As a patient with Barrett's oesophagus you have been invited because you have been diagnosed with Barrett's oesophagus. A total of 3,400 patients with Barrett's oesophagus will be recruited from across the UK during a 3 year period and followed up for a further 10 years.

What will happen to me if I take part?
Since we do not know the best way of managing patients with Barrett's oesophagus we need to make comparisons. If you agree to go into the study you will be randomly allocated to one of two groups:

3. You will be invited for a planned endoscopy every two years or in between times if you need one

   OR

4. You will only be offered an endoscopy if you need one.

For some of you, this may mean that you will no longer receive regular invitations for endoscopy although you did in the past. Regardless of which group you are in you can still be referred back to the hospital consultant for further tests and investigations if necessary.

The groups are selected by a computer, i.e. allocation is by chance, like tossing a coin. Patients in each group then have different management and these are compared. The Trial is much fairer if people are assigned to groups by chance, not by choice.

You will also be registered with the Medical Research Information Service (MRIS) or Information Service Division (ISD) to follow your health outcome in the longer term, even if you have moved away and we haven't got your address.

What do I have to do?
Everyone taking part in the study will receive a questionnaire every two years for up to ten years. The questionnaire will ask you about the medicines you currently take for your Barrett's oesophagus and your general well-being. If you are not in the group who are having regular endoscopies this will be sent to you by the BOSS study office. You will also be asked to complete a questionnaire after each endoscopy that you have during the period of the study.

Any additional information we might need about your condition will be provided by your local hospital doctor.

What are the possible benefits of taking part?
We cannot promise that taking part will benefit you. However, the information we get from this study may help us to treat future patients with Barrett's oesophagus more effectively and given the long term nature of the condition this might include you.

What if I don't want to take part?
Your hospital doctor will discuss the most appropriate way of monitoring your Barrett's oesophagus and treating the symptoms.

If you decide not to take part we would like to collect some information about you and your condition. This will help us to find out if the people who choose to take part in the study are

any different than those who do not. This may be important information to consider at the end of the study. The information will not identify you. You do not have to agree to this.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about what is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.
Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?
If the project were to stop early then your care will return to the best available at that time. At the end of the project we will look at the findings and then make recommendations about what changes in care there should be.

What if something goes wrong?
We believe that this study is basically safe and do not expect you to suffer any harm or injury because of your participation in it. The NHS indemnity scheme will compensate you if you are harmed due to someone's negligence but there is no compensation scheme for harm that was not caused by negligence.

Will my taking part in this study be kept confidential?
If you decide to participate in BOSS, the information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored at the BOSS Trial Office at Gloucestershire Royal Hospital on paper and electronically, under the provisions of the 1998 Data Protection Act. Your name and address will also be given to dedicated staff at the BOSS Trial Office when you first enter the study, so that they can send Quality of Life questionnaires to your home address. This information will not be accessed by any other personnel. Any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. You will be allocated a study number, which will be used as a code to identify you on all study forms. Only the BOSS Trial Office and your hospital will be able to identify you from this number. With your permission, your GP and the other doctors involved in your clinical care will be kept informed, but otherwise all information about you and your treatment will remain confidential.

With your permission, your relevant medical records may be inspected by authorised individuals from the research team or the Gloucestershire Hospitals NHS Foundation Trust (the study Sponsor). They may also be looked at by the regulatory authorities. The purpose of this is to check that the study is being carried out correctly.

What will happen to the results of the research study?
The results of the research will be published in one or more papers in medical journals so that they are available to all doctors. At the end of the study you can request a copy of the results from your research doctor. No individual patients will be identified in any publication or report.

Who is organising and funding the research?
The trial has been organised by Prof Hugh Barr, a surgeon specialising in Barrett's oesophagus at Gloucestershire Hospitals NHS Foundation Trust. The study is funded by the NHS Health Technology Assessment Programme. The doctor conducting the research is not

paid for including patients in the study and for looking after them. These costs are borne by the NHS.

Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Once you have decided to take part you are still free to withdraw at any time and without giving a reason. Your decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What if I have any further questions?
Please contact the doctor who is conducting the study in your local hospital:

<insert name and contact details here>
Name of Consultant
Job Title
Address

Telephone Number

Thank you for reading this.

National Institute for Health Research

NIHR Health Technology Assessment programme funded project

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

The BOSS study
(Barrett's Oesophagus Surveillance Study)
Consent form for randomised study

Title: **A randomised controlled trial of surveillance for patients with Barrett's oesophagus**

Study Doctor	**Name:**	**Study Site:**

Patients Name:	**Trial No.:**

Patient Statement and Signature

To be completed by the patient
Please initial the boxes below if you agree

1. I have received and read a copy of the BOSS Patient Information Sheet (version 10a or 10b, dated July 2011 – *delete as appropriate*) and have had an opportunity to ask questions, and all of my questions have been answered. ☐

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason, without my medical care or other legal rights being affected ☐

3. I give my permission for information held by the NHS and records maintained by the Medical Research Information Service (MRIS) or Information Service Division (ISD) to be used to keep in touch with me and follow up my health status. ☐

4. I also understand that sections of any of my medical notes may be looked at by responsible individuals from the BOSS Trial Office (Gloucestershire Hospitals NHS Foundation Trust - sponsor) and regulatory agencies where it is relevant to my taking part in this research study. I give permission for these individuals to have access to my records that identify me by name. ☐

5. I understand that I will not be identified in any reports or publications resulting from the study. ☐

	Yes	No
6. I give my permission for a letter and information about the BOSS study to be sent to my GP, which tells them that I have decided to take part in the study	☐	☐

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered**.**

I freely agree to participate in this study.

Signature _____	**Name *(print)*:** _____	**Date Signed:** / /

You will be sent a signed and dated copy of this consent form along with a letter that will inform you to which study group you have been allocated in the next few weeks.

Investigator Statement and Signature

To be completed by the person taking consent

I have discussed this clinical research study with the patient and/or his or her authorised representative, using a language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and its possible benefits and risks and I believe the participant understood this explanation.

Signature _____	**Name *(print)*:** _____	**Date Signed:** / /

1 copy for patient, 1 for patient's notes and 1 for investigator's file

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

The BOSS study
(Barrett's Oesophagus Surveillance Study)
Consent form for data collection ONLY

Title: **A randomised controlled trial of surveillance for patients with Barrett's oesophagus**

Study Doctor Name:	**Trial No: BS**
Study Site:	

Patient Statement and Signature

To be completed by the patient
Please initial the boxes below if you agree

1. I have received and read a copy of the BOSS Patient Information Sheet (version 10a or 10b, dated July 2011 – *delete as appropriate*) and have had an opportunity to ask questions, and all of my questions have been answered. ☐
2. I do not wish to participate in the study but agree that the study team can use information about me and my condition providing that it does not identify me. ☐
3. I understand that I will not be identified in any reports or publications resulting from the study. ☐

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered.

I freely agree to the use of my anonymised information in the study.

Signature	_____	**Name *(print)*:**	_____	**Date Signed:**	/ /

You will be given a signed and dated copy of this consent form to take away with you

Investigator Statement and Signature

To be completed by the person taking consent

I have discussed this clinical research study with the patient and/or his or her authorised representative, using a language that is understandable and appropriate. I believe the participant understood this explanation.

Signature	_____	**Name *(print)*:**	_____	**Date Signed:**	/ /

1 copy for patient, 1 for patient's notes and 1 for investigator's file

NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

BOSS Initial History Sheet

Site:	Investigator:	
Patient Trial Number: BS	Date of Birth: dd __ mm __ yyyy	Gender: Male / Female *(delete as appropriate)*

Inclusion criteria – please tick box to confirm that these are met

Aged 18 or over ☐

Barrett's oesophagus of either:

- at least 1cm from gastro-oesophageal junction ☐ Yes ☐ No
- or at least a 2cm non circumferential tongue / island(s) ☐ Yes ☐ No

Are the results Histologically *(please tick one):* ☐ Definite ☐ Consistent with ☐ or Corroborative

Able to give written consent ☐

Patient informed of risk of Barrett's oesophagus developing into cancer ☐

Fit for endoscopy ☐

Resident in UK ☐

Endoscopy findings available from within last 2 years ☐

Please tick one box.

This patient has consented to be randomised into the study ☐

This patient has consented to provide anonymised information only ☐
(complete Sections 2 and 3 ONLY)

SECTION 1

Title	***First Name****	***Family name****
Address* ***Post code****		
NHS Number*		

or affix an addressograph here and initial the bottom right hand corner to confirm that you have checked the details are correct:

*essential information

Form completed by:

Name:	**Signature:**	**Date:**
Job title:		

Following completion of ALL parts of this form please fax all three pages to the central trial office on 08454 225469
No cover sheet is required

BOSS Initial History Sheet

Site:	Investigator:	
Patient Trial Number: BS	Date of Birth: dd | mm | yyyy	Gender: Male / Female *(delete as appropriate)*

SECTION 2

Please calculate amount of pure alcohol consumed per week, using the conversion table below

1 pt of beer	2 units
Spirit (25 ml)	1 unit
Spirit (35 ml)	1.5 units
Glass of wine (125 ml)	1.5 units

ALCOHOL INTAKE

Yes ☐ No ☐

If yes, please specify amount/week: ☐☐☐ . ☐ units

SMOKING HISTORY

current smoker ☐ previous smoker ☐ never smoked ☐

For current and previous smokers

Years of smoking: ☐☐ Number per day: ☐☐☐

BARRETT'S HISTORY

Duration of reflux symptoms: ☐☐ Year(s)

Date of endoscopy confirming Barrett's oesophagus Date : dd \| mm \| yyyy

Date of most recent endoscopy if different from above Date : dd \| mm \| yyyy

Regular surveillance for Barrett's oesophagus prior to trial entry No ☐ Yes ☐

ENDOSCOPY FINDINGS AT STUDY ENTRY (OR WITHIN 2 YEARS)

No Yes (please tick)

Mucosal break(s) / Oesophagitis ☐ ☐ (if yes - Los Angeles Classification grade A ☐ B ☐ C ☐ D ☐)

Length of circumferential Columnar Lining **C** ☐☐ . ☐ cm

Length of Tongues / Island(s) of Columnar Lining (maximal extent) **M** ☐☐ . ☐ cm

Was intestinal metaplasia found?	No	☐	Yes	☐
Was high grade dysplasia present?	No	☐	Yes	☐
Was low grade dysplasia present?	No	☐	Yes	☐
Was indefinite dysplasia present?	No	☐	Yes	☐
Was **adenocarcinoma** present?	No	☐	Yes	☐

HELICOBACTER TEST

Not taken ☐

Taken ☐ (please complete HP up-date form when results known)

Form completed by:

Signature:	***Date:***

BOSS Initial History Sheet

Site:	Investigator:	
Patient Trial Number: BS	Date of Birth: dd ⊥ mm ⊥ yyyy	Gender: Male / Female *(delete as appropriate)*

SECTION 3

FAMILY HISTORY – digestive tract related conditions only

Relation to patient (brother, sister, parent, or child)	**Heartburn**	**Barrett's**	**Age at diagnosis**	**Oesophageal Cancer (type)**	**Age at diagnosis**

UPPER GI SURGERY

Previous upper gastrointestinal surgery: **No** ☐ **Yes** ☐ (please give details, below)

Type of Surgery	**Date of Surgery**	**Outcome**
	mm ⊥ yyyy	
	mm ⊥ yyyy	
	mm ⊥ yyyy	

CURRENT MEDICATION – digestive tract related medication only

Drug (brand name)	***Dose*** (Including units)	**Frequency**	**Route** e.g. IV	**Form** e.g. tablet	**Indication**	**Start Date**
						mm ⊥ yyyy
						mm ⊥ yyyy
						mm ⊥ yyyy
						mm ⊥ yyyy
						mm ⊥ yyyy

OTHER DETAILS

Height	ft	ins	**OR**	cm
Current weight	st	lbs	**OR**	kg

Form completed by:

Signature:	***Date:***

Following completion of ALL parts of this form please fax all 3 pages to the central trial office
Fax number 08454 225469 (No cover sheet is required)

SITE USE ONLY	**DATE COMPLETED**
Group randomised	
Patient informed of randomisation	
Copy of consent form sent	
GP letter sent	

NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

BOSS Quality of Life Questionnaire	
Site:	Investigator:
Patient Trial Number: BS	Date of birth: dd / mm / yyyy
Baseline QoL ☐ *(tick if appropriate or provide the date of Endoscopy)*	Date of Endoscopy: dd / mm / yyyy

We would like to ask you some questions about how your current health and about the effects that heartburn and indigestion have had on you. Please answer the following questions as best you can.

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today. ***Do not tick more than one box in each group***.

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

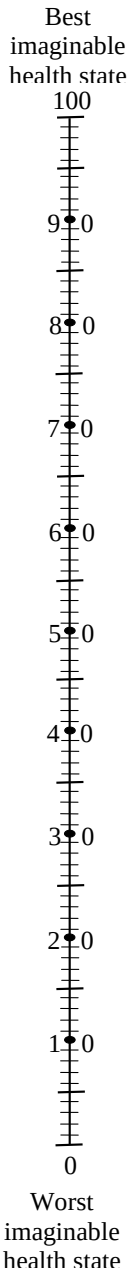
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

BOSS Quality of Life Questionnaire	
Site:	Investigator:
Patient Trial Number: BS	Date of birth: dd / mm / yyyy

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



BOSS Quality of Life Questionnaire	
Site:	Investigator:
Patient Trial Number: BS	Date of birth: dd / mm / yyyy

Current Health Questionnaire

Are you taking of the following medications for indigestion/heartburn?	No	Yes	Dose	Duration [i.e. months/yrs]
Antacid (e.g. magnesium trisilicate, gaviscon)	☐	☐		
Zantac (Ranitidine)	☐	☐		
Tagamet (Cimetidine)	☐	☐		
Losec (omeprazole)	☐	☐		
Nexium (esomeprazole)	☐	☐		
Protium (pantoprazole)	☐	☐		
Pariet (rabeprazole)	☐	☐		
Axid (nizatidine)	☐	☐		
Pepcid AC (famotidine)	☐	☐		
Zoton (lansoprazole)	☐	☐		
Other (please specify)	☐	☐		

Over the last *3 months* have you

1. Had to have any time off work because of heartburn / indigestion?
   No ☐ **Yes** ☐ (specify)..... days
2. Had to visit your GP because of heartburn / indigestion?
   No ☐ **Yes** ☐ (specify).....visits
3. Had to visit a specialist because of heartburn / indigestion?
   No ☐ **Yes** ☐ (specify)..... visits
4. Been admitted to hospital because of heartburn / indigestion?
   No ☐ **Yes** ☐ (specify)..... admissions
   i. How many days did you spend in hospital because of heartburn / indigestion?
   ……..…….....days

Have you experienced a serious illness in the last year? YES NO

Please could you give us some brief details, below?

Are you currently? ***(please circle one option)***

In employment retired seeking work carer home
other (please specify)……

Date you completed this questionnaire dd / mm / yyyy

Please return this questionnaire in the enclosed envelope

BOSS Trial Office use only

Date Received dd / mm / yyyy

NHS
National Institute for Health Research

BOSS Study
c/o Gloucestershire Research & Development Support Unit
Leadon House
Gloucestershire Royal Hospital
Great Western Road
Gloucester
GL1 3NN
Telephone: 08454 225465
Facsimile: 08454 225469

PRIVATE & CONFIDENTIAL

DATE:

TO:

FAX NO:

RANDOMISATION DETAILS FOR:

Name:		
Date of Birth:		
BOSS Trial Number *To be used in every communication with trials office*	BS	
Randomisation group:	**2 yearly Endoscopy (and at need)**	**Endoscopy at need ONLY**

Age: Under 65 65 or over

Length of Barrett's Oesophagus (M):

<2cm 2-3cm >3 up to 8cm >8cm

Duration of diagnosis: New diagnosis Existing Diagnosis

Details checked by:

Paperwork: Name: _____ Signature: _____ Date: _____

Randomisation Form: Name: _____ Signature: _____ Date: _____

Details entered by: Name: _____ Signature: _____ Date: _____

Randomisation validation *(stratification and entry)* Name: _____ Signature: _____ Date: _____

BOSS Randomisation fax back form - Version 4 09/06/2011

NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

BOSS Endoscopy and Pathology Form

To be completed at each endoscopy

ISRCTN no:4190466

Site:	Investigator:
Patient Trial Number: BS	Date of Birth: dd ⊥ mm ⊥ yyyy

Date of Endoscopy: dd ⊥ mm ⊥ yyyy

Scheduled / un-scheduled *(delete one)* **If un-scheduled, list reason(s):**
.....
.....

QoL Questionnaire was this given to the patient?

☐ Yes ☐ No

Are the results Histologically:

Definite	☐ Yes	☐ No
Consistent with	☐ Yes	☐ No
Or Corroborative	☐ Yes	☐ No

Type of Endoscopy: .....
(Examples: High Resolution, NDI and Olympus)

Is the patient currently an: Outpatient / Inpatient *(delete one)*

If an inpatient, please give reason for admission: .....

Endoscopy Report Date : dd ⊥ mm ⊥ yyyy **Report No**: _____ **Lab No**: _____

	No	**Yes**	**(please tick)**
Mucosal break(s) / Oesophagitis	☐	☐	(if yes - Los Angeles Classification grade A ☐ B ☐ C ☐ D ☐)

Length of circumferential Columnar Lining (to nearest 0.5 cm) **C** ⊥⊥ . ⊥ cm

Length including Tongues/Island(s) of Columnar Lining *(maximal extent to nearest 0.5 cm)* **M** ⊥⊥ . ⊥ cm

Helicobacter Test:

Not Done	☐	
Negative	☐	
Awaiting Result	☐	*(please complete HP up-date form when results known)*
Positive	☐	*(please complete HP up-date form when results known)*

Pathology Report Date : dd ⊥ mm ⊥ yyyy **Report / Lab No**: _____

Was intestinal metaplasia found?	No	☐	Yes	☐
Was high grade dysplasia present?	No	☐	Yes	☐
Was low grade Dysplasia present?	No	☐	Yes	☐
Was indefinite for dysplasia present?	No	☐	Yes	☐
Was oesophageal **adenocarcinoma** present?	No	☐	Yes	☐

If yes, please give staging information **T**…….. **N**…….. **M**……..

Comments (any other clinically relevant features / information including plans for follow-up care and planned endoscopy**)**

Completed by: _____ (print name) Signed: _____ Date : DD ⊥ MM ⊥ YYYY

BOSS EndoscopyPathForm v6.0 27/07/2011

Endoscopy and Pathology Form

SITE: Hospital name

INVESTIGATOR: The consultant responsible for randomising (and care of) the patient, must be listed on the BOSS Site Responsibilities Sheet.

TRIAL NUMBER: This **must** be completed and is the unique number that identifies this patient in the BOSS study.

DATE OF BIRTH: The patient's date of birth must be written in the following format dd/mm/yyyy, e.g. 03/02/1978.

ALL QUESTIONS MUST BE COMPLETED

DATE OF ENDOSCOPY: The date must be written in the following format dd/mm/yyyy, e.g. 03/02/1978

HISTOLOGY: Please indicate whether the results are Histologically – Definite, Consistent with or Corroborative

SCHEDULED / UNSCHEDULED – any endoscopy that is not within 3 months prior to the planned date or three months afterwards is classified as unscheduled.

OESOPHAGUS: Tick No or Yes

- **Length of Circumferential Lining** – specify length in centimetres from the oesophago-gastric junction
- **Length of Tongues / Island(s) of columnar lining (maximal extent)** – specify length in centimetres

HELICOBACTER TEST: Please indicate the result of the most recent Helicobacter test or specify, not done or awaiting result if applicable

ENDOSCOPY REPORT

- **Endoscopy Report Date** - The date must be written in the following format dd/mm/yyyy, e.g. 03/02/1978
- **Report Number** – please record the unique number that identifies the endoscopy report
- **Lab Number** – please record the number that identifies the lab

PATHOLOGY REPORT

- **Pathology Report Date** - The date must be written in the following format dd/mm/yyyy, e.g. 03/02/1978
- **Report/Lab Number** - Please record the unique number that identifies the pathology report

COMMENTS: Record any other clinically relevant information including plan for follow-up care including proposed endoscopy

COMPLETED BY: Print name clearly, sign and provide the date when the form is completed in the correct format (see above).

Please note: Forms must be completed in black ball-point pen
Cross out errors with a single stroke, insert the correction and initial & date the change.
Correction fluid and /or sticky labels must not be used

NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

BOSS Helicobacter up-date form		
Site:	Investigator:	
Trial number: BS	Date of Birth: dd ⊥mm⊥yyyy	Gender: male / female (delete as appropriate)

Helicobacter test result

Type of test Date of test dd ⊥mm⊥yyyy Negative ☐ Positive – no treatment ☐ Positive and treated ☐			
please give details of medication	Drug	Dose	Duration

Please complete another up-date form each time a further test is taken

Form completed by:

Name:	***Signature:***	***Date:***
Job title:		

Following completion of this form please fax all to the central trial office on 08454 225469
No cover sheet is required.

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

Date

Patient Name
Address

Dear ***Patient Name***

You kindly agreed to take part in this national UK trial, funded by the National Health Service Health Technology assessment Programme, and run by the Research and Development Support Unit based at Gloucestershire Hospitals NHS Foundation Trust.

The aim of the study is to see whether routine endoscopies every 2 years is better than only carrying out an endoscopy if symptoms get worse for patients who have been diagnosed with Barrett's oesophagus.

You have been randomised to receive **endoscopic surveillance** which means that you will receive an endoscopy every 2 years for the duration of the study. The hospital will send your next appointment for an endoscopy when it is due. You will also be asked to complete a short questionnaire following each endoscopy.

Your GP will also be able to request an endoscopy, for you; before the 2 year period is up if your symptoms suggest that this might be necessary. If this happens, you will be asked to complete an extra questionnaire.

If you have any questions about the study or your treatment, please contact the BOSS research nurse, ***Name of Nurse*** on ***Tel: ……***

Yours sincerely

Name of Principal Investigator

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

Date

Patient Name
Address

Dear ***Patient Name***

You kindly agreed to take part in this national UK trial, funded by the National Health Service Health Technology assessment Programme, and run by the Research and Development Support Unit based at Gloucestershire Hospitals NHS Foundation Trust.

The aim of the study is to see whether routine endoscopies every 2 years is better than only carrying out an endoscopy if symptoms get worse for patients who have been diagnosed with Barrett's oesophagus.

You have been randomised to receive **endoscopy at time of need** which means that you will only receive an endoscopy should you need one. Your GP will still be able to request an endoscopy, for you, if your symptoms suggest that this might be necessary. If this happens, you will be asked to complete an extra questionnaire.

You will also be asked to complete a short questionnaire which will be sent to you by post every 2 years for the duration of the study.

If you have any questions about the study or your treatment, please contact the BOSS research nurse, ***Name of Nurse*** on ***Tel: ……***

Yours sincerely

Name of Principal Investigator

Trust Headed Paper

BOSS Study
c/o *Name of Department / Organisation*

TO BE PRINTED ON LOCAL HEADED PAPER ALONG WITH NIHR and HTA LOGO

Date

Name of General Practitioner
Address

Dear *Name of General Practitioner*

Patient:
DoB:

Your patient has kindly agreed to take part in this national UK trial, funded by the National Health Service Health Technology assessment Programme, and run by the Research and Development Support Unit based at Gloucestershire Hospitals NHS Foundation Trust.

The aim of the study is to see whether a protocol of endoscopic surveillance is better than endoscopic surveillance if needed for the prevention of early mortality in patients diagnosed with Barrett's oesophagus.

The study randomises patients to receive a standard upper gastrointestinal endoscopy with biopsy every two years for 10 years or no endoscopic surveillance. All patients will receive a biannual postal questionnaire to record their medication and other health related data.

**please delete as appropriate*
Your patient has been randomised to receive:

- **endoscopic surveillance**
- **endoscopy only if required**

Please continue to manage this patient as you would have done regardless of their participation in the trial. All patients (including those in the endoscopy at need arm) should be offered an urgent endoscopy if they develop dysphagia, unexplained weight loss of > 7lb, iron deficiency anaemia, recurrent vomiting, or worsening upper gastrointestinal symptoms.

If you need to refer this patient for an endoscopy it would be preferable if you could refer them to *[insert name of Principal Investigator].*

There are no prescribing restrictions and no bar on other investigations should they become necessary. The patient can receive medication as you feel appropriate for their symptoms and can also be referred for endoscopy should it be clinically indicated if their symptoms change or deteriorate.

Please contact us if you require more information.

Yours sincerely

Name of Principal Investigator

GP Letter Version 2.3 08/12/09

HOSPITAL ADMISSION FORM

Hospital Admission Form

BOSS TRIAL TEAM
GLOUCESTERSHIRE HOSPITALS NHS FOUNDATION TRUST
Fax No: 08454 225469

BOSS is collecting short reports of all hospital inpatient stays of trial participants, and these will be used in the economic evaluation. For these, only the reason for and duration of admission are needed, plus the duration of any spells in high-cost environments (CCU, HDU and / or ICU).

However, any inpatient admission (or prolongations of existing admissions) that may be related to a trial procedure may constitute a Serious Adverse Event, which should be reported on the Serious Adverse Event Reporting Form, within strict timescales. For these, more details are needed, so that the trial office can determine whether the admission is an SAE that needs reporting.

HOW TO COMPLETE THIS FORM AND WHEN TO SUBMIT IT

Inpatient stays not related to a trial procedure

Please complete the Hospital Admission form as soon as you are aware that a hospital stay took place and is now complete (discharge or death). We only need one form per hospital stay. Your Trust R&D Manager does not need a copy.

A days admission to hospital will be calculated from the admission and discharge dates, there will be no need to enter times of admission and discharge. An important measurement within health economics for BOSS is length of stays in high cost areas such as CCU, HDU and / or ICU. Therefore when completing this form we would require the total number of days that each patient spent in those areas. So if the participant went to HDU on two separate occasions for a stay of 2 and 4 days respectively during their whole stay in hospital then we would require 6 days to be noted on the form.

The ICD 10 code identifies the International Classification of Disease, which can be obtained from your hospital coders, however this information does not need to be obtained at the time of completion and submission of this form but can be forwarded at a later date. We will chase missing codes once a year or at site visit(s). The ICD 10 code will be used by the Health Economists to calculate the costs of a stay in hospital.

Inpatient admissions that may be related to a trial procedure

Should be reported on the Serious Adverse Event Reporting Form and because of the reporting timelines for Serious Adverse Events, we need to know about these as soon as you are made aware of the admission.

Please complete the Serious Adverse Event Reporting Form with as much detail as is available at the time of admission, tick “initial report” and fax it to 08454 225469 within 24 hours of becoming aware of the admission. Also forward the form, to your Trust R&D Manager. Once the stay is complete, please collect the necessary clinical detail, complete the form again, tick “on Discharge / Death” and fax it to us within 24 hours, again forwarding it to your R&D Manager.

HOSPITAL ADMISSION FORM

Please complete details of any hospital admissions from the time of informed consent

Please fax this form to the BOSS Trial Team on 08454 225469

NOT TO BE USE IF ADMISSION RELATES TO A BOSS PROCEDURE – PLEASE COMPLETE SAE FORM

STUDY DETAILS	
Study Title	**BOSS (Barrett's Oesophagus Surveillance Study)**

PATIENT / TREATMENT DETAILS			
Patient Study Number	☐☐☐☐☐☐☐☐☐☐☐☐		
Date of Birth	☐☐☐☐☐☐☐☐ (d d m m y y y y)	**Weight**	☐☐☐.☐ kg
Gender	☐ Male	☐ Female	
Responsible Clinician		**Institution**	
Randomisation Details	☐ Surveillance	☐ Endoscopy at Need	

Type of report: ☐ **Initial** ☐ **on Discharge / Death** *(please delete as appropriate)*

REASON FOR ADMISSION – please explain

	Outcome
	☐ Resolved ☐ Persisting ☐ Worsened ☐ Fatal ☐ Not assessable

Admission date ☐☐☐☐☐☐ (d d m m y y)

Discharge date ☐☐☐☐☐☐ (d d m m y y)

Date of Death ☐☐☐☐☐☐ (d d m m y y)

Total number of days admitted to :

☐ CCU ☐ HDU ☐ ICU

ICD 10 Code

Signature *[Authorised health professional]*	Print name	**Date of report** ☐☐☐☐☐☐ (d d m m y y)

BOSS TRIAL OFFICE USE ONLY		
Date received ☐☐☐☐☐☐ (d d m m y y)		
Form checked by (signature)	Print name	Date ☐☐☐☐☐☐ (d d m m y y)

Comments:

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SERIOUS ADVERSE EVENT REPORTING

NHS National Institute for Health Research

BOSS Barrett's Oesophagus Surveillance Study

Serious Adverse Event Reporting Form

(BOSS RELATED INCIDENTS ONLY)

drugs, devices and interventions

BOSS TRIAL TEAM
GLOUCESTERSHIRE HOSPITALS NHS FOUNDATION TRUST
Fax No: 08454 225469

Any inpatient admission (or prolongations of existing admissions) that may be related to a trial procedure will constitute a Serious Adverse Event and should be reported on this Serious Adverse Event Reporting Form. For the purpose of this trial please report any oesophageal or endoscopy related SAEs.

Please complete the entire form with as much detail as is available at the time of admission, tick "initial report" and fax to 08454 225469 within 24 hours of becoming aware of the admission. Also forward the form, to your Trust R&D Manager. Once the stay is complete, please collect the necessary clinical detail, complete the form again, tick "on Discharge / Death" and fax it to us within 24 hours, again forwarding it to your R&D Manager.

Definition of SAE:

An SAE can be defined as: *an untoward medical occurrence in a subject during clinical research involving a pharmaceutical product, medical device, or clinical intervention that: is fatal; is life threatening; results in persistent or significant disability / incapacity; requires inpatient hospitalisation or prolongs a current hospitalisation; results in a congenital anomaly in offspring; or an event that may jeopardise the participant or may require intervention to prevent one of the outcomes listed above.*

For the purpose of this trial please report any oesophageal or endoscopy related SAEs.

INITIAL REPORTING:

For all initial reporting of any Serious Adverse Events / Incidents this form must be completed **fully** (hard copy or fax) and sent to the BOSS Clinical Trial Team and the Trust R&D Manager for the site within 24 hours of the incident occurring or being known.

FOLLOW-UP INFORMATION:

For subsequent follow-up reporting of an SAE, a new SAE reporting form should be completed with just administration details and all new or missing information **only filled in** and forwarded to the BOSS Clinical Trial Team and the Trust R&D Manager for the site as soon as possible. All SAEs must be followed up until closure.

NOTES:

A days admission to hospital will be calculated from the admission and discharge dates, there will be no need to enter times of admission and discharge. An important measurement within health economics for BOSS is length of stay(s) in high cost areas such as CCU, HDU and / or ICU. Therefore when completing this form we would require the total number of days that each patient spent in those areas. So if they went to HDU on two separate occasions for a stay of 2 and 4 days respectively during their whole stay in hospital then we would require 6 days to be noted on the form.

The ICD 10 code identifies the International Classification of Disease, which can be obtained from your hospital coders, however this information does not need to be obtained at the time of completion and submission but can be forwarded at a later date. We will chase missing codes once a year or at site visit(s). The ICD 10 code will be used by the Health Economists to calculate the costs of a stay in hospital.

Please complete details of any SAE from the time of informed consent. For guidance on which events to report please refer to the study protocol. **Please fax this form to the BOSS Clinical Trial Team on 08454 225469 within 24 hours of notification of the event.**

SERIOUS ADVERSE EVENT REPORTING

National Institute for Health Research

Please complete details of any SAE from the time of informed consent. For guidance on which events to report please refer to the study protocol

Please fax this form to the BOSS Clinical Trial Team on 08454 225469

Initial Notification *[fax within 24 hours of event]* ☐ **Further Information after Initial Notification** *[fax within 1 week of initial notification]* ☐

STUDY DETAILS	
Study Title	**BOSS (Barrett's Oesophagus Surveillance Study)**
R&D Project ID No.	

PATIENT / TREATMENT DETAILS			
Patient Initials		**Patient Study Number**	
Date of Birth (d d m m y y y y)		**Weight**	. kg
Gender	☐ Male ☐ Female		
Patient Hospital Number			
Responsible Clinician:		**Institution:**	
Randomisation Details	☐ Surveillance ☐ Endoscopy at Need		

Type of report	☐ **Initial** ☐ **on Discharge/Death**	Was the Chief or Principal Investigator informed of this event prior to the completion of this form?	☐ Yes ☐ No

REASON FOR ADMISSION – please explain	Outcome
	☐ Resolved ☐ Persisting ☐ Worsened ☐ Fatal ☐ Not assessable

Admission date (d d m m y y) Discharge date (d d m m y y) Number of days in admission to : ☐ CCU ☐ HDU ☐ ICU ICU 10 Code

WHY WAS THIS ADMISSION RELATED TO A BOSS PROCEDURE – please explain	Event Type
	☐ Resulted in death * *(Please record date of death below)* ☐ Life -threatening ☐ Prolonged existing hospitalisation ☐ Resulted in persistent or significant disability / incapacity ☐ Other *(specify)* _____

Data of most recent Endoscopy before Event (d d m m y y y y)

Date of death (d d m m y y y y)

Why was the event serious? *(choose most serious)*	Where did the event take place?	Outcome
☐ Resulted in death	☐ Home	☐ Resolved
☐ Life-threatening	☐ Out-patient clinic	☐ Persisting
☐ Required inpatient or prolonged existing hospitalisation	Hospital Admission date (d d m m y y) Discharge date (d d m m y y)	☐ Worsened
☐ Resulted in persistent or significant disability/incapacity	☐ Other *(specify):*	☐ Fatal

☐ Other Important Medical Event *(specify)* _____	_____	☐ Not assessable

Serious Adverse Event Term ***(enter the Main Event in the first row followed by any associated symptoms. There should be one MAIN Event per form. If there are two events, please complete two forms)***	**Date of Onset**	**SAE Status** 1 – resolved 2 – Resolved with sequelae 3 – ongoing 4 – worsened 5 - Fatal	**Date resolved**
	☐☐ ☐☐ ☐☐ d d m m y y	☐	☐☐ ☐☐ ☐☐ d d m m y y
Associated symptoms:			
	☐☐ ☐☐ ☐☐ d d m m y y	☐	☐☐ ☐☐ ☐☐ d d m m y y
	☐☐ ☐☐ ☐☐ d d m m y y	☐	☐☐ ☐☐ ☐☐ d d m m y y

INVESTIGATOR ASSESSMENT OF RELATEDNESS TO ENDOSCOPY ***[to be completed only when all information is to hand]***

Not related	Unlikely to be related	Possible related	Probably related	Very likely related
☐	☐	☐	☐	☐

Data of most recent Endoscopy before Event ☐☐ ☐☐ ☐☐☐☐ d d m m y y y y

ACTION TAKEN

*Treatment delayed	*Treatment delayed and	Treatment permanently	Name of person making decision
☐	☐	☐	

Treatment given for management of SAE

Treatment	**Total daily dose**	**Route** 1 = oral 2 = intravenous 3 = subcutaneous 4 = other	**Start date**	**Ongoing?**	**End date**
			☐☐ ☐☐ ☐☐ d d m m y y	☐ Y ☐ N	☐☐ ☐☐ ☐☐ d d m m y y
			☐☐ ☐☐ ☐☐ d d m m y y	☐ Y ☐ N	☐☐ ☐☐ ☐☐ d d m m y y

Any concomitant medications? ☐ **Y** ☐ **N** *(If yes, please specify below and continue on separate sheet if necessary)*

Treatment	**Total daily dose**	**Route** 1 = oral 2 = intravenous 3 = subcutaneous 4 = other	**Start date**	**Ongoing?**	**End date**
			☐☐ ☐☐ ☐☐ d d m m y y	☐ Y ☐ **N**	☐☐ ☐☐ ☐☐ d d m m y y
			☐☐ ☐☐ ☐☐ d d m m y y	☐ Y ☐ **N**	☐☐ ☐☐ ☐☐ d d m m y y

Any relevant tests / laboratory data? ☐ **Y** ☐ **N** *(If yes, please specify below /continue on separate sheet if necessary or attach print outs)*

Any other relevant information? ☐ Y ☐ N *(If yes, please specify below and continue on separate sheet if necessary)*

Principal Investigator's assessment of expectedness	Expected ☐	Unexpected ☐	*Is the event listed in the reference document, (study protocol)?*

Event summary description *(Give a concise medical description of the event including all relevant symptoms. Please specify the grade for all related symptoms and complete page overleaf for all that meet the definition of serious)*

Signature *[Authorised health professional]*	Print name	**Date of report** ☐☐ ☐☐ ☐☐ d d m m y y

Number of pages of supplementary reports to follow: ☐

OFFICE USE ONLY

Date SAE reported to R&D Unit ☐☐ ☐☐ ☐☐ d d m m y y	Date SAE reviewed ☐☐ ☐☐ ☐☐ d d m m y y
Date reported to Main REC ☐☐ ☐☐ ☐☐ d d m m y y	Reported to all other PIs ☐ Y ☐ N

Form checked by (signature)	Print name	Date d d m m y y
Comments:		

BOSS Serious Adverse Event Reporting Form (version 4, 27/07/2011)

APPENDIX 24

NHS
National Institute for Health Research

BOSS Participant Details (up-dated)	
Site:	Investigator:
Patient Trial Number: BS	

Title	
First Name*	
Family Name*	
Date of Birth*	
Gender*	
Address*	
Post code*	
NHS number*	

**** essential information***

Form completed by:

Name:	***Signature:***	***Date:***
Job title:		

Following completion of this form please fax it to the central trial office on 08454 225469
No cover sheet is required

BOSS Participants details updated Version 2 081209

NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

BOSS Study Exit Form

Site:	Investigator:	
Trial number: BS	Date of Birth: dd ⊥mm ⊥yyyy	Gender: male / female (delete as appropriate)

Date of exit	dd ⊥mm ⊥yyyy	
Tick all that apply	Consent for study withdrawn	Yes / No
	The patient is happy for Medical Research Information Service (MRIS) or Information Service Division (ISD) data to be obtained	Yes / No
	Consent not withdrawn *(as the patient is happy for the BOSS team to continue to collect basic data, i.e. details of Endoscopies and Helicobacter Tests)*	Yes / No
	If reason given, please give details:	
	- No reason given	
	- Loss of capacity – please give details	
	- No longer fit for Endoscopy – please give details	
	- Other Clinical decision – please give details	
	- No longer resident in UK	
	- Move to area where participation no longer possible	
	- Lost to follow-up	
	- Death – please give primary cause Date of Death: dd / mm / yyyy	

Form completed by:

Name:	***Signature:***	***Date:***
Job title:		

Following completion of this form please fax to the central trial office on 08454 225469 and post a copy to the participant's GP (No cover sheet is required)

BOSS Study Exit form - Version 4 27/07/2011