

# Acetic acid-guided biopsies in Barrett's surveillance for neoplasia detection versus non-targeted biopsies (Seattle protocol): A feasibility study for a randomized tandem endoscopy trial. The ABBA study

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## ABSTRACT

**Background and study aims** Barrett's esophagus is a potentially pre-cancerous condition, affecting 375,000 people in the UK. Patients receive a 2-yearly endoscopy to detect cancerous changes, as early detection and treatment results in better outcomes. Current treatment requires random mapping biopsies along the length of Barrett's, in ad-

dition to biopsy of visible abnormalities. As only 13% of pre-cancerous changes appear as visible nodules or abnormalities, areas of dysplasia are often missed. Acetic acid chromoendoscopy (AAC) has been shown to improve detection of pre-cancerous and cancerous tissue in observational studies, but no randomized controlled trials (RCTs) have been performed to date.

**Patients and methods** A "tandem" endoscopy cross-over design. Participants will be randomized to endoscopy using mapping biopsies or AAC, in which dilute acetic acid is sprayed onto the surface of the esophagus, highlighting tissue through a whitening reaction and enhancing visibility of areas with cellular changes for biopsy. After 4 to 10 weeks, participants will undergo a repeat endoscopy, using the second method. Rates of recruitment and retention will be assessed, in addition to the estimated dysplasia detection rate, effectiveness of the endoscopist training program, and rates of adverse events (AEs). Qualitative interviews will explore participant and endoscopist acceptability of study design and delivery, and the acceptability of switching endoscopic techniques for Barrett's surveillance.

**Results** Endoscopists' ability to diagnose dysplasia in Barrett's esophagus can be improved. AAC may offer a simple, universally applicable, easily-acquired technique to improve detection, affording patients earlier diagnosis and treatment, reducing endoscopy time and pathology costs. The ABBA study will determine whether a crossover "tandem" endoscopy design is feasible and acceptable to patients and clinicians and gather outcome data to power a definitive trial.

## Introduction

Barrett's esophagus (BO) is a change in the cells of esophageal tissue and a precursor to esophageal cancer. BO carries a risk of cancer 30 to 150 times greater than that for an age-matched population without BO, and affects 375,000 people in the UK

[1,2]. Esophageal cancer is the fifth most common cancer in the UK and carries a poor 5-year survival rate of <5% [3,4]. Current guidelines recommend regular surveillance (between 2–5 years according to length of Barrett's) to detect and remove early dysplasia, [5] as patients diagnosed with esophageal can-

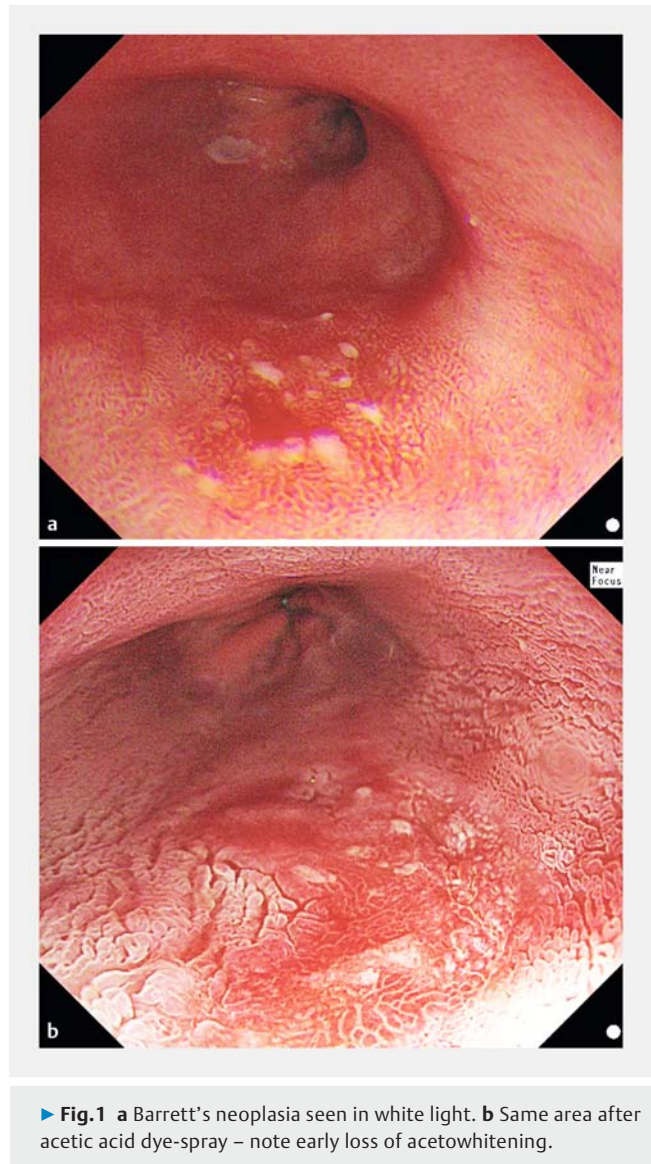
cer within a surveillance program have earlier-stage disease and longer survival times [6, 7].

The current gold-standard technique for detecting dysplasia in surveillance programs involves quadrant esophageal biopsies every 2 cm during endoscopy (Seattle protocol). This is necessary as only 13% of dysplastic changes appear as visible nodules [8]. However, up to 40% of early cancers are missed, as despite multiple biopsies, only a small proportion of the total surface area of the esophagus is sampled [9]. In practice, only 50% of surveillance endoscopies are estimated to adhere to this method as it is laborious and time-consuming, poorly tolerated by patients, and expensive to process biopsies [10]. Research to improve surveillance effectiveness and test performance has been recognized as a priority [11].

Currently, the key limitation to Barrett's surveillance is the macroscopic invisibility of Barrett's dysplasia. Methods proposed to enhance dysplasia visibility, thus permitting targeted biopsies, include dye sprays, [12–14] electronic image intensifiers built into the endoscope namely: narrow band imaging, [15] Fujinon intelligent color enhancement [16] and autofluorescence imaging [17]. However, evidence focuses on high-risk populations where dysplasia has already been identified, or in the follow-up of patients treated endoscopically for dysplasia. It is lacking in a surveillance population, where dysplasia prevalence is significantly lower.

When sprayed on Barrett's mucosa, acetic acid (AA) highlights specific surface patterns including dysplasia and cancer, which can be readily recognized by the trained endoscopist [18]. After application of AA, dysplastic tissue appears red against the surrounding Barrett's making it easily visible (► Fig. 1) [19]. This process is reversible, causes no damage to tissues and can be repeated. Two large cohort studies have demonstrated the efficacy of AA for detection of Barrett's dysplasia in a high-risk population, reporting sensitivities of 90% to 95% and specificities of 75% to 85% [20, 21]. Further research suggested that the number of biopsies could be substantially reduced using AA-targeted biopsies instead of quadrant biopsies, reducing pathology costs by 97% [22]. A recent retrospective study suggested that the AA method may detect more dysplasia than protocol-guided biopsies in a Barrett's surveillance population; 4.3% vs 1.4%, however, that study had a number of limitations in that it did not control for endoscopist, was retrospective and liable to confounding [23].

The 2 methods need to be compared in an RCT. However, prior to a definitive study, a feasibility study is required to establish whether a cross-over design involving 2 endoscopies per participant is acceptable, by assessing recruitment and retention rates and exploration through qualitative interviews. It is also important to ascertain the efficacy of training clinicians to use the technique, and their perceptions of a change in the endoscopic method. Estimates of diagnostic accuracy for both groups are required to power a definitive trial.



► Fig. 1 a Barrett's neoplasia seen in white light. b Same area after acetic acid dye-spray – note early loss of acetowhitening.

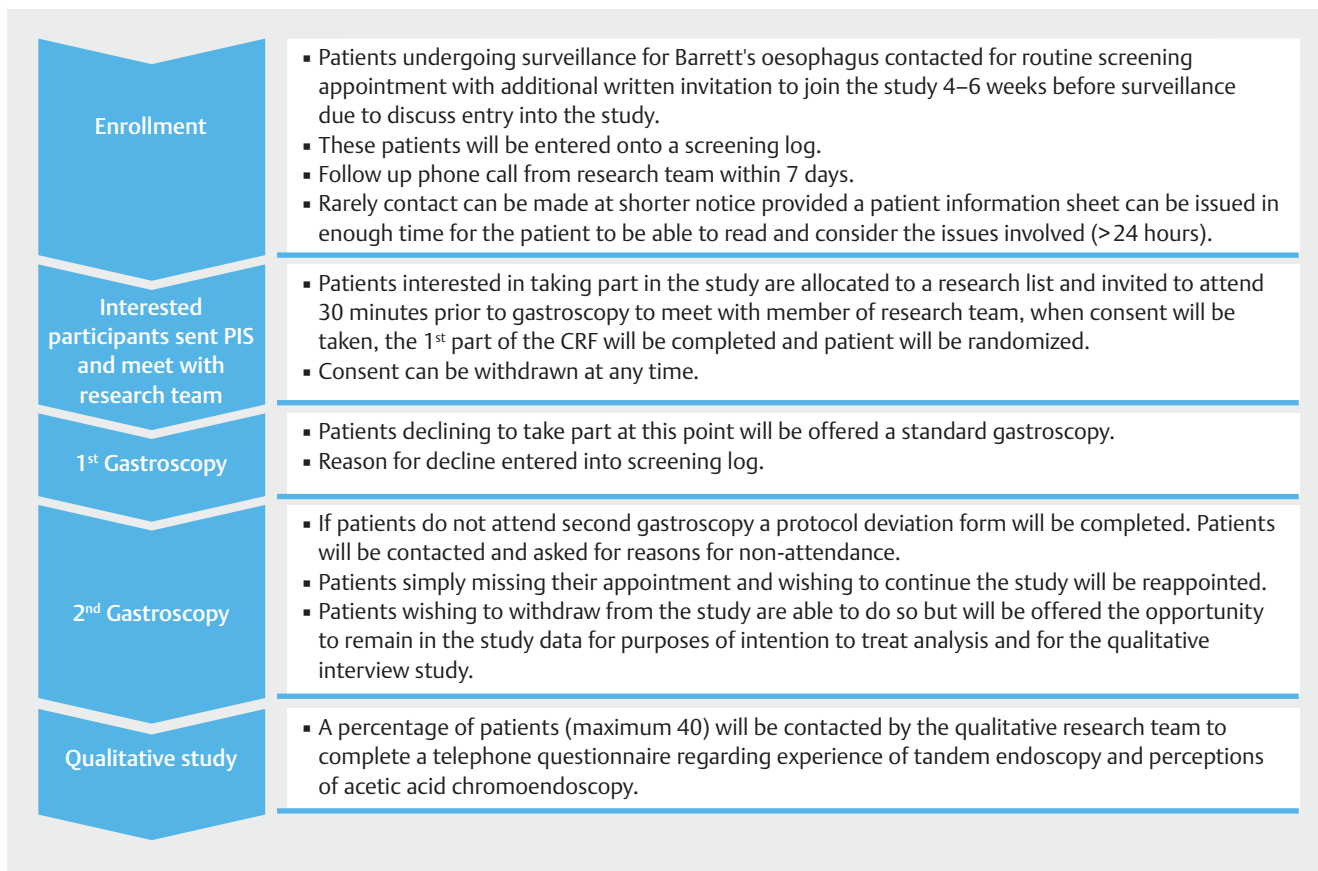
## Patients and methods

### Research question

Is a trial to investigate the diagnostic accuracy of AAC in a Barrett's surveillance population feasible and acceptable to patients and endoscopists?

### Objectives

This feasibility study will investigate: (1) the outcomes of a novel training program for AA-guided dysplasia detection for endoscopists; (2) feasibility of recruiting 200 Barrett's surveillance patients in 18 months; (3) eligibility rate of screened patients; (4) recruitment rate of eligible patients; (5) the rate of attendance for second endoscopy (retention rate) and reasons for non-attendance; (6) participant acceptability of the study design and acceptability of a change in surveillance technique; (7) the difference in dysplasia detection rates between AA endoscopy and standard endoscopic practice to inform the



► **Fig. 2** Study design for participants.

power calculation for a definitive study; (8) AE types and frequencies; and (9) perceptions, values and opinions of endoscopists of changing surveillance technique in practice.

## Design

A mixed-methods feasibility study will be conducted with 3 components: (1) training and assessment of endoscopists in the AA (intervention) and Seattle biopsy (current standard) technique; (2) multicenter randomized, cross-over tandem endoscopy trial examining diagnostic accuracy of 2 methods of detecting cellular changes in patients with BO; and (3) telephone interviews to gather qualitative data from patients and endoscopists regarding study design and acceptability of implementation of the AA technique as standard care.

## Endoscopist training

1. Validation of image and video library: Images and videos of AA chromoendoscopy in normal and dysplastic Barrett's validated by 2 international expert endoscopists will form a training and assessment library. The accuracy and inter-observer agreement between experts will be calculated and used to set the pass mark for the assessment tool.
2. Web-based training and assessment: The web-based training tool will be developed to provide a robust model suitable for training endoscopists for the definitive trial. Baseline knowledge will be assessed, followed by a tutorial of images

and videos from the library to demonstrate the AA appearances of normal, dysplastic and cancerous Barrett's, including the Portsmouth AA classification. A series of practice questions for a diagnosis (normal or dysplastic Barrett's) will be administered. Endoscopist trainees will be given immediate feedback including a detailed description of what was in the image or video to facilitate improved knowledge.

3. Face-to-face training: All endoscopists will attend an interactive workshop, including lecture-based training and interactive discussion with experts, followed by observing live procedures over a video-link. Trainees will then repeat the assessment tool. Once endoscopists achieve adequate accuracy scores, defined as achieving scores within 5% of experts, they will perform an endoscopy list under the direct supervision of an expert in AA at their own institutions.

## Participants

Participants will be recruited from 6 centers in the UK, i.e. Portsmouth, Leicester, Gloucestershire, Western Sussex, Brighton and Sussex, and Royal Bournemouth and Christchurch trusts. The study design summarized in ► **Fig. 2** and ► **Fig. 3** demonstrates the schedule of enrollment, interventions and assessments. Recruitment commenced in July 2015 at Portsmouth Hospitals NHS Trust, the lead trial site.

Timeline (months)	1–3	4–6	7–12	13–15	16–18	19–21	22–24	25–27	28–31
Study set up	█								
Trial co-ordinator established in post	█								
Sponsor checks and research & ethical approval secured	█								
Trial management group and trial steering group convened	█								
NIHR portfolio form submitted	█								
Site feasibility and capacity assessments	█								
R&D submission and approval obtained for all sites	█								
<b>Training of study endoscopists</b>		█							
Image and video based training tools developed		█							
Dates for training days finalised and study endoscopists invited to attend		█							
Training of the study endoscopists for cross-over study		█							
Assessment of study endoscopists prior to commencing cross-over study		█							
Qualitative assessment of confidence/attitudes of study endoscopists		█							
<b>Randomized cross-over diagnostic study</b>			█	█	█	█	█		
Patient invitation and recruitment begins			█	█					
All sites recruiting					█				
Recruitment			█	█	█	█	█	█	
Quarterly meeting of the trial steering committee			█	█	█	█	█	█	
Monthly meeting of the trial management group			█	█	█	█	█	█	
Complete recruitment into cross-over study								█	
Closure of cross-over study									
<b>Qualitative patient and clinician study</b>			█	█	█	█	█		
Invitation			█	█					
Scheduling of telephone interviews			█	█					
Telephone interviews					█	█	█	█	
Complete recruitment into qualitative study								█	
Study closure								█	█
<b>Analysis of data</b>								█	
Quantitative cross-over study data analysis								█	
Qualitative study data analysis								█	
<b>Dissemination and publication of data</b>									█
Dissemination of data at conferences and through patient groups									█
Publication of data in research journals									█

► Fig. 3 Study timeline.

## Eligibility criteria

### Inclusion criteria

1. aged 18 years or above
2. biopsy (histologically) proven Barrett's metaplasia
3. at least 2-cm length of Barrett's esophagus
4. informed consent

### Exclusion criteria

1. significant oesophagitis
2. known or prior esophageal cancer or esophageal dysplasia
3. previous endoscopic therapy for dysplasia
4. known allergy to acetic acid
5. previous inclusion in the study

## Recruitment

### Cross-over tandem endoscopy study

Patients scheduled to attend surveillance gastroscopy endoscopy will receive a letter 4 to 6 weeks before the visit, followed by a letter of invitation and patient information sheet for interested individuals.

Thirty minutes prior to gastroscopy, potential participants will discuss the study with the research team and provide informed consent.

## Qualitative interviews

### Patients

For qualitative data collection, a probabilistic sample size calculation was not appropriate. Instead, a purposive sampling framework to include male and female participants of all ages, and across the study sites will be selected for interview. Data collection will cease when saturation of data has been achieved

or no new insights are forthcoming. In this way, we will be confident that the data will truly reflect the views and perspectives of the range of study participants

On enrollment into the endoscopy study, participants will be asked whether they would consent to being contacted to take part in a telephone interview up to 4 weeks after the endoscopies are completed, and written information will be given to them. Patients who do not wish to take part in the endoscopy study will be asked for their consent to be interviewed about their experience of hearing about the study and why they decided not to participate.

### Endoscopists

Prior to the endoscopy training program, endoscopists will be asked to take part in telephone interviews at the completion of the trial (minimum of 8 interviews).

### Randomization and blinding

Participants will be randomized using permuted blocks, stratified by center in a 1:1 ratio, to initial endoscopy of either the standard procedure (Seattle protocol mapping biopsies) or AA endoscopy (targeted biopsies). The secure randomization website, <https://www.sealedenvelope.com> will be used. Patients will be unable to detect whether acetic acid had been used and thus will be blinded to the procedure method. The endoscopist will be blinded to the histological results of the previous endoscopy for an individual participant. It will not be possible to blind the histopathologist as the Seattle protocol produces a greater number of biopsies for processing.

### Study intervention

Study participants will receive an endoscopy using both methods, at an interval of 4 to 10 weeks, with the initial endoscopy method determined by randomization allocation. The endoscopies will be performed with high-definition processors (Olympus Lucera Elite or Spectrum and Pentax EPKi7000) and high-definition gastroscopes (Olympus HQ290 or H260 and Pentax i10 series) without use of electronic chromoendoscopy or alternative dye sprays. All study endoscopies will be videoed and 10% of non-dysplastic cases reviewed by the study team, in addition to all cases of dysplasia.

### Acetic acid method

Following a pre-endoscopy mucosal cleansing drink, the Barrett's segment will be inspected using standard white light and visible abnormalities noted. A spray catheter will be inserted through the biopsy channel of the endoscope and AA 2.5% sprayed onto the Barrett's mucosa. Excess fluid will be removed and mucosa inspected for abnormalities, which will be biopsied. Each biopsy will be sent to the laboratory in an individual cassette. Areas for biopsy will be identified using the Portsmouth Barrett's Acetic Acid Classification (PREDICT Classification) [24], and the tissue will be categorized into non-dysplastic, dysplastic or cancer. If no visible neoplasia is seen, no biopsies will be taken.

### Control method

The control arm involves a standard gastroscopy according to the Seattle protocol of quadrantic biopsies taken every 2 cm, in addition to biopsies from any visible abnormalities.

### Histological methods

Biopsies will be analyzed and reported by accredited NHS hospital laboratories at each site according to clinical pathology accreditation (CPA) ISO 15189 quality control procedures. Specimens where a histological diagnosis of dysplasia is suspected will be examined by 2 expert gastrointestinal pathologists, and a third opinion will be sought in case of disagreement.

### Measurement of outcomes

#### Training assessment

Sensitivity, specificity, positive predictive value and negative predictive value will be calculated for all image and video assessments performed by the endoscopists. Kappa scores will be used to assess interobserver agreement. Endoscopists will be asked how confident they would be to switch practice at each stage of the training process (pre-online training, post-online training, post-training day). Following training, they will be asked what the components of an AA training program should be.

#### Study process

Information will be gathered from trial documentation, including numbers of patients recorded on screening logs, consent logs and withdrawal forms (e.g. detection of cancer on first endoscopy or patient-led withdrawal prior to second endoscopy).

### Endoscopic and histology outcomes

Endoscopy process outcomes include duration of endoscopy, use of sedation and level of patient discomfort using a 10-point scale (1 = no discomfort, 10 = severe discomfort). Diagnostic outcomes include the length of Barrett's observed, islands of Barrett's reported according to the Prague criteria, presence of endoscopically visible inflammation, visible abnormalities requiring targeted biopsies (recorded as per Paris classification and Prague criteria), number of biopsies performed, and endoscopic diagnosis (metaplasia, dysplasia or cancer) [25, 26]. Dysplasia will be categorized as low- or high-grade [5].

### Study visit schedule

Baseline information includes: demographics, educational achievement and occupation, lifestyle (smoking, alcohol), history of Barrett's (date of first diagnosis, previous histology), current medications (including aspirin, clopidogrel, non-steroidal anti-inflammatory medicines, proton-pump inhibitors) and significant medical history.

The first endoscopy will be performed, followed by a second endoscopy after a 6-week interval (-2/+4 week window), permitting the esophagus to heal.

During endoscopy, data will be collected concerning sedation (dose and type administered), procedure duration, charac-



teristics of Barrett's, number of biopsies and patient discomfort. Histology results from both endoscopies will be released as per standard care as soon as possible after the second endoscopy has been completed.

### Safety reporting

AEs will be collected during the procedure and in the following 24 hours. Data collected include a description of the event, date/time of onset, intensity, relatedness to the procedure, whether the event was categorized as a serious adverse event (SAE), action taken, date of resolution (if resolved) and final outcome of the event [27].

### Sample size

Based on the historical cohort studies and wide consultation within the British Society of Gastroenterology research committee and consultation with experts in the field, it was estimated that 200 patients would be reasonable for recruitment to enable the reproducibility and generalizability of the data to be established. The purpose of this study is not to produce statistically significant data in itself but to establish likely event rates and effect size to inform the power calculation for the definitive study. Within the target sample size of 200 patients, the intention is to recruit at least 30 patients per site over 6 centers.

### Data management

Data will be managed by the Gloucester Clinical Trials Unit (GCTU), using a Structured Query Language database (Transact-SQL 2008, Microsoft, USA), including an electronic audit trail.

### Statistical analysis

The study will be reported in accordance with the Consolidated Standards of Reporting Trials statement and ICH Guidelines for Good Clinical Practice.

There are no planned interim analyses. All participants will be included in analysis. Participants who do not attend the second endoscopy will have their first endoscopy data included with analysis of the appropriate treatment group. Analyses will be performed using Stata (College Station, Texas). As this is a feasibility study and was not powered to be able to test for differences between the 2 endoscopy methods, formal statistical testing is not appropriate. Descriptive statistics will be used for each arm in order to inform a further definitive trial. The proportion of patients not attending the second endoscopy will be calculated, and for purposes of the feasibility analysis, the results of the endoscopy will be included in the descriptive statistics for each group. This will allow collection of preliminary data to inform the sample size calculation for a definitive trial, and therefore, all data collected will be included to provide better information.

### Study process indicators

These include: (1) total participant recruitment, by site and month of study; (2) screening success rate (eligible patients/patients screened); (3) consent rate (patients recruited/eligible patients); (4) rate of attendance to first and second endos-

copies; and (5) rate of withdrawal from study, and reasons where provided.

### Neoplasia yield

Rates of dysplasia detection, (endoscopies with dysplasia/total endoscopies), will be calculated for both methods of endoscopy. True histology is defined as the combination of results from both endoscopies (targeted + mapping biopsies). The dysplasia detection rate for each technique is defined as patients with biopsy confirmed dysplasia by each technique/total patients with dysplasia.

### Additional endoscopy outcomes

These will be presented according to the endoscopy technique. Descriptive statistics (proportions, means, standard deviations, confidence intervals) will describe the following: duration of gastroscopy; use of sedation; endoscopic diagnosis (metaplasia, dysplasia or cancer); Barrett's length; presence of Barrett's islands; visible abnormalities leading to targeted biopsies during all procedures and total number of biopsies; suspected diagnosis (metaplasia, dysplasia); patient discomfort (10-point scale).

### Safety

The frequency and severity of AEs of interest, grouped by type, namely chest infection/aspiration, bleeding and other complications considered to be related to the procedure will be reported.

### Qualitative methods

Patient participants: an introductory letter, contact details and a photograph of the lead qualitative researcher will be provided prior to the telephone interview. Informed consent will be taken prior to the interview. Telephone interviews will take place a minimum of 2 days, but no longer than a month after the end of study participation and last approximately 30 minutes. Topics include experiences of study participation, views of the impact for patients if the AA technique became standard practice, and facilitators and barriers to recruitment and retention for a definitive trial. Following the interview, brief field notes will be taken to record any immediate reflections and emerging themes.

Endoscopist participants: At least 8 endoscopists who had participated in delivering the ABBA trial will be recruited to take part in telephone interviews at the completion of the trial. Topics for the interview include concerns regarding the procedure prior to training, experience of training, perception of usefulness and suitability of the AA technique and feasibility study methods for the definitive trial.

### Data analysis

Participants will be identified by a unique number in the database and audio recordings. Audio recordings will be transcribed and entered into NVivo 10 (QSR International, Melbourne, Australia).

Data will be analyzed through a process of thematic analysis using the Framework approach. Categories will be independ-

ently coded by 2 researchers, and a member of the steering group will read a sample of transcripts to generate a preliminary framework without knowledge of the original researchers' list. In case of disagreement, a solution will be sought to clarify the meaning of a code/theme developed. A deductive approach to map themes from the 2 groups of participants (patients and endoscopists) will enable us to compare and contrast similarities and differences of attitudes, perceptions and experience.

## Public patient involvement

Patients, carers and the public from Heartburn Cancer UK and the University of Portsmouth School of Health Sciences and Social Work ENGAGE group were involved in the grant application, study design including interview schedules, and will be involved in study delivery.

## Ethics

Favorable ethical approval for this study was given by the National Research Ethics Service (NRES) Committee, South Central – Berkshire, reference 15/SC/0085.

Because the study involves 2 endoscopies, participants will be exposed to the risk of experiencing endoscopy-related AEs twice. However, the overall risk of such events is very small, and the benefit:risk of having 2 methods of detecting potential dysplasia may outweigh the small increased risk of AEs. Secondly, there is a delay of a maximum of 6 weeks for histology to become available due to the requirement for blinding of the second endoscopy. However, in the case that cancer is detected during either endoscopy, samples will be prioritized, immediate referral for treatment made, and the participant withdrawn so as not to delay treatment.

## Funding

The ABBA study is funded by National Institute of Health Research (NIHR) Research for Patient Benefit (RFPB) program (Project Number PB-PG-1013-32045).

## Dissemination

The results of this feasibility study will be disseminated to all groups who are able to offer input and suggestions for further work, i. e. patients with Barrett's and patient support groups, gastroenterologists, pathologists, and those involved in managing the workflow for the Barrett's surveillance program within the British Society of Gastroenterology (BSG).

## Discussion

The ABBA feasibility study is the first randomized cross-over trial exploring the use of acetic acid chromoendoscopy (AAC) in a Barrett's surveillance population. It has been designed to provide comprehensive quantitative and qualitative data to inform and power a definitive, multicenter RCT. It will clarify whether a crossover tandem endoscopy design is a feasible approach for this study for patients and endoscopists, or whether a larger trial would require a parallel design.

When introducing any new technique into mainstream clinical practice it is vital that we understand how to train clinicians

to perform the technique safely. This has been lacking in the introduction of other endoscopic techniques, e. g. indigocarmine chromoendoscopy in ulcerative colitis surveillance or colonic polyp *in vivo* diagnosis, where efficacy has been demonstrated by experts, but with no consideration of how to train all practicing endoscopists on the technique [28, 29]. Evidence from *in vivo* diagnosis studies of colonic polyps showed results obtained in expert hands can be very different to those obtained in a general hospital, [30] and therefore development and assessment of appropriate training is a key element of this study. This activity also promotes cross-working of endoscopists across units, and enables up-skilling as well as skill-sharing which will benefit endoscopists normal practice. It also grows and strengthens the existing network of clinicians with an interest in Barrett's research, and contributes to timely delivery of trials in this area, to maximise patient benefit.

The use of qualitative methods to examine patient and clinician barriers and facilitators to the adoption of AAC is essential to inform future pathways to implementation. Health care should be patient-centered. If a change in practice is to be recommended, it is important we understand the best way of making these changes, and the best way of presenting information on new techniques to patients to reduce potential anxiety and to reassure patients that they are still receiving the best care.

Finally, we would like to highlight the essential role of the Public Patient contributors in providing feedback throughout study development and delivery, and working within the research team to ensure the patient-facing aspects of the study are kept pragmatic and appropriate for patients.

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## Competing interests

None. The ABBA study is funded by the National Institute for Health Research, Research for Patient Benefit (Project Number PB-PG-1013-32045).

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