UNIVERSITY OF BIRMINGHAM

Institute of Translational Medicine Birmingham

Trial Protocol

A randomised controlled trial of the prediction of diminutive/small polyp histology: a comparison between didactic training versus self-directed computer based training

This protocol has regard for the HRA guidance

Protocol development and sign off

As per EC guidance (ENTR/CT2) the protocol should be signed by the CI and by the Sponsor to confirm approval of the protocol. NOTE: For UoB sponsored trials, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required. The sponsor must be notified of all amendments to the protocol, both substantial and non-substantial. Review of amendments by the sponsor will act as the confirmation that the sponsor confirms approval of the amended protocol.

Key Protocol Contributors

The following people have contributed to the writing of this protocol:

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Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained

This protocol has been approved by:

Trial Name:	Diminutive training module: didactic training versus computer based self-learning- a multicentre international study
Protocol Version Number:	Version: 1.0
Protocol Version Date:	09/01/2018

CI Name:	Dr Marietta Iacucci
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Administrative Information

Use this page to document the key contact personnel for the trial.

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Trial Summary

Title

A randomised controlled trial of the prediction of diminutive/small polyp histology: a comparison between didactic training versus self-directed computer based training

Background

Colonoscopy is the gold standard for detection of colonic polyps and colorectal cancer. Novel endoscopic enhancement by virtual electronic chromoendoscopy such as narrow-band imaging [NBI, Olympus, Japan], Fuji Intelligent Chromo Endoscopy [FICE, Fujifilm, Japan], i-scan [Pentax, Japan], techniques have been developed to aid endoscopists to better characterize colonic polyps and predict histology thus facilitating the adoption of the new paradigm of resect and discard i.e. the PIVI-ASGE strategy resulting in cost savings and avoidance of complications in patients. Several training modules have been developed and used in prior studies evaluating the performance of endoscopic image-enhancement technologies. Different training methods, have been evaluated and include face-to-face, interactive didactic teaching or web-based/computer-based self-learning teaching modules. The superiority of one training method over the other has not been well evaluated.

Trial Design

Multi-centre, international randomised controlled trial

Methodology

Participant Population

Participants will be consultants (gastroenterologists or surgeons) who are experienced in colonoscopy, training gastroenterologists, nurse endoscopists and junior doctors/medical students (who are naive in colonoscopy).

We aim to recruit 10-20 consultants/attending, 10-20 trainees/GI fellows, 10-20 nurse endoscopists (if applicable) and 10-20 junior doctors (non-GI trainees) from each centre. The participants will be randomised to receive self-directed computer based learning or face-to-face classroom didactic computer training module.

The above will be replicated at other centres: UK, USA, Italy, Germany and Japan.

Study duration: 2 years

Statistical Methodology

Performance characteristics of the participants for diagnosing colonic neoplastic vs. non neoplastic lesions (sensitivity, specificity, NPV, PPV and accuracy) will calculated by comparing predicted histology with actual histology for all polyps and for those diagnosed with high confidence.. These performance characteristics between the two groups (face-to-face classroom training vs. self training module) will be compared using the Fisher's ex- act test. A P value of <0.05 will be considered to be statistically significant. *Kappa* statistic will be used to determine inter-observer agreement in polyp video classification during the training session.

Sample size

Assuming a non-inferiority trial with one-sided distribution (face to face training versus computer based training), and power of 90% the sample size is 375 observations (observation=1 video scored). This falls to 271 observations if 0.80 1-beta error is set. As we will use 60 videos per participants, we would need a minimum of 7 participants in each centre. To minimise any potential errors we aim to recruit 10-20 participants from each group (as described above) from each centre.

Objectives

To assess the impact of didactic face-to-face training vs. self-directed computer based training module.

To evaluate the impact of an educational training module has on the ability of clinicians to differentiate small/diminutive polyps.

Outcome Measures

A pre-training assessment will be completed by participants. Performance at predicting histology (neoplastic vs. non-neoplastic) will be assessed using sensitivity, specificity, PPV, NPV and accuracy. The proportion of high and low confidence diagnoses will be also documented.

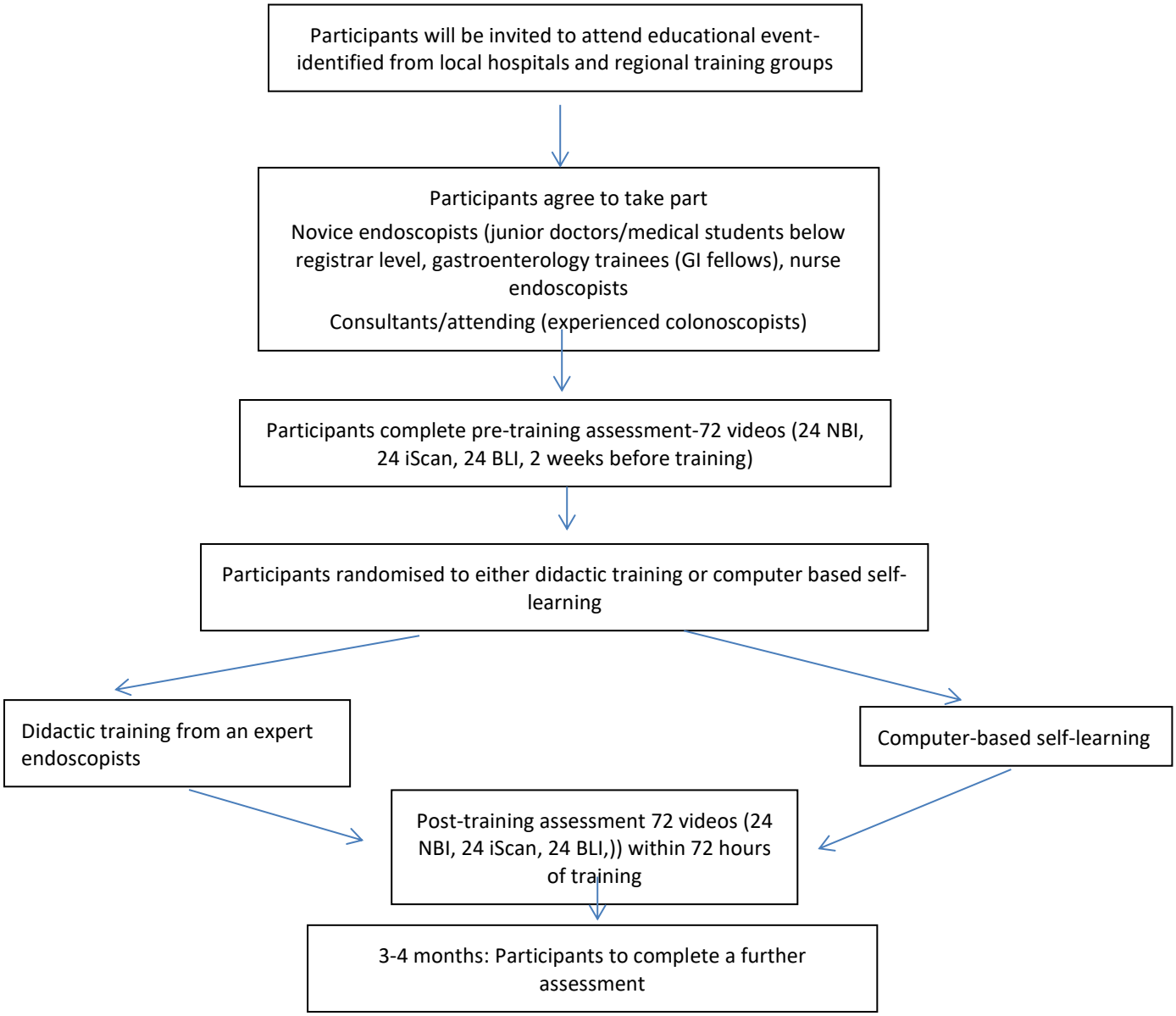
Following training, participants will immediately complete a post-training assessment and performances will be observed comparing with pre-training assessment. A follow up assessment at 6 months will be completed to assess the retention and sustainability of skills acquired.

Kappa inter-observer variability between the raters will be assessed.

Intervention

Training module: didactic face-to-face classroom training or computer-based self-learning training module

Trial Schema



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1. Background and Rationale

Colonoscopy is the gold standard for screening for bowel cancers and detection of pre-cursors to colorectal cancer (polyps). Early detection of polyps, allows endoscopic removal and therefore reduction in colorectal cancer. With improvements in technology endoscopists are detecting more lesions within the bowel with the majority small/diminutive <5mm (80%), however the clinical relevance of these lesions is minimal as the risk of advanced histology or cancer is <1%[1,2,3]. The current practice involves removing these lesions and sending for histopathological assessment, incurring a significant risk to the patient, cost and is time-consuming, with very little benefit[4,5]. Novel imaging techniques including Narrow-band imaging (NBI-Olympus, Japan), i-Scan Optical enhancement (OE-Pentax, Japan) and Blue-light laser imaging (BLI- Fujifilm, Japan) can help endoscopists characterise these small lesions between being neoplastic and non-neoplastic (hyperplastic) [6,7,8,9]. NBI involves the narrowing of bandwidths of light using a light filter. The light at this end of the spectrum is absorbed by haemoglobin (protein found within blood) therefore making blood vessels more pronounced. During the process whereby a polyp develops and later becomes neoplastic, there is an increase in blood vessels compared with normal tissue or hyperplastic polyps (benign), therefore NBI can be used to detect such lesions [10,11]. I-Scan OE is an alternative imaging technique which enhances the pattern of the surface of polyps as well as the blood vessels, by manipulating dark-light borders and red, blue and green components of light. Blue laser imaging (BLI) is also new system for image-enhanced endoscopy using laser light. Blue laser imaging utilizes two monochromatic lasers (410 and 450 nm) instead of xenon light. A 410 nm laser visualizes vascular microarchitecture, similar to narrow band imaging, and a 450 nm laser provides white light by excitation.

These novel technologies have been demonstrated to be superior over standard white light endoscopy with NBI the most extensively investigated. A systematic analysis of 6 studies >500 polyps, resulted in a pooled sensitivity of 92%, spec 86%, accuracy of 89% at differentiating neoplastic from non-neoplastic lesions when using NBI [12]. Head to head studies of NBI versus white light endoscopy (WLE) have shown NBI is better at differentiating between neoplastic and non-neoplastic lesions [10, 13, 14]. Similar results have been found with i-Scan, with performances better than WLE and like NBI are similar to chromoendoscopy (a technique that involves spraying dye over bowel mucosa which is time-consuming and costly) [15, 16]. BLI is a newer imaging platform, with the current evidence suggesting it is effective at differentiating polyps (neoplastic versus non-neoplastic) with

accuracies of 95.2%[17], and when comparing with white light endoscopy the miss rate of adenoma was significantly lower with BLI (1.6% versus 10.0% p=0.001)[18].

In order to characterise between neoplastic and non-neoplastic lesions, endoscopic scoring systems have been developed to assist endoscopists. Examples include NICE (NBI International Colorectal Endoscopic)[3] (Appendix 1).

Recently Iacucci et al have developed a simplified classification system (SIMPLE- Simplified Identification Method for Polyp Labelling during the Endoscopy) for optical diagnosis of small and diminutive adenomas, SSA/Ps and hyperplastic polyps using the newly introduced OE-iSCAN system which achieved a high degree of diagnostic accuracy for small/diminutive polyp diagnosis. Furthermore, they have showed that a training module on SIMPLE classification resulted in an overall NPV of 91.3%[19]. This user-friendly classification system can be used by experienced and non-experienced gastroenterologists on multiple endoscopy imaging platforms to differentiate neoplastic from non-neoplastic polyps (Appendix 1). A classification system developed by Bisschops R et al recently using BLI called BASIC (BLI Adenoma Serrated International Classification). This takes into account the polyp surface, pit appearance and vessels, which has shown to have a high concordance amongst experts[20].

In the hands of experts using NBI-NICE classification system accuracies of 98.9%, sensitivity 98%, specificity 100%, NPV 97.7% and PPV100% were demonstrated when diagnosis was made with high confidence. Essential to the adopted use of these classifications is training for endoscopists, both experienced and those in training. There is good evidence that there is a short learning curve involved when using NBI[21]. One study using a self-administered computer based training module, community based gastroenterologists (non-expert) were able to reach excellent NPV of >90% but fell short of other requirements (prediction of surveillance intervals) [22]. Much like NBI, the learning curve at acquiring the skills in order to differentiate between hyperplastic and adenomatous lesions using i-Scan has been investigated. An early study by Neumann et al demonstrated a rapid learning curve with 4 endoscopists without previous experience with i-scan reached an accuracy of at least 85% after reviewing 67-110 lesions (with individualised feedback) following a 1 hour teaching session on pit pattern analysis[23].

There have attempts at identifying the most effective training tool and method at teaching non-experts how to characterise lesions effectively. Studies have used still images of lesions[24],

however this is limited as it does not reflect real-life practice as it does not allow views from different angles. It is thought videos simulate real-life practice as close as possible. A study using videos has demonstrated trainees were able to achieve accuracies of 90%[25].

More recently Rastogi's group sought to identify which training method was more effective in prediction of diminutive polyp histology amongst trainees: didactic face to face training versus computer-based self-learning [26]. The participants were randomised to either receive didactic training in the form of a classroom training session or self-learning via computer-based material on characterisation of polyps using NBI. Trainees reviewed 40 videos of diminutive polyps with the histology being revealed and explained. Both groups were given a further 40 videos for testing. This study found those taught in the didactic group characterised polyps with higher confidence, but the overall performance was similar in the two groups. The accuracy and sensitivity were slightly better in the self-learning group (93.9% vs 85.7% p 0.01 and 95.0% vs 86.9%; p0.03 respectively) in those polyps assessed with high confidence. This study demonstrates that a computer-based training module can be as effective in didactic training, perhaps a reflection on the amount of online self-learning trainees are exposed to.

We aim to recruit participants to receive either didactic face-to-face training or self-directed computer based learning, whereby participants will be taught how to characterise lesions using the NICE, BASIC and SIMPLE classification. We aim to recruit trainees, novice endoscopists and experienced endoscopists to compare the different groups. Pre- and post-training assessments will be completed allowing us to examine the impact of training, which will consist of 40-60 videos (equal proportion of NBI, iScan OE and BLI) in the pre-training assessment and 40-60 videos (different set of videos but also equal proportion of NBI, iScan OE and BLI) in the post-training assessment. A follow up assessment will be completed at 6 months to assess the retention of skills and sustainability of colonic polyp characterisation using the optical diagnosis techniques. An existing library of NBI and OE-iScan videos will be used and further videos will be collected during routine colonoscopies with patients consenting for images to be used for teaching purposes.

1.1. Trial Rationale

We hypothesise that following the training module there will be an improvement in performance between the pre-training and post-training assessments. We also hypothesise that there will be no difference between the didactic face-to-face group and the self-training group.

This is an important study as better characterisation of small polyps may eventually lead to a 'resect and discard' strategy in the future. This involves characterising small or diminutive polyps (<10mm) as either non-neoplastic or neoplastic, resecting the lesion but not sending for histopathological analysis, which has significant cost savings. In order to do this training is essential. Whilst didactic training is attractive, it is costly and resource heavy. The option of self-directed learning is an attractive one as it can be delivered at times that suit the user, at their pace and can be delivered in greater volumes.

This study is unique as it is examining the impact of the training module on different groups of participants (novice, training and experienced endoscopists), using multiple endoscopic platforms(NBI, i-Scan OE and BLI) at a multicentre, international level. It will enable us to assess whether the training module improves performance using different imaging modalities.

1.2. Justification for participant population

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The participants included will be those that will need better polyp characterisation in everyday endoscopic practice, so they are ideal candidates. Novice endoscopists will be invited to examine the effect of the training module on participants without previous experience.

1.3. Justification for design

The training module will be carried out on the same day as the post-training assessment, in order to avoid any bias with erosion of knowledge/skills over time.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

Hypothesis: performances at predicting the histology of small/diminutive polyps improves following both the didactic face-to-face feedback training and self-directed computer based training. We also hypothesise that there will no overall difference between the two teaching groups.

2.2. Outcome Measures

Outcome measures will include accuracy of polyp prediction, sensitivity, specificity, positive predictive value and negative predictive value. Proportion of high confidence diagnoses will also be recorded. Kappa statistics will be used to determine interobsever agreement in polyp video classification.

3. Trial Design and Setting

3.1. Trial Design

A multi-centre international randomised controlled trial.

3.2. Trial Setting

University of Birmingham/academic setting, plus other international centres (UK, USA, Japan, Italy, Germany)

4. Eligibility

4.1. Inclusion Criteria

- Experienced colonoscopists: fully independent and have completed >1000 procedures
- Nurse endoscopists: fully independent colonoscopists (if applicable)
- Training colonoscopists: gastroenterology trainee in the process of training in colonoscopy
- Novice colonoscopists: junior doctors/medical students who have no experience of colonoscopy

4.2. Exclusion Criteria

- Inability to consent to take part in the study.

5. Recruitment, Consent, Enrolment and Randomisation

5.1. Recruitment

Participating centres will be identified by the chief investigator (MI) and co-investigator (SS). Potential participants will be approached via email via lead investigators from each centre. Once participants have agreed to take part they will be randomised using sealed envelope software/Microsoft excel). No patient records will be accessed for the purposes of this study.

5.2. Consent

Consent to collect data, store the information at the University of Birmingham and publish the final data collected will be sought from all participants online prior to the collection of the pre- and post-training assessment.

The videos used will not contain any patient identifiable information and consent for their use for educational purposes has already been sought via a written consent form and have been used in other studies.

5.3. Randomisation

Participants will be randomised into either didactic face-to-face training or computer self-training module. This will take place prior to the training event and participants will be informed of which group they have been allocated on the day by using a computerized stratified randomisation sequence where a computer-generated random number will be assigned to each participant and then randomized to each arm to ensure a balanced number in both groups.

5.4. Blinding

Due to the nature of the intervention, participants cannot be blinded.

6. Trial procedures and assessments

6.1. Summary of assessments

	Enrolment	Allocation
TIMEPOINT**	***At teaching sessions***	
Eligibility screen	X	
Informed consent	X	
INTERVENTIONS:		
[Didactic training]	x	
[Computer based training]	x	

6.2. Schedule of Assessments

Participants who agree to take part in the study will complete a pre-training assessment prior to the training day. Assessment material will be uploaded on REDCap, hosted via the University of Birmingham. Each participant will receive a link via email to complete the assessments. Each participant will be asked to assess: Quality of video High/Low, NICE classification, SIMPLE classification, BASIC classification, High/Low confidence and Hazewinkel criteria for each video. This will be completed at least 2 weeks prior to the training day. On the training day participants will receive either didactic face-to-face feedback training or computer-based training (identical).A post-training assessment will be completed within 72 hours of training (same videos as pre-training but in a different randomised order). The website will self-populate the data in Microsoft Excel documents. Participants will then be invited to complete a final assessment at 3-4 months, which will conclude the study.

7. Data Handling and Record Keeping

7.1. Source Data

The source data will be completed directly on to the forms provided to participants. This will include:

Experience: number of colonoscopies in lifetime/year, experience with NBI/iScan OE/BLI, stage of training if applicable.

Excel spreadsheets will be utilised to enter: quality of video (low/high), NICE (adenoma, hyperplastic polyp, invasive carcinoma), SIMPLE (hyperplastic, SSA, adenoma) and Hazewinkel criteria for SSA, and high/low confidence prediction.

7.2. Data Management

Data will be collected on Microsoft excel via canvas.bham.ac.uk. Participants will be allocated an ID number (centre initials followed by participant initials). This will be anonymised.

7.3. Archiving

Data collected during this study, will be kept in locked filing cabinet at all times, any online data that is received will be stored on a secure system, which only the study team will have access too. The data will be stored for use until the findings and paper are written. After this time, it will be archived for a minimum on 10 years as per study procedure.

8. End of Trial Definition

This teaching project will be held on one day, participants will be followed up at 6 months following the training to repeat the post-training assessment. This will signal the end of the study.

9. Statistical Considerations

9.1. Statistical Analysis

Performance characteristics of the participants for diagnosing colonic neoplastic vs. non neoplastic lesions (sensitivity, specificity, NPV, PPV and accuracy) will calculated by comparing predicted histology with actual histology for all polyps and for those diagnosed with high confidence.. These performance characteristics between the two groups (face to face classroom training vs. self-training module)will be compared using the Fisher's ex- act test. A P value of <0.05 will be considered to be statistically significant. *Kappa* statistic will

be used to determine inter-observer agreement in polyp video classification during the training session.

9.1.1. Planned Randomisation Methodology

A Computer-generated randomisation system will allow us to allocate the participants into two teaching groups.

9.1.2. Planned Sub Group Analyses

Subgroup analysis will include didactic training vs. computer based self-learning. We will also compare the performance of predicting histology of NICE versus SIMPLE versus BASIC in all observations as well as only taking high confidence predictions. We will compare the inter-observer agreement between NICE, SIMPLE and BASIC.

9.1.3. Planned Final Analyses

Final analysis will take place after the initial training day and after the 6-month follow up assessment.

9.1.4. Power Calculations

Assuming a non-inferiority trial with one-sided distribution (face-to-face training versus computer based training), and power of 90% the sample size is 375 observations (observation=1 video scored). This falls to 271 observations if 0.80 1-beta error is set. As we will use 60 videos per participants, we would need a minimum of 7 participants in each centre. To minimise any potential errors we aim to recruit 14 participants from each centre (7 randomised to face-to-face training and 7 to the computer group).

10. Trial Organisational Structure

There is no trial steering committee needed for this teaching project, The members involved are outlined in the administrative information at the start of this protocol.

10.1. Sponsor

University of Birmingham will be the sponsor for this teaching project.

10.2. Trials Office

This project will be run and conducted by the Institute of Translational Medicine

11.Confidentiality and Data Protection

Consent for the holding of participant data and publication of findings will be gained from participants online prior to starting the pre and post training assessments.

12.Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

13.Access to the final trial dataset

Dr Marietta Iacucci, Dr Samuel Smith and Hollie Caulfied will have access to the full data set throughout this study

14.Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences such as the British Society of Gastroenterology annual meeting, the United European Gastroenterology Week (UEGW) and the Digestive Diseases Week (DDW) and in peer-reviewed scientific journals such as *Endoscopy, Gastrointestinal Endoscopy* and *Gut.*

Results will also be disseminated to the local primary care groups, the Oxford and Wessex 'Gut Club' and also to patients via the endoscopy staff and patient forum.

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Appendices

Appendix 1.

NICE classification:

Type 1: Hyperplastic

Colour: same or lighter than background

Vessels: none, or isolated lacy vessels coursing across the lesion

Surface pattern: dark or white spots of uniform size, or homogenous absence of pattern.

Type 2: Adenoma

Colour: browner relative to background (verify colour comes from vessels)

Vessels: brown vessels surrounding white structures

Surface pattern: oval, tubular or branched white structures surrounded by brown vessels.

Type 3: deep submucosal invasive cancer

Colour: brown to dark brown relative to background; sometimes patchy white areas

Vessels: Has area (s) of disrupted or missing vessels

Surface pattern: Amorphous or absent surface pattern

The SIMPLE (Simplified Identification Method for Polyp Labelling during the Endoscopy) classification (Iacucci M et al Endoscopy in press) was recently developed with the addition of criteria for Sessile Serrated Adenoma (SSA):

Type 1: Hyperplastic

Surface pattern: Round pit

Vessels: None, isolated lacy

Lesion border: Regular

Type 2a: Sessile serrated adenoma/lesion

Surface pattern: Open/dilated (dark) pit

Vessels: None, isolated lacy

Lesion border: Irregular/indistinctive

Type 2b: Adenoma

Surface pattern: Not round structure: oval, tubular, branched

Vessels: Thick vessels

Lesion border: Regular