CONSCOP 2 - Randomised controlled trial of contrast enhanced colonoscopy in the reduction of right sided bowel cancer. (The CONSCOP 2 study)

V3.0 16TH SEPTEMBER 2020

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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 relevant trial regulations, GCP guidelines, and CTR's SOPs.

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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Director **Approved by email**		**29.09.2020**
Name: Dr Richard Adams	**Signature**	**Date**
Chief Investigator **Approved by email**		**02.01.2020**
Name: Dr Sunil Dolwani	**Signature**	**Date**

General Information This protocol describes the CONSCOP 2 clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR

Contact details – Chief Investigator & Co-Investigator/s

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Trial Co-ordination:

The CONSCOP 2 trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the CONSCOP 2 Trial Management Group (TMG).

For **all queries** please contact the CONSCOP 2 team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email:	CONSCOP2@cardiff.ac.uk	
Trial Manager:	Georgina Gardner	Email: CONSCOP2@cardiff.ac.uk
Data Manager:	Terri Kitson	
Senior Trial Manager	Dr Lisette Nixon	
Trial Statistician:	Dr Chris Hurt	
Director:	Dr Richard Adams	
Safety Officer	Safety Team	Email: CTR-Safety@cardiff.ac.uk

Randomisations:

Randomisation	
Internet (Anytime):	https://conscop2.ctr.cardiff.ac.uk
If there is an emergency or an issue with randomisation and you need to contact a member of the team please telephone (Mon – Fri, 9am-5pm):	
Telephone (Mon-Fri 9am – 5pm) :	02920 687950 or 02920 687542 (if internet unavailable)
E-mail (Mon-Fri):	CONSCOP2@cardiff.ac.uk

Clinical queries:

Clinical queries
CONSCOP2@cardiff.ac.uk
All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to CTR-Safety@Cardiff.ac.uk within 24 hours of becoming aware of the event (See section 16 for more details).
Contact details: CTR-Safety@Cardiff.ac.uk

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CF	Consent Form
CI	Chief Investigator
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trials Authorisation
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
EUCTD	European Union Clinical Trials Directive
FIT	Faecal Immunochemistry Test
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GP	General Practitioner
HB	Health Board
HE	Health Economics
HTA	Health Technology Assessment
IC	Informed consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat
IU	International Unit
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIMP	Non-Investigational Medicinal Product
NLI	No Local Investigator
NPSA	National Participant Safety Agency
NRR	National Research Register
PCCRC	Post Colonoscopy Colorectal Cancer
PCT	Primary Care Trust
PI	Principal Investigator
PIAG	Participant Information Advisory Group
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAR	Serious Adverse Reactions
ScHARR	School of Health and Related Research
SL	Serrated Lesion
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SSL	Sessile Serrated Lesion
SSP	Specialist Screening Practitioner
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measures

1 Amendment History

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

Amendment No. (specify substantial/non-substantial)	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
01	V3.0	16.09.2020	• Update randomisation details • To include the sentence in the trial design schema by request of BCSP: ***If patient is happy to be contacted about the study, then a member of the research team will make contact.*** • Process evaluation reworded to accommodate COVID19 restrictions on face to face contact for interviews/training • Clarification on withdrawal levels • Minor changes to practice due to COVID19 • To include option to scan slides • Change to remote data capture rather than paper CRF

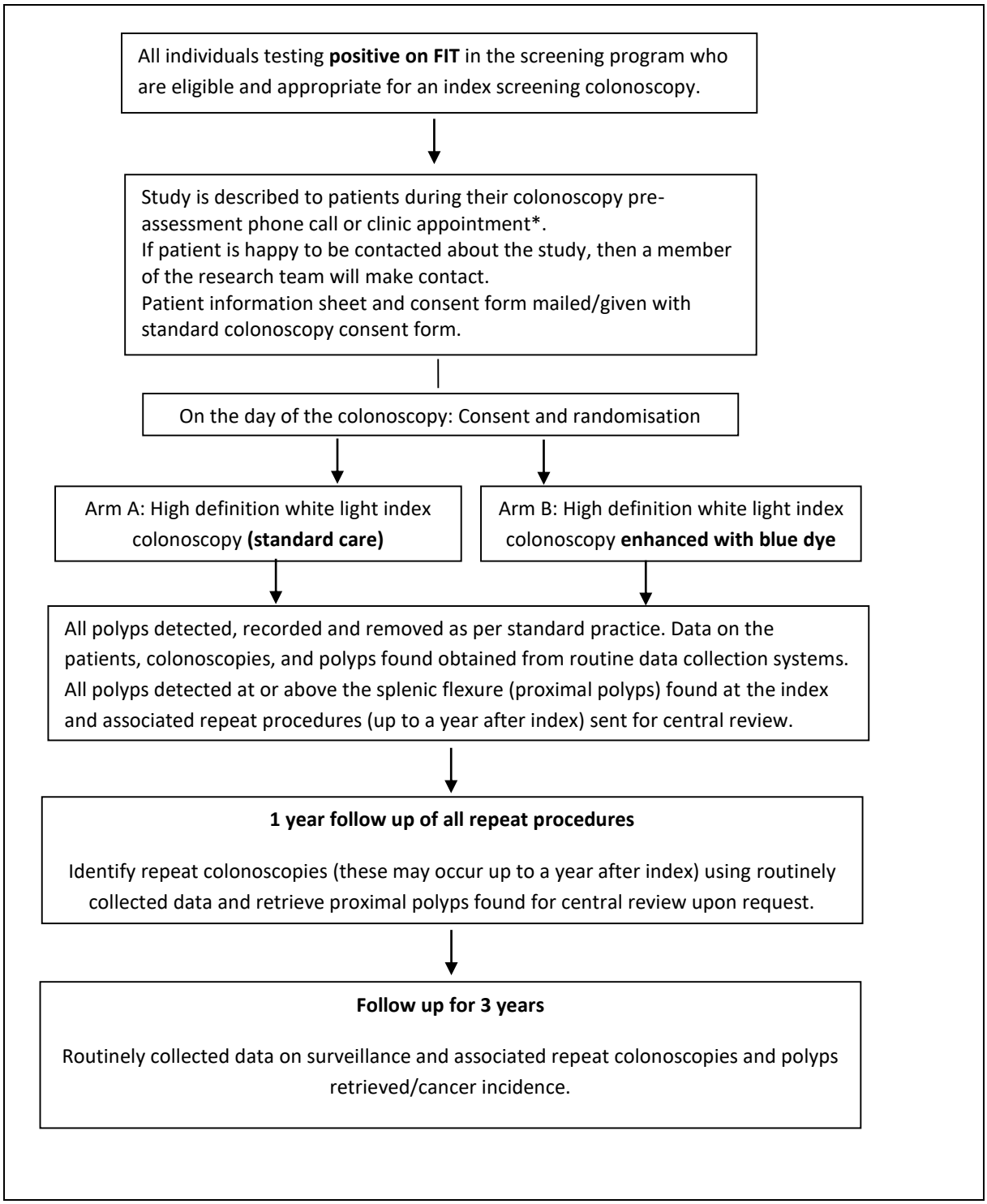
2 Synopsis

Short title	Randomised controlled trial of contrast enhanced colonoscopy in the reduction of right sided bowel cancer.
Acronym	The CONSCOP 2 study
Funder and ref.	NIHR HTA: NIHR127914
Trial design	A randomised open controlled trial (RCT) of contrast-enhanced vs non-enhanced colonoscopy in index bowel cancer screening to reduce bowel cancer mortality. The data obtained in this study will establish whether or not chromocolonoscopy should be used instead of standard white light for index colonoscopies within the UK bowel cancer screening programmes.
Trial participants	Participants in the UK bowel screening programmes (Wales, England, Scotland) who test positive on the FIT test and are eligible for an index screening colonoscopy.
Planned sample size	2652
Planned number of sites	20
Inclusion criteria	All FIT-positive people in the participating centres, eligible for index screening colonoscopy using high definition scopes.
Exclusion criteria	• Previous resectional colorectal surgery (as this would influence both study methods and outcomes depending on the length of residual colon in the individual), • Known allergy to food colouring agent (as the Indigo Carmine dye is a safe food colouring agent but extremely rarely there may be individuals with a specific allergic response to this in the past).
Recruitment duration	24 months
Follow-up duration	36 months
Planned trial period	60 months
Primary objective	Compare proximal advanced serrated lesion detection rates for chromocolonoscopy and standard colonoscopy

Secondary objectives	• Compare other lesion detection rates (e.g. advanced neoplasia, serrated lesions, advanced adenomas) for chromocolonoscopy and standard colonoscopy. • Assess the impact of FIT thresholds on serrated lesion detection rates in each arm of the study. • Evaluate the longer-term economic impact of chromocolonoscopy within the screening setting. • Model and compare the post-colonoscopy interval advanced polyp and cancer detection rates for the two arms. • Assess the association between demographic and lifestyle factors and serrated lesions at index colonoscopy. • Assess the association between demographic and lifestyle factors and the presence of serrated lesions at index and surveillance colonoscopies in order to inform the stratification and optimisation of surveillance frequency.
Primary outcomes	Polyp types detected and location within the bowel
Intervention	Chromocolonoscopy (Indigo Carmine dye)

3 Trial summary & schema

3.1 Trial schema



* England: pre-assessment clinic to assess fitness for colonoscopy. Scotland: Nurse appointment to offer colonoscopy. Wales: Specialist Screening Practitioner phone call.

3.2 Trial lay summary

People testing positive on a bowel cancer screening stool test are offered colonoscopy (bowel camera examination). About half of those have cancers or polyps (small abnormal growths that might lead to cancer in the future) found on colonoscopy. Studies have shown that screening reduces cancer development (through removing polyps found) and deaths from cancer in the lower bowel. However, in the upper bowel, the types of polyps often found (known as serrated) are flat, subtle and hard to find with standard colonoscopy and deaths from cancer of the upper bowel are not reducing. Up to 1 in 5 bowel cancers may actually have developed from these subtle serrated polyps. Almost 1 in 12 bowel cancers found in England are missed despite a seemingly clear colonoscopy in the previous 3 years. This study investigates if spraying a blue dye in the upper large bowel helps the doctor to *detect* more flat polyps during the colonoscopy. At the moment we do not know if spraying the dye in the upper large bowel is the best way to improve detection so we need to randomly assign people who are due to have a screening colonoscopy into two groups, one to have a standard colonoscopy and the other to have a colonoscopy using the dye spray. We will then be able to compare what happens between the two groups.

4 Background

Screening has been shown to reduce colorectal cancer (CRC) incidence and mortality.[1] This benefit is substantial in the reduction of distal CRCs, but modest for proximal colon cancers.[2,3] A higher proportion of cancers developing after an index colonoscopy, post-colonoscopy CRCs (PCCRCs), are proximal and have worse survival outcomes.[4] PCCRC rates within 3 years after colonoscopy range from 3.4 - 9% of all CRCs (English NHS 8.6%) and their incidence is associated with colonoscopy quality measures.[5,6] Participants may be falsely reassured by screening colonoscopy and findings at further surveillance in 12 months may reflect lesions not detected at the initial procedure. Two types of factors may contribute to the occurrence of proximal PCCRCs: 1) technical (operator/procedure quality) dependent factors which can result in missed lesions, lower detection rates, and incomplete resection of lesions, and 2) polyp biology dependent factors due to morphology, accelerated growth, and molecular characteristics.[7-10] Apart from the traditional adenoma to carcinoma pathway for polyps, it is widely recognised that subsets of a different type of polyp – sessile serrated lesions (SSLs) - cause cancer via the alternative serrated neoplasia pathway and this may be responsible for up to 35% of all sporadic CRCs.[11] Several studies have demonstrated that SSLs are common precursors to

proximal PCCRCs.[10] These polyps are flat or non-polypoid in morphology making them more difficult to detect endoscopically and studies show wide variation in detection rates (1-20%) amongst endoscopists.[12,13] The NHS bowel cancer screening programmes in Scotland, England and Wales will have all changed over from faecal occult blood (FOB) to faecal immunochemical test (FIT) based screening through 2018-19. This change is expected to result in an increased sensitivity and improvement in detection of CRC along with a consequent increased requirement for colonoscopy and accurate surveillance. Current surveillance frequency does not accurately match the future risk of developing CRC and is based only on the number and size of *adenomas* detected.[14]

4.1 Rationale for current trial/Justification of Treatment Options

Pan-colonic chromocolonoscopy already forms part of standard practice in colonoscopic surveillance in high-risk cases of inflammatory bowel disease and is part of evidence based national and international guidelines.[15] We recently completed a parallel group randomised controlled, open label multicentre feasibility trial (CONSCOP) within the bowel cancer screening programme in Wales with 740 participants randomised to either standard white light colonoscopy or colonoscopy enhanced with blue dye (chromocolonoscopy).[16] We demonstrated that chromocolonoscopy is safe and feasible within a population based CRC screening programme and increased detection of proximal serrated neoplasia and all other polyp types. We also calculated the additional time and cost associated with this intervention. A Cochrane review of chromocolonoscopy vs standard colonoscopy concluded that there was strong evidence that chromocolonoscopy enhances the detection of neoplasia in the colorectum.[17] However, none of the previous RCTs assessed SSL detection and none were powered to detect differences in significant lesions (advanced forms of SSL and adenomas). There was a difference in the numbers assigned to further surveillance based on having three or more polyps but only if studies using high definition colonoscopies were excluded. To the best of our knowledge, there have been no RCTs of chromocolonoscopy investigating detection of polyps since the review. Existing literature therefore supports the feasibility and importance of comparing high definition white light colonoscopy to high definition chromocolonoscopy for the clinically relevant outcome of proximal advanced SL detection.

The CONSCOP2 study seeks to improve the effectiveness of the bowel cancer screening programme in reducing the incidence and mortality from proximal colon cancer. This study will do this by examining whether or not:

- chromocolonoscopy is more effective in achieving improved significant serrated polyp (i.e. advanced forms of serrated polyp) detection at the initial procedure
- chromocolonoscopy is more effective and cost effective at reducing the numbers of polyps and cancers found at the subsequent surveillance colonoscopy
- follow-up frequency for different groups of patients can be optimised by long term modelling using routine data taking proximal SL prevalence and patient characteristics into consideration

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

Compare proximal advanced SL detection rates for chromocolonoscopy and standard colonoscopy.

5.2 Secondary objectives

- Compare other lesion detection rates (e.g. advanced neoplasia, serrated lesions, advanced adenomas) for chromocolonoscopy and standard colonoscopy.
- Assess the impact of FIT thresholds on serrated lesion detection rates in each arm of the study.
- Evaluate the longer-term economic impact of chromocolonoscopy within the screening setting.
- Model and compare the post-colonoscopy interval advanced polyp and cancer detection and death rates for the two arms.
- Assess the association between demographic and lifestyle factors and SLs at index colonoscopy.
- Assess the association between demographic and lifestyle factors and SLs at surveillance colonoscopies in order to inform the stratification and optimisation of surveillance frequency.

5.3 Primary outcomes measure(s)

The primary endpoint of the study (significant serrated proximal polyp detection) relies on subjective pathologist assessments of polyp characterisation. After identifying the patients who had any proximal polyps using routinely collected screening data, slides will be collected from all proximal polyps detected. These will all be centrally reviewed by at least 3 expert pathologists to minimise any inter-observer variability bias in order to achieve consensus agreement on polyp classification. All proximal polyps collected at the index and associated repeat procedures will be collected.

5.4 Secondary outcomes measure(s)

- Types of all proximal polyps will be obtained from the central review described for the primary outcome measure. Types of all distal polyps detected at index and associated repeat procedures will be obtained from local histopathology reports and screening data.

- Outcomes of procedures (further assessments within the screening programme e.g. surveillance) will be collected from routinely collected screening datasets.

- Types of all polyps detected at surveillance procedures will be obtained from local histopathology reports and routinely collected screening datasets.

- Cancers and deaths will be obtained from routinely collected health datasets.

5.5 Aims of the Process Evaluation

Training in chromocolonoscopy is a potential contributing factor to the success of the intervention and future implementation. We will therefore conduct a process evaluation within the CONSCOP2 trial that particularly focusses primarily on training for the intervention. It will also explore barriers and facilitators to chromocolonoscopy and inter-observer effects of pathologists as these may affect training and future implementation. We will specifically address the following questions:

1. What was the dose (how much training was accessed online and the pattern of access e.g. all in one session or repeat visits etc) and reach (how many took part) of the training?
2. Was there a learning effect for ability to detect advanced significant polyps during the time of the trial?
3. Was there variation and correlation in the training accessed and the outcomes for SSL detection between individuals?
4. Did detection rates vary by prior experience of chromocolonoscopy?
5. What did the screening colonoscopists think were the benefits and shortcomings of the training?
6. What did the screening colonoscopists think were the barriers and facilitators to implementing chromocolonoscopy?
7. What was the inter-observer variability among the pathology reports from the local pathologists and central review panel?

Further information regarding the process evaluation can be found in section 25.

6 Trial design and setting

This is a multicentre, open-label, individually randomised (1:1) controlled trial of standard (High Definition White light - HDWL) versus HDWL + additional chromocolonoscopy. CONSCOP2 will recruit 2652 participants from ~20 centres in England, Wales and Scotland attending index colonoscopies within the bowel screening programme and will follow them up through routinely collected data systems. Recruitment will take place over a 2-year period and the last trial intervention will occur when the last patient has their index colonoscopy. Data about index colonoscopies will be collected on CRFs and from routinely collected health datasets within the NHS. Longer term follow-up of participants will continue for 3 years using routinely collected data.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This also includes an assessment of the risk of the COVID-19 pandemic on the study as well as individuals participating in it. This risk assessment has been completed in accordance with the MRC/DH Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed
- How the risk of SARS COV2 infection will be minimised/managed

This trial has been categorised as a low risk, where the level of risk is comparable to the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

This trial will be carried out at participating sites within Wales, England and Scotland. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the CONSCOP2@Cardiff.ac.uk trial email account (see contact details on page 4):

- The approval letter from the site's R&D Department, following submission of the Local Information Pack
- Favourable opinion of host care organisation/PI from Main Ethics committee
- A signed Trial Agreement
- Current Curriculum Vitae of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial supplies and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by attendance at site or by teleconference/Videoconference if attendance of key personnel is unfeasible. All site research nurses or SSPs and colonoscopists must have attended site initiation training.

8 Participant selection

Participants are eligible for the trial if they meet all the following inclusion criteria (Section 8.1) and none of the exclusion criteria apply (Section 8.2). All queries about participant eligibility should be directed to the Trial Manager before randomisation. Any queries will be raised with the CI or one of the clinical Co-Investigators in the CI's absence.

The SSP/Research Nurse should identify eligible patients prior to ringing patients to conduct the telephone assessment Clinic to discuss their colonoscopy (Wales), pre-assessment clinic to assess fitness for colonoscopy (England) or an appointment to offer colonoscopy (Scotland).

8.1 Inclusion criteria

Patients meeting the following criteria may be included in the trial:

1. All participants testing positive on faecal immunochemical test (FIT) in the screening program who are eligible and appropriate for an index screening colonoscopy will be offered participation in the study.
2. The patient has provided written informed consent.

8.2 Exclusion criteria

If any of the following criteria apply, patients cannot be included in the trial:

1. Any participants not deemed fit for colonoscopy on the screening program or undergoing alternative investigation such as CT pneumocolon or minimal prep CT scan as their index procedure instead.
2. Participants who have undergone previous resectional colorectal surgery will be excluded from the study though their standard management in the screening program will continue unchanged. Non colorectal abdomino-pelvic surgery is not an exclusion provided they are considered feasible to undergo colonoscopy
3. Anyone with a known allergy to a food colouring agent.

9 Recruitment, Screening and registration

9.1 Participant identification

In Wales, patients testing positive on the FIT test are invited to a colonoscopy at a Telephone Assessment Clinic. In Scotland, patients testing positive on the FIT are invited to a telephone assessment to assess fitness for colonoscopy. In England, patients testing positive on the FIT test are invited to a physical pre-assessment clinic to assess fitness for colonoscopy. SSPs/RN should ensure that they are fully protected with PPE as per National and local organisational infection prevention and control guidance before conducting any face to face clinical assessments.

During the respective physical clinic/virtual appointment, the SSP will undertake the pre-assessment and book the participant in for colonoscopy as part of standard practice. They will then ask the participant if they would be happy to speak to a nurse who is trained in the research trial who will describe the study to the patient and tell the patient that they will be sent more information about the study (the CONSCOP2 Patient Information Sheet (PIS)) through the post along with two consent forms:

- the standard colonoscopy consent form
- and the CONSCOP2 informed consent form.

The patient should be asked to bring these to their colonoscopy appointment. A contact number for someone at the site will be on the PIS should the patient wish to discuss any aspect of the trial.

9.2 Screening logs

A screening log of all patients assessed for eligibility will be kept at each site so that consent rates can be monitored and any problems with the eligibility criteria can be found. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the CONSCOP2@cardiff.ac.uk every month (see section 22 and 23 for further detail on data monitoring/quality assurance).

9.3 Recruitment rates

A total of 2652 participants will be recruited at an average rate of 110 per month.

9.4 Informed consent

On the day of the procedure after booking at the reception desk, patients will be taken to the admissions bay as usual. Routine admissions procedures for the patient will be followed as per BSG and JAG guidance for processes prior to endoscopic procedures in the unit. The patient will then be seen by the SSP/Research Nurse to confirm that they are happy to participate in the trial and written consent forms will be collected in accordance with the principles of GCP**.** They should sign just the standard colonoscopy consent form if they do not wish to participate in the trial. If they do wish to participate in the trial, then they must also sign the CONSCOP2 consent form. Once consent has been obtained, the patient can be randomised (see section 9.5).

The participant's written informed consent must be obtained using the CONSCOP2 Consent Form, which follows the Participant Information Sheet. The participant will be given sufficient time after the initial invitation to participate before being asked to sign the Consent Form. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. Consent may be taken by a member of the clinical staff at each site (SSP, Research Nurse or consultant) as long as this has been recorded on the Site Delegation Log (see section 7). The consent form includes mandatory permission to follow up the health of patients using routinely collected NHS data for the purposes of the trial research objectives and related ancillary research. To allow this, consent is requested to collect patient identifiers (BSN/NHS/CHI number, date of birth, name) at Cardiff University where they will be held securely. Optional consent will also be sought to bank the routinely collected polyps for future not-for-profit (including genetic) research but all samples will be anonymised. Please note, only when written informed consent has been obtained from the participant and they have been randomised into the trial can they be considered a trial participant.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her/their further treatment.

One copy of the CONSCOP2 informed consent form should be given to the participant but the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes.

9.5 Randomisation

This is a randomised controlled trial therefore neither the participants nor their physicians will be able to choose the participant's colonoscopy method. The method will be allocated randomly (1:1) using a centralised computer-based algorithm (using minimisation stratified by centre with an 80:20 random element). This is to ensure that the groups of participants receiving each of the different methods are similar.

The site must confirm the eligibility of a patient in the patient's medical notes prior to randomisation.

On the day of a colonoscopy, after informed consent is obtained, a member of staff delegated to do so should randomise the patient to either an enhanced or non-enhanced colonoscopy. This can be done either by internet , e-mail or by telephone

Randomisation	
Internet (Anytime):	https://conscop2.ctr.cardiff.ac.uk
If there is an emergency or an issue with randomisation and you need to contact a member of the team please telephone (Mon – Fri, 9am-5pm):	
Telephone (Mon-Fri 9am – 5pm) :	02920 687950 or 02920 687542 (if internet unavailable)
E-mail (Mon-Fri):	CONSCOP2@cardiff.ac.uk

Please consult the additional "CONSCOP2 Trial Randomisation Service User Guide" document for detailed instructions as to how to do this.

Once randomisation is complete, the SSP/Research Nurse should enter the trial number that they are given by the central system onto a label on the patient's notes.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

In consenting to the trial, participants are consenting to trial investigations, trial follow-up and data collection. Participants may withdraw from the trial at any time. All withdrawal forms should be emailed to CONSCOP2@cardiff.ac.uk

Patients may:

Level 1: Withdraw of consent to use samples in future research.

Level 2: Completely withdraw from the trial – participants withdraw permission for longer term follow-up and use of samples in future research.

Withdrawal for any reason requires a completed CONSCOP2 Withdrawal CRF to be faxed to the CTR with the hard copy to follow soon after. Participants do not have to give a reason for their withdrawal but sites should make a reasonable attempt to find out why.

Data and samples collected prior to any participant withdrawal will be collected and used for trial analysis by the CTR.

Patients who withdraw consent prior to the initial colonoscopy should be completely withdrawn from the trial.

11 Trial Intervention

All participants will undergo a routine colonoscopy test as part of the UK bowel screening programmes. An approved Screening Colonoscopist who has satisfied the training requirements to carry out colorectal cancer screening on a designated bowel cancer screening endoscopy list will carry out the colonoscopic procedure. During the endoscopy test, titrated sedation and analgesia in the form of a benzodiazepine (midazolam) and or an opioid analgesic (Pethidine, fentanyl) and or Nitrous Oxide inhalational gas are offered to the participant as and if considered appropriate by standard clinical criteria as per standard practice. The nurse present in the endoscopy room then monitors the participants' physiological parameters and comfort scores closely during the course of the procedure. During the procedure, antispasmodic agents may be given if there is no contraindication. In addition to endoscopy nurses, every colonoscopy list has an SSP and or research nurse who is present in the room and will collect data about the procedure. All procedure and trial related processes within the

endoscopy units and procedure rooms will follow Infection prevention and control guidance as per local and national guidelines including those where appropriate on social and physical distancing and to minimise any risk of infection.. If there are any polyps detected then they will be removed in the standard manner. The process described above is standard practice in the UK bowel screening programmes.

11.1 Trial Arm A: Colonoscopy without enhanced dye

Participants will undergo colonoscopy as per standard procedure described above.

11.2 Trial Arm B: Colonoscopy with enhanced dye

For eligible participants who are randomised to the dye-enhanced colonoscopy group, standard procedure described above will be followed. In addition to this, once the caecum is reached a contrast dye (indigo carmine) will be sprayed on the surface of the right colon either using a spray pump or spray catheter through the colonoscope on withdrawal. This will require specific training (to be provided by the Research Team to the local colonoscopists and SSPs) to ensure standardisation of technique of spraying the dye as well as recognise appearances of adenomas and serrated polyps under indigo carmine dye. The standard colonoscopy procedure takes on average 30 minutes with the enhanced procedure estimated to take an extra average of 6 minutes based on robust trial data from CONSCOP1. Overall procedure times may vary depending on therapy being required for polyp removal.

Indigo carmine is a blue contrast dye that pools between the mucosal projections and highlights topography and surface morphology on polyps and it does not stain cells. It is a safe food colouring agent (Food standards agency-EU approved additive E number: E132) and is already used routinely in various endoscopy procedures in standard clinical practice. There are no known interactions of any medicinal products with Indigo carmine. Anyone with a known allergy to a food colouring agent will be excluded. Supply of dye to sites will be organised by the CONSCOP2 Trial Manager.

11.3 Compliance

Colonoscopists undertaking screening in this cohort are all accredited and some will have previous experience of pan-colonic dye spray use in the context of chronic inflammatory bowel disease and Lynch syndrome. We will ensure that all participating colonoscopists attend an online training event

including quizzes of images and video prior to and after the training, access to an online training resource for reference, as well as lectures and video tutorials on technique and lesion detection with and without indigo carmine dye spray. We will also include training on the PARIS classification, Kudo classification and lesion characterisation with virtual and dye based chromocolonoscopy.

For participants allocated to the chromocolonoscopy arm with inadequate bowel preparation on the day, dye will be used at the subsequent adequately prepared colonoscopy, otherwise repeat procedures will use high definition white light colonoscopy. Colonoscopists are allowed to use the irrigation pump with water for washing colonic mucosa without any restriction in both trial arms.

12 Trial procedures

The only trial procedure, the colonoscopy, occurs at the routine index colonoscopy visit. All assessments are conducted routinely.

12.1 Assessments

CRF data collection

On the day of the index colonoscopy (or, if inadequate bowel preparation, the first subsequent repeat procedure with adequate bowel preparation), the CONSCOP2 eCRF should be completed. Other than the height and weight measurements, no additional assessments above routine are required but the CRF will collect data items not routinely collected e.g. aspirin use, family history of bowel cancer, and whether or not the patient has given the optional consent to polyp sample collection.

12.2 Follow-up

Patients will be followed up in routinely collected data for 3 years after the last patient has their colonoscopy. Data on all colonoscopies conducted on trial participants within the screening programme over this period (including repeats and surveillance) and their outcomes will be collected from sites and associated centralised screening programme databases. At the end of this follow up period data on cancers and deaths in any of the trial participants will be obtained from country specific registries (Wales: Welsh Cancer Intelligence and Surveillance Unit (WCISU); Scotland: Electronic Data Research and Innovation Service (eDRIS); England: Public Health England Office for Data Release (ODR); or equivalents).

Pathology reports and central pathological review

Once per fortnight the research team will send a list of patients to the site for whom they require a copy of any pathology reports associated with screening colonoscopies or associated repeats for clearance (see section 16.2).

Clinical members of the central research team will review local pathology reports associated with all colonoscopies. They will record details (size, location, morphology) of all polyps found into the central research database at Cardiff University.

For the index colonoscopy (or first repeat with adequate bowel preparation) only, the central study team will liaise with the local team to ensure that all relevant slides from polyps detected are scanned onto the central secure pathology slide server for expert pathology review and where this is not feasible then slides/blocks from polyps found at the splenic flexure or above in all trial participants will be requested directly by letter to the appropriate local pathology department for central review by an expert panel of at least three independent expert pathologists within the UK NHS. The letter will give instructions as to where to send the requested paraffin blocks and the trial team will liaise with sites to facilitate their transfer and subsequent return. The expert panel will review all slides independently blinded to the original report. Cases without diagnostic agreement will be re-reviewed by all three pathologists to reach a consensus diagnosis.

13 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and safety specialist email to CTR-safety@Cardiff.ac.uk unless the SAE is specified as not requiring immediate reporting (see section 13.2).

13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with their involvement in the study.

Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued use of a trial intervention would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

Only adverse events occurring within 30 days of the index colonoscopy (or, if inadequate bowel preparation, the first repeat procedure with adequate bowel preparation) should be reported. We will ask local teams and research nurses to monitor their participant re-admissions within 30 days for those in the study aligned to existing local governance arrangements.

13.3 Causality

Causal relationship will be assessed for the intervention and procedures:

Intervention: Indigo carmine dye **Procedures:** Colonoscopy, polyp removal

The Principal Investigator (or another delegated medically qualified doctor from the trial team) will assess each SAE to determine the causal relationship and the Chief Investigator (or another appropriately qualified member of the Trial Management Group) can also provide this assessment where necessary:

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the intervention?**
Unrelated	There is no evidence of any causal relationship with the intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the protocol is considered unexpected.

The list below provides the expected adverse reactions associated with the colonoscopy procedure:

- Abdominal Pain
- Heavy bleeding (including from polyp removal) requiring unexpected admission, surgery or transfusion
- Perforation of bowel requiring unexpected admission, surgery or transfusion
- Allergy to dye
- Hyperventilation
- Vasovagal episode
- Anxiety

13.5 Reporting procedures

13.5.1 Participating Site Responsibilities

The PI (or delegated appropriately qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, partial date of birth (mm/yy) and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number: 0203 043 2376
A fax number is available if you are unable to email an SAE form.

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 30 days after the participant has their colonoscopy.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 16.

13.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

For all non-CTIMP studies, including clinical investigations of medical devices, only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC. These should be sent within 15 days of the chief investigator becoming aware of the event. Reports of related and unexpected SAEs in double-blind trials should be unblinded. There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

13.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Randomisation

Randomisation will take place on a secure online service (see section 9.5) or centrally at the CTR by e-mailing the trial team (see section 9.5). Participants will be randomised using minimisation stratified by centre (with 80:20 random element maintained). Randomisation will have an allocation ratio of 1:1.

14.2 Sample size

To have 90% power to detect an odds ratio of 2.81 in the detection rate of proximal advanced SL (increasing from 0.8% and 2.4% in favour of chromocolonoscopy) at a two-sided 5% significance level would require 2652 patients randomised 1:1. To consent this number we anticipate that 3315 eligible patients will need to be invited to participate (>80% consent rate in CONSCOP). This odds ratio was found in the CONSCOP feasibility study and is considered to be clinically meaningful. [16]

For Stage 2, based on current estimates of those who are beyond the screening programme age limit of 74 years and of drop outs we estimate that we will follow up 930 (~35%) patients at surveillance visits up to 3 years. Based on simulated data from CONSCOP we predict this would allow us to estimate the proportion of significant polyps missed or additionally detected under various alternative

surveillance strategies (that incorporate lifestyle factors) with a standard error of at most 0.15. Again, this is a conservative estimate given that the uptake and sensitivity of screening will increase with the introduction of FIT across the UK.

14.3 Missing, unused & spurious data

We do not expect missing data for the primary outcome and there will be no data imputation for missing data in the primary endpoint. Imputation methods for missing data in the secondary endpoints will be fully documented in the SAP.

14.4 Procedures for reporting deviation(s) from the original SAP

Any deviation(s) from the final statistical plan will be described and justification given in the final report.

14.5 Termination of the trial

After Stage 1, following review of the primary analysis by the IDMC/TSC, if no significant difference is seen in the primary endpoint then the trial will stopped and will not proceed to Stage 2.

15 Analysis

15.1 Stage 1

At the end of stage 1 (when patients have all been followed up for 1 year to collect data on repeat procedures), the following analyses will be conducted:

Primary analysis

All randomised patients will be included in an intention-to-treat (ITT) analysis using logistic regression to calculate odds ratios for the trial arm effect on proximal advanced SL detection rates with the operator as a random effect.

Secondary analyses

Multivariable sensitivity analyses (both proximal and overall) will include important prognostic variables (smoking, obesity, sex, family history of cancer, aspirin use), as well as centre as a random

effect, using multilevel mixed-effects logistic regression. Additionally, operator will be used as a random effect in a further sensitivity analyses if available.

ITT logistic regression will also be used to compare detection rates, both proximal and overall, of advanced neoplasia, SLs, and advanced adenomas including important prognostic variables (smoking, obesity, sex, family history of cancer, aspirin use), as well as screening centre as a random effect.

The primary analysis will also be conducted in subgroups of different FIT thresholds.

15.2 Stage 2

Follow up of participants through routinely collected data will be conducted 3 years after the last patient is recruited to collect data on cancer and death rates, surveillance colonoscopy outcomes, and polyps retrieved.

During the first CONSCOP study, a health economics evaluation was conducted, focussing primarily on the per procedure cost of a chromocolonoscopy procedure vs standard. Here, a health economic evaluation of the longer-term impact of the intervention on surveillance outcome will be conducted. Should the Stage 1 analyses show the intervention to be effective at detecting proximal advanced SLs, then - under current guidelines - significantly more surveillance colonoscopies would be expected. Mathematical models (MiMiC-Bowel) developed at ScHARR (School of Health and Related Research, University of Sheffield), enhanced by estimates from the data analyses in Stage 2, will explore the likely cost-effectiveness of rolling out chromocolonoscopy under the current surveillance guidelines, the likely downstream cancer and advanced polyp detection rates, as well as possible revised thresholds and surveillance intervals for undertaking surveillance, some of which will include stratification on risk factors. The model takes an NHS perspective and enables predictions of the lifetime impact of different screening and surveillance strategies on resource use, cancer incidence, cancer mortality and QALYs. The model includes both phenotypic (e.g. age, lifestyle) and genomic individual level characteristics. The model represents colonoscopy using the following parameters: sensitivity to precancerous conditions (currently subdivided as low or high risk adenomas), sensitivity to CRC, completion rate, compliance with invitation to colonoscopy, cost of colonoscopy. To represent chromocolonoscopy within the economic model, data on the cost of the procedure and the differential detection rates for precancerous conditions (specifically serrated lesions) findings from Stage 1 will be used. MiMiC-Bowel will be further developed to represent different characteristics of precancerous conditions and specifically to include the serrated polyp pathway. This will be achieved by undertaking a review to obtain the best available data on serrated polyp prevalence and progression rates. MiMiC-

Bowel will be used to predict the long-term economic impact of replacing standard colonoscopy with chromocolonoscopy in the screening programme. Predicted outcomes will include – cancer cases prevented, changes in stage at diagnosis, reduction in CRC mortality. Prediction for surveillance outcomes will also be generated such as: number of first surveillance procedures required, number of second surveillance procedures required, number of surveillance interval cancers, etc. The second step of the economic analyses will be to validate the model predictions via comparison to both the 3 year surveillance data collected in Stage 2 as well as longer term (5-6 year) follow up of surveillance of ~750 patients in the original CONSCOP feasibility trial. If required, the model may be further refined following validation and new predictions generated.

Currently the surveillance algorithm used in the UK bowel screening programmes uses the number, size and histo-pathology of adenomas detected at index procedures to allocate a patient to have a further colonoscopy in 3 years or be returned to routine recall. It is anticipated that in the future surveillance could be determined based on an individual predicted risk of CRC in the next 5/10 years. A risk model for future CRC risk will in addition utilise demographic, lifestyle, genomic and screening/surveillance history. The data produced by this and the first CONSCOP feasibility trial will provide a unique, large, high quality dataset to inform the development of this model. Critical elements not available in other datasets include aspirin use, chromocolonoscopy use, and serrated polyp characteristics. Using parametric regression models, we will use the Stage 1 data to estimate the functional form and strength of the impact of baseline characteristics, such as smoking status, BMI, aspirin use etc, on the findings from both index and follow-up colonoscopies, as well as on the outcomes of CRC incidence, stage at diagnosis, and mortality. This will then allow us to proceed with Stage 2, in which we will build a mathematical model, to investigate how CRC incidence (and mortality), as well as the total number of follow-up colonoscopies performed, might hypothetically be changed by altering the protocol through which surveillance frequency is decided. In particular, we will investigate the cost-benefit implications of making them dependent on colonoscopy quality, patient and polyp characteristics, as well as changing the way in which surveillance depends on the outcomes of the index colonoscopy. In a second step, we will consider not simply changing how patients are allocated to the 36m-surveillance groups based on their personal characteristics and index colonoscopy findings, but also consider other options, such as 48m- or 60m-surveillance, which will require the incorporation of mathematical models for polyp formation/detection into ours. Since these will be based on assumptions, we will investigate the robustness of our conclusions to departures from these assumptions by varying them within reasonable ranges. All of the above will be done both under the assumption that all colonoscopies are performed using standard colonoscopy

and under the assumption that all colonoscopies are performed using chromocolonoscopy in order to evaluate the differential (and, we hypothesise, superior) cost-benefit implications that could be achieved under the roll-out of chromocolonoscopy as opposed to standard. This will also involve subtle assumptions for the translation of findings from index to follow-up colonoscopies, the sensitivity to which we shall investigate, since in Stage 2, none of the follow-up colonoscopies are performed by chromocolonoscopy. Throughout, we will use the mathematical model to propagate all statistical uncertainty from our Stage 1 estimates into our uncertainty when comparing hypothetical scenarios in Stage 2. By this we mean that parameter values informed by Stage 1 will be repeatedly drawn from their derived sampling distributions in each new Monte Carlo run of the Stage 2 model, leading to a range of plausible answers to each of our "what if" questions at Stage 2.

16 Data Management

16.1 Source data

Trial data	Source Data					
	CRF	Routinely collected screening database	Site file	Pathology report	SAE form	Cancer/death routine datasets
Informed consent			**X**			
Demographic data	**X**	**X**				
Colonoscopy outcomes	**X**	**X**				
Polyps removed		**X**		**X**		
Cancer/death						**X**
Adverse events					**X**	

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Source data include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised in the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. Sites will retain all original source of data from these investigations for future reference. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant ID, not by name.

16.2 Completion of Electronic CRFs

It is intended that data recording for this trial will be through use of a web-based system. This is a secure encrypted system accessed by an institutional password and complies with General Data Protection Regulation 2016.

Details of how to access the system will be supplied to investigators as part of site set up. A user password will be supplied to investigators upon completion of all processes required prior to opening.

Participating sites will be provided with training and instructions on how to complete and return the CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to answer the data query or correct data on the data clarification form. The CRF pages should not be altered.

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be scanned to CONSCOP2@Cardiff.ac.uk and returned to the CTR and a copy retained at the site along with the participants' CRFs.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

Scanning Pathology Reports

Please scan and e-mail a copy of all pathology reports to CONSCOP2@cardiff.ac.uk. Please redact any patient identifier information from the reports so that only the allocated patient CONSCOP2 trial number is included.

17 Translational research or sub trial

Sample collection for future research

We will obtain consent from patients to use their routinely collected tissue samples and images/video in future research.

Site visits by the principal investigator to improve recruitment in a multicentre randomized trial

We will randomise sites to either be visited by the Chief Investigator and/or Clinical Research Fellow part way through recruitment to discuss the trial in order to assess impact on recruitment. All required outcome data would already be collected through screening logs.

Face to face vs telephone screening

This will be investigated in a non-randomised study. Scotland and Wales have telephone pre-assessments with people testing positive with FIT in the screening programmes whereas England has face-to-face pre-assessments. It will be at these pre-assessments that the study is first mentioned (although informed consent will be taken on the day of the colonoscopy). Because we are collecting detailed screening data (see section 8 on project management) we will be able to compare consent rates across these different pre-assessment modalities. We will be able to this study as part of our monitoring of recruitment at no extra cost.

Effect of type of recruiting clinician/nurse on consent rates

In the screening data that we ask sites to collect, we will identify the staff type who screened and consented the participants (either general colorectal nurse, specialist screening practitioner, or research nurse). This will give us, albeit non-randomised, data to assess the rates of identifying and consenting participants for each staff type that can be used to guide both the delivery of this trial and future trials in this patient group. This will be relevant to the NIHR and wider research community in comparing recruitment to trials with designated research nurses as compared to embedding research into existing NHS workforce roles. We will be able to undertake this study as part of our monitoring of recruitment at no extra cost.

18 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it.

19 End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as three years after the last patient has an index colonoscopy.

The Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review by the HRA approval process.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

21.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the Director of the Cancer Division at the Centre for Trials Research.

This includes collection of NHS number (or equivalent), to follow up the health outcomes in routinely collected data within the UK NHS and Departments of Health.

21.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.
- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

21.4 Trial sponsorship

Cardiff University will act as Sponsor for the trial. The Sponsor will be delegating certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

The Sponsor shall be responsible for ensuring that the trial is performed in accordance with the following:

- Conditions and principles of GCP.
- Declaration of Helsinki (1996).
- UK Policy Framework for Health and Social Care Research.

- The General Data Protection Regulation (2016).
- Other regulatory requirements as appropriate.

The Sponsor has delegated the following responsibilities to the CTR and Chief Investigator:

- Obtaining favourable ethics committee opinion and subsequent amendments
- Selection of investigators and ensuring each site has full trial documentation
- Keeping records of all AEs reported by PIs
- Ensuring recording and prompt reporting of SARs to the CI
- Ensuring PIs are informed of SUSARs
- Providing annual listing of all SARs to investigators using the Annual Safety Report, or Investigator Safety Report
- Reporting serious breaches of GCP or trial protocol within 7 days of initial notification
- Having quality assurance systems in place to ensure that the study is conducted according to GCP at all participating sites
- Monitoring of the study

The following responsibilities are delegated to the Principal Investigator at individual participating sites:

- Have in place arrangements to adhere to GCP and the applicable regulatory requirements.
- Have in place arrangements to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions, and maintain a list of appropriately qualified persons to whom the Principal Investigator has delegated significant trial-related duties.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the CTR in the CRFs and in all required reports.
- Keep a copy of all essential documents (as defined in ICH-GCP) and ensure appropriate archiving and destruction once the study has ended.
- Take appropriate urgent safety measures.
- Report urgent safety measures to CTR immediately and no later than 24 hours.

- Report serious breaches of GCP or trial protocol to CTR immediately and no later than 24 hours.

21.5 Funding

The CONSCOP 2 trial is being funded by the HTA and is thus part of the NIHR portfolio of clinical trials.

22 Trial management

22.1 TMG (Trial Management Group)

The Trial Management Group (TMG) will be responsible for the day-to-day running of the trial and will meet initially every month in order to closely manage the study. The TMG members will include the Chief Investigator, Co-investigators, CTR representatives, and specialist advisors.

TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter

22.2 TSC (Trial Steering Committee)

- An independent **Trial Steering Committee** (TSC) which is a committee of independent members that provides overall supervision of the trial. The role of the TSC is to act on behalf of the Sponsor and funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent Chairman. The TSC will decide on continuing or stopping the trial, or modifying the Protocol. It will meet at least annually and will consider the results of other trials and new information which has arisen, and recommend appropriate action.
- TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

22.3 DMC (Data Monitoring Committee)

DMC members will be required to sign up to the remit and conditions as set out in the DMC Charter.

The DMC will be independent of the investigators, funder and Sponsor and will comprise of an independent statistician and at least two other independent experts. DMC members will be required to sign up to the remit and conditions as set out in the DMC Charter.

The DMC will review accruing trial data and assess whether there are any safety issues that need to be addressed, or if there are any reasons to terminate the trial. Reports to the DMC will be prepared and presented by the trial statistician prior to the DMC meeting. The trial statistician may be called in to the DMC meeting to answer questions, and the DMC may request additional reports or information. The DMC Chairperson will report the DMC recommendations to the TSC. The report may also be submitted to the TMG and if required, the REC.

The Committee's terms of reference, roles and responsibilities will be defined in a charter.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the CONSCOP 2 trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan based on experience from CONSCOP1.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

23.2 Audits & inspections

The trial may also be participant to inspection and audit by the Cardiff University under their remit as Sponsor, and the CTR under their delegated duties in managing the trial.

The CI, or PIs and participating sites, will permit audits and REC review, providing direct access to source data and documents.

24 Publication policy

Data from all sites will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the writing committee

and advise on the nature of publications, subject to the Sponsor's requirements. Publication will be according to the publication policy of the CTR and the CONSCOP2 publication plan.

Principles regarding authorship and writing

- All proposals for publications using CONSCOP2 data must be approved by the TMG.
- A lead author and wider writing team will be established for each identified paper.
- All potential contributors will have the opportunity to opt into a writing team.
- It is the responsibility of the Chief Investigator (CI) and Study Lead to ensure balance and inclusivity in writing teams across the range of likely study publications, to ensure everyone is appropriately acknowledged and has the opportunity to be involved as an author.
- It is the responsibility of the CI to decide authorship order, usually in discussion with the lead author and Study Lead.
- All named authors must meet authorship criteria (e.g. see http://www.bmj.com/about-bmj/resources-authors/article-submission/authorship-contributorshipauthorship)).
- Submission of abstracts for conference presentation should be agreed in advance with the TMG. Authors should allow sufficient time for their request to be reviewed. This may be completed via email. However, if there is insufficient time for the TMG to review such a request, the CI can make a decision on behalf of the TMG. The body of the presentation (including posters) should be reviewed by the TMG prior to presentation. This may be completed via email.

25 Process Evaluation

25.1 Trial training

As mentioned in section 11.3, specific training will be provided by the Research Team to all colonoscopists and SSPs to ensure standardisation of technique of spraying the dye as well as recognise appearances of adenomas and serrated polyps under indigo carmine dye. This will take the form of an online training module and webinar for opportunity for interaction and questions.

25.2 Methods

The process evaluation will include the use of logs and reports collected as part of the trial and pre-trial training as well as semi-structured telephone or video interviews with a sub-sample of screening colonoscopists. Within the introduction of the online pre-trial training, , screening colonoscopists will be asked to complete a training session registration form (see Appendix 1). They will be informed that information relating to them will be collected on the, quiz (at the end of the training session) and patient case report forms (CRFs) as part of the trial in order to report on the process of the trial.

25.2.1 Screening colonoscopists logs and quiz

Screening colonoscopists accessing online training will be asked to complete a registration form (Appendix 1) for the session and logs from the online training support will be captured including any interactive components of the training module e.g. in any question and answer content. This will allow us to assess how much training was received and by whom. A short quiz will be given to screening colonoscopists as part of the initial training to assess their knowledge prior to and after the online training. They will also be asked to complete a short online evaluation questionnaire following completion of the training.

Prior experience of chromocolonoscopy for each colonoscopist in the intervention arm will be recorded in order to compare detection rates between those with different levels of experience. Screening colonoscopists will be asked to indicate the years of experience they have of chromocolonoscopy (if any) and type of background (e.g. gastroenterologist, colorectal surgeon, nurse) on a registration form (Appendix 1).

Proximal advanced serrated lesion rates for colonoscopists will be collated and compared between the start and end of study. This will provide information about potential learning effects, i.e.

improvement in detection rates over time both for types of colonoscopy. The screening colonoscopists name will be added to the CRF for each patient, thus noting who undertook the colonoscopy. The SSP or Research Nurse will complete this on the CRF.

25.2.2 Pathology reports

In order to assess the level of inter-observer variability for pathology reports, clinical members of the central research team will review local pathology reports associated with all colonoscopies through routine data collection systems. They will record details (size, location, morphology) of all polyps found into the central research database at Cardiff University.

For the index colonoscopy (or first repeat with adequate bowel preparation) only, all slides/blocks from polyps found at the splenic flexure or above in all trial participants will be requested directly by letter to the appropriate local pathology department for central review by an expert panel of at least three pathologists within the UK NHS. The letter will give instructions as to where to send the requested paraffin blocks or for scanning of slides for secure electronic transfer of images and slide review and the trial team will liaise with sites to facilitate their transfer and subsequent return (in case of physical slide and block transfer). The expert panel will review all slides independently blinded to the original report. Cases without diagnostic agreement will be re-reviewed by all three pathologists to reach a consensus diagnosis.

25.2.3 Interviews with screening colonoscopists

Semi-structured telephone or video interviews with up to twenty screening colonoscopists will be conducted to gain their views on the training and future implementation of chromocolonoscopy within a screening programme. A purposive sample will be used for the interviews to ensure colonoscopists with different backgrounds (gastroenterologists, colorectal surgeons and nurse endoscopists) and varying levels of prior chromocolonoscopy experience are included. Screening colonoscopists will be recruited from six study sites (two from each country with two different size hospitals from each country - large tertiary/teaching hospital or district general/smaller hospital). A consent script will be used at the beginning of the interview and consent will be audio-recorded. The topic guide (Appendix 2) will include the following: experiences of chromocolonoscopy (both before and within the trial), benefits and shortcomings of the training sessions, suggestions for improvements to training, barriers and facilitators to chromocolonoscopy implementation. Interviews will be planned

to take place approximately three to six months after training has been completed. Interviews will be audio-recorded and transcribed verbatim. Following the interview participants will be sent a thank you email (Appendix 4).

25.2.4 Recruitment for interviews

As part of the online training, screening colonoscopists will receive a copy of the interview information sheet asked to indicate whether they would be willing to be contacted to be invited to take part in a research interview. Responses will be used to select screening colonoscopists to be invited. The study invitation pack (consisting of Appendix 3, participant information sheet and consent script) will be emailed to those purposively selected to be invited to confirm their interest. Those who agree to take part will be asked to suggest suitable times for the interview, and an interview will be arranged at a mutually convenient time. A consent script will be used at the beginning of the interview and consent will be audio-recorded.

25.3 Analyses

25.3.1 Training dose and reach

Descriptive statistics will be used to report the usage of the online training support, including duration and timings of access (using the web logs). Descriptive statistics (numbers and percentages) of the professional background (e.g. nurse, gastroenterologist) of training session attendees will also be calculated.

25.3.2 Prior experience and learning effect

Descriptive statistics of the prior experience of colonoscopists will calculated for both any vs. no experience (number and percentage) as well as for length of experience (average, range) for those who have any.

The association between proximal advanced serrated lesion detection rate and prior experience, prior baseline knowledge, use of the online training support, professional background and knowledge (assessed at the end of training) will be assessed using logistic regression.

Proximal advanced serrated lesion detection rates of screening colonoscopists will be calculated three months into the trial (or following their first 20 chromocolonoscopies) and then in the last three months of the trial (or their last 20 chromocolonoscopies). These will be compared using logistic regression.

25.3.3 Inter-observer variability

Kappa statistics will be calculated to assess the inter-observer agreement on polyp pathology and correlation between endoscopist classification and pathology category.

25.3.4 Views on training and implementation

Interviews and responses to the training evaluation questionnaire will be analysed using a framework approach[18]. Following familiarisation of with the transcripts, a thematic framework will be identified consisting of themes (or codes). This framework will then be systematically be applied to each transcript (indexing) and grouped by theme (charting). Finally, the data is interpreted by searching for patterns and seeking explanations.

25.4 Data protection and confidentiality

Cardiff University is the Data Controller for the study. All data collected during the research will be kept strictly confidential. Names, contact details audio-recorded consent and study data provided by participants will be stored securely within Cardiff University (electronically on a secure shared drive, paper-based in a locked cupboard). Data will be pseudonymised using a study identification number.

The audio recordings will be transferred from the digital voice recorder or Cardiff University laptop to the secure university shared drive as digital files. This will be done as soon as possible after each interview has been completed. The digital recordings of the interviews will be sent to a transcription company to be transcribed. A study identification number will be used for the filename, not the participant's name. A data processing agreement will be in place between Cardiff University and the transcription company.

Study data will be stored for 15 years after the study has been completed, in line with Cardiff University retention policy. After this time they will be disposed of.

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Appendix 1 – CONSCOP 2 - Training Session Registration Form.

As part of the CONSCOP-2 trial and training evaluation we would be very grateful if you could provide the following information.

1. Dates of training initiation and completion	
2. Name of hospital or trust	
3. Name	
4. Professional background	
5a. Prior experience of chromocolonoscopy	Yes / No
5b. If yes to 5a, number of years	
6a. Willing to participate in a telephone/video interview for CONSCOP2	Yes / No
6b. If yes to 6a, please provide a contact email address	Email:

Appendix 2 - Interview topic guide

Can you tell me about you experiences of chromocolonoscopy?

Prompts: preference compared with regular colonoscopy, perceptions of skill level, differences before and within the trial (i.e. pre and post training), time to complete, patient comfort.

What do you think the benefits and shortcomings were of the CONSCOP2 chromocolonoscopy training session?

Prompts: perceived effectiveness of training, career/skill development, length of session, follow up, trainer, size of group, quality of training.

Are there any improvements that you think could be made to the training session?

Prompts: relate to shortcomings mentioned, link with speciality training or screening colonoscopist QA, CPD points.

If you used the online training support material, what did you think about it?

Prompts: usage (how many times, how much time spent), content, accessibility, improvements.

Can you tell me about any barriers and facilitators you think there might be with implementing chromocolonoscopy into the screening programme?

Prompts: effectiveness, practicalities (time, dye provision, equipment), patient comfort/satisfaction/willingness, training, trainer (ability, relationship).

Appendix 3 - Invitation cover email

Subject: CONSCOP2 invitation for research telephone/video interview

Dear <name>

Thank you for indicating at the CONSCOP2 training session on your registration form that you are willing to take part in a research telephone or video interview for CONSCOP2. I have attached the information sheet (the same as that you received at the training session) and consent script.

I am contacting you to coordinate a date and time at your convenience in the near future for you to take part in an interview. If you are still willing to take part, please could you suggest some possible dates/time for the interview to take place and let me know whether you would prefer the interview to be conducted via telephone or video.

Many thanks for your help. Your input will be an important part of our assessment of training in chromocolonoscopy if it were implemented more widely across the service.

[named researcher]

Appendix 4 - Thank you email

Subject: CONSCOP2 research telephone/video interview

Dear X

Thank you for taking part in an interview for CONSCOP2. It was very helpful to hear your thoughts about the CONSCOP2 training and future implementation of chromocolonoscopy. We very much appreciate all the time that you gave.

Do feel free to contact me if you have any further questions about the study, and I will be in touch if there is anything that would be helpful to clarify from the interview.

Many thanks

[named researcher]