CONSCOP

CONSCOP - Feasibility of reduction in right sided bowel cancer through CONtrast enhanced colonoSCOPy

A feasibility randomised controlled trial (RCT) of contrast enhanced vs non-enhanced colonoscopy in index bowel cancer screening to reduce bowel cancer mortality

Clinical Trial Protocol

Version: 4.0

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General Information

This protocol describes the CONSCOP 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 patients. 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, but sites entering patients for the first time are advised to contact the Wales Cancer Trials Unit (WCTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to the WCTU.

Compliance

This trial will adhere to the conditions and principles of Good Clinical Practice. It will be conducted in compliance with the protocol, the Declaration of Helsinki (South Africa, 1996), the Research Governance Framework for Health and Social Care (Welsh Assembly Government November 2009 and Department of Health 2nd July 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding

The CONSCOP trial is being funded by National Institute for Social Care and Health Research (NISCHR) Research for Patient and Public Benefit Wales and is thus part of the NISCHR portfolio of clinical trials.

This trial is supported by Cancer Research UK core funding at the WCTU and by the NISCHR Cancer Registered Research Group.

Trial Co-ordination

The CONSCOP trial is being coordinated by the WCTU, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

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

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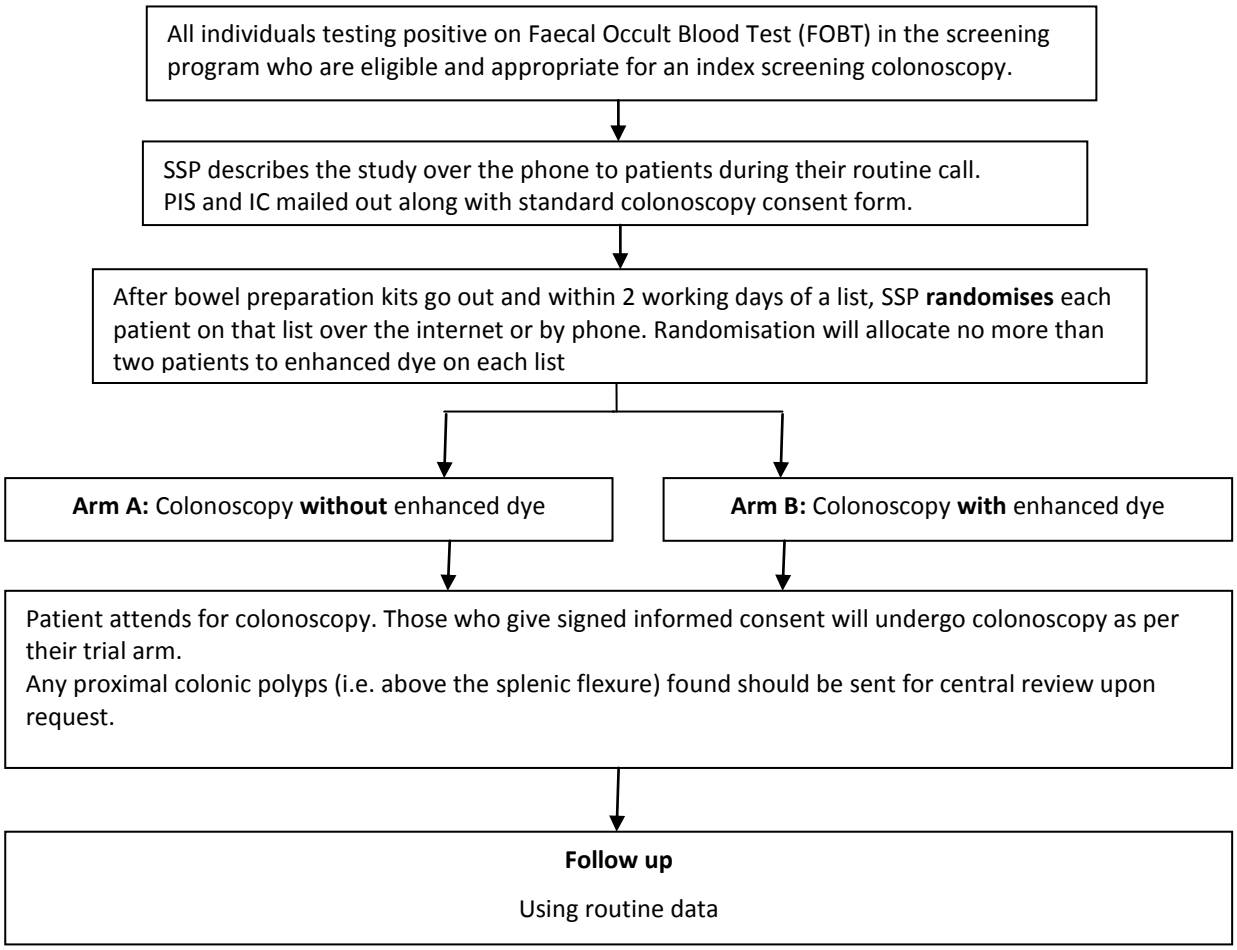
Abbreviations and glossary

AE	Adverse event
AR	Adverse reaction
ASR	Annual Safety Report
BCSP	Bowel Cancer Screening Programme
BSIMS	Bowel Screening Information Management System
BSW	Bowel Screening Wales
CI	Chief Investigator
CRF	Case Report Form
CR-UK	Cancer Research UK
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DH	Department of Health
FOBT	Faecal Occult Blood Test
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
Individual	An individual who may be eligible for the trial but has not yet consented to participate in any trial related activities.
ISF	Investigator Site File
MREC	Main Research Ethics Committee
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	National Health Service
NIHR CSP	National Institute for Health Research Co-ordinated System for Gaining NHS Permission. This system defines and carries out checks that only need to be done once, and those that are required for each NHS location/organisation.
Patient	A patient under care who may be eligible for the trial but has not yet consented to participate in any trial related activities.
Participant	An individual who has given written informed consent and is participating in trial related activities.

PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
Sponsor	The primary organisation that oversees and is legally responsible for the clinical trial.
SSA	Site-Specific Assessment
SSP	Specialist Screening Practitioner
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSF	Trial Site File
UKCRC	United Kingdom Clinical Research Collaboration
WCTU	Wales Cancer Trials Unit

1.0 Trial schema



2.0 Trial synopsis

Study title:	Feasibility of reduction in Right Sided Bowel cancer through Contrast enhanced Colonoscopy				
Study acronym:	CONSCOP				
Short title:	A feasibility randomised controlled trial (RCT) of contrast enhanced vs non-enhanced colonoscopy in index bowel cancer screening to reduce bowel cancer mortality				
ClinicalTrials.gov No:	NCT01972451				
Funder:	NISCHR	Funder's No:	RfPPB –1021		
Chief Investigator:	Sunil Dolwani				
Sponsor:	Cardiff University	Sponsor No:	**SPON 1325-14**		
Study period:	2 years	Phase: Feasibility	Feasibility	Number of arms:	2
Number of participants:	1320				
Investigational Medicinal Products(s) (IMP)	None				

Objectives

1. To assess whether enough participants can be recruited into the study (uptake by both participants and screeners) to suggest that it is feasible to run a future, larger scale trial investigating the impact of enhanced colonoscopy on polyp detection and rate of interval cancer detection on follow up.
2. To assess whether the enhanced colonoscopy takes an acceptable length of additional time to conduct
3. To estimate the proximal serrated polyp detection rate in the intervention arm to inform the sample size calculation of a future trial by allowing an assessment of the possible magnitude of improvement in cancer detection
4. To estimate the proportion of samples that are able to be collected as per protocol to inform the design of the translational element of the future trial
5. To assess the feasibility of incorporating an economic evaluation into a larger scale trial by exploring issues relating to collection of data on resource utilization, costs and outcome measures.

Main inclusion criteria:

1. All participants testing positive on Faecal Occult Blood Test (FOBT) in the screening program who are eligible and appropriate for an index screening colonoscopy will be offered participation in the study.
2. Written informed consent

See Section 6.1 for full inclusion criteria.
Main exclusion criteria: 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 colorectal surgery will be excluded from the study though their standard management in the screening program will continue unchanged. 3. Anyone with a known allergy to a food colouring agent. 4. Previous inclusion in the trial See Section 6.2 for full exclusion criteria.
Interventions: Arm A: Colonoscopy without enhanced dye Arm B: Colonoscopy with enhanced dye
Trial assessments: At colonoscopy data will be collected on the procedure logistics (time, completion, resource utilisation), associated adverse events, results and patient comfort (see section 9). Additionally, after local reporting, all proximal colonic polyps (i.e. above the splenic flexure) should be sent for central analysis (see section 13)
Endpoints: • Proportion of screening service providers who agree to participate in the trial • Proportion of eligible patients who give consent. • Procedure time • Colonoscopy completion rate • Proximal serrated polyps detection rate • Proportion of proximal polyp samples that are able to be collected as per protocol • Resource utilisation: staff time, consumables used during the procedures, use of sedation and other agents to improve patient comfort. • Adverse events • Patient comfort scores

2.1 Lay summary

Colorectal cancer is the second leading cause of cancer deaths in the UK (1). The Bowel Cancer Screening Programme (BCSP) was implemented to reduce deaths by the early prevention and detection of bowel cancer. Results from the first few years of screening and previous smaller studies show that while in its current form it will save many lives, there continue to be polyps and cancers in the right side of the colon that may be difficult to detect. There is some evidence that these types of polyps (serrated polyps) may be at least partly responsible for cancers missed at the initial colonoscopy and have a faster rate of growth to cancer compared to conventional polyps (adenomas).

We propose to examine participants undergoing screening colonoscopy with the addition of a contrast dye (a safe food colouring agent base already used in various bowel camera procedures in standard clinical practice). This has been shown to improve detection of conventional polyps significantly (2) and only takes a few more minutes of extra time. The study is a randomised controlled feasibility study comparing two groups, with and without use of dye spray throughout the right colon. Our primary aim is to study the feasibility of undertaking these procedures (i.e. assessment of acceptability by participants and colonoscopists, including time and costs involved in undertaking the enhanced approach). In addition to this we will also be assessing whether this technique helps to improve the detection rates of right-sided polyps in order to inform the sample size for a larger study. Removal of these polyps will enable further laboratory analysis of a collection of polyp samples in order to assess if such a sample collection might be able to answer the question of biological behaviour and growth pattern to cancer in a larger subsequent study within the BCSP. This will help to inform further studies to assess the impact of improved detection and potentially reduced incidence of interval or missed bowel cancers in longer term follow up.

We aim to recruit 1320 participants (660 per group) over a 12-month period involving all participating bowel cancer screening centres in Wales. All eligible participants (eligibility confirmed by SSP) undertaking the BCSP will be invited to the study and participant randomisation will be performed centrally. The data collected by the BCSP nurse will include all the performance parameters already undertaken as part of the BCSP.

3.0 Background, rationale and objectives

Background

Bowel cancer screening started in 2006 in the UK subsequent to evidence from large-scale randomized trials on stool based faecal occult blood testing followed by colonoscopy for those individuals testing positive (3-6). This strategy has clearly been proven to reduce mortality from bowel cancer by 15% (6). Although colonoscopic prevention of colorectal cancer (CRC) through removal of pre-malignant polyps and earlier detection of cancer has proven to be generally safe as well as effective, its effectiveness seems to be variable and somewhat limited in the proximal colon (7, 8). Some studies have cast doubt over the effectiveness of colonoscopy at reducing the incidence and mortality of proximal bowel cancer (7, 9), as relatively high incidence rates of these cancers are found after colonoscopy, referred to as interval cancers (10). Reported incidence rates of interval cancers vary greatly, ranging from 1 in 130 to 1 in 1,000 colonoscopies, or 1 out of 13 to 1 out 45 of all diagnosed CRCs (8, 11).

The incidence of these interval cancers is therefore significant and it may also falsely reassure screened individuals. Two types of factors may contribute to the occurrence of interval CRCs, namely technical, endoscopist dependent factors possibly due to the quality of the procedure and biology dependent factors i.e. potentially due to different morphology and rate of growth of these right-sided polyps (12, 13). Overall, the exact contribution of each of these factors remains largely unknown though it would seem logical to minimize any operator or procedure dependent factors in order to achieve the best outcome and yield from colonoscopy.

Current evidence on right side or proximal colonic polyps found at colonoscopy is mostly based on relatively small retrospective studies partly responsible for the variation in incidence of these. Some studies have suggested that these right-sided polyps are more likely to be “Flat” or non-polypoid in morphology thus making them more difficult to detect (14, 15). Other studies have suggested that right sided polyps are more likely to be serrated polyps as compared to those in the left or distal colon and that they follow an accelerated different pathway to colorectal cancer as compared to the conventional adenomas following the traditional adenoma carcinoma sequence (16). The current available evidence on serrated polyps in the right colon, their natural history, pathways of progression to colorectal cancer and difficulties with detection are all based on relatively small retrospective studies with wide variation in incidence and prevalence of these (17). They are thought to account for a significant proportion of missed or interval colorectal cancers (18). Unlike conventional colonic adenoma surveillance, the appropriate surveillance interval for these serrated polyps is uncertain due to the paucity of accurate data on their detection rates and contribution to cancer and are again based on small retrospective studies and consensus recommendations with a relatively low evidence base (10, 17).

The technique of contrast enhanced colonoscopy with the use of dye spray has been investigated in numerous studies in different settings and in almost all studies has been demonstrated to increase polyp detection rates (19-23). In contrast, newer methods of digital contrast enhancement though very promising and of help in morphological characterization of polyps and cancers have failed to conclusively demonstrate a significant increase in polyp detection rates when controlled for other variables (24). Digital contrast enhancement technology also varies between commercial products for colonoscopy unlike the dye spray technique that is universally applicable. A Cochrane review on the topic of contrast enhanced colonoscopy has also analysed studies using the dye spray technique though not in the setting of screening and found a positive correlation between polyps detected and use of the technique (21). Pan colonic dye spray during colonoscopy already forms part of standard

practice in other settings such as colonoscopic surveillance for neoplasia detection in high risk cases of inflammatory bowel disease and is part of national guidelines (25) in that setting.

Various studies have demonstrated that there are a number of variables that potentially affect adenoma, polyp and cancer detection rates such as quality of bowel preparation, training and experience of the Colonoscopist, various factors related to technique as well as others including those mentioned above. The bowel cancer-screening program provides the appropriate setting to therefore investigate the research question with the best current standardization of these variables. Colonoscopists in England & Wales have to undergo a rigorous assessment and accreditation process in order to achieve a high quality minimum standard and minimum standard criteria such as adenoma detection rates, withdrawal times etc. that are monitored (26). Patient related outcomes including comfort scores, lesions detected and plans and outcomes of management of these are also strictly monitored. It would therefore seem logical to integrate this very clinical and patient focused research question with the health service as it potentially provides an accurate assessment of impact as well as route to improve the service provided to screened individuals and possible reduction in the incidence of interval cancers. The outcomes would still be applicable to colonoscopy even outside the setting of screening and would thus have a wider impact. It is therefore important particularly in the context of the screening program to assess the feasibility of this change in colonoscopic technique through dye spray being acceptable in the first instance to participants, colonoscopists and the program and NHS.

Prior to committing resource to any intervention to potentially reduce interval cancers it seems sensible to analyse and justify the clinical and cost effectiveness of the approach if appropriate. If the intervention is deemed feasible (and we outline the specific criteria for this in the application) then a larger longer-term study would be justified to answer the question of outcomes with regard to interval cancer detection and also appropriate surveillance for serrated polyps that do not follow the same pathway to cancer as conventional adenomas. This study aims to test the feasibility of undertaking such an intervention within the setting of the BCSP in Wales in order to inform the above.

Research Question

Is it feasible and acceptable to participants, professionals and the screening program to undertake an enhanced colonoscopy technique during screening and is the time taken and resource needed for this likely to be considered feasible and acceptable by organisations in charge of screening?

Specific Objectives

1. To assess whether enough patients can be recruited into the study to suggest that it is feasible to run a future, larger scale trial investigating the impact of enhanced colonoscopy on cancer detection

2. To assess whether the enhanced colonoscopy takes an acceptable length of additional time to conduct

3. To estimate the proximal serrated polyp detection rate in the intervention arm to inform the sample size calculation of the future trial by allowing assessment of the possible magnitude of improvement in cancer detection

4. To estimate the proportion of samples that are able to be collected as per protocol to inform the design of the translational element of the future trial

5. To assess the feasibility of incorporating an economic evaluation into a larger scale trial by exploring issues relating to collection of data relating to resource utilization, costs and outcome measures.

4.0 Study design

A feasibility randomised open controlled trial (RCT) of contrast enhanced vs non-enhanced colonscopy in index bowel cancer screening to reduce bowel cancer mortality. The data obtained in this study will enable the assessment of the feasibility and design of a future RCT that will be powered to look for a reduction in bowel cancer mortality.

4.1 Risk assessment

A Trial Risk Assessment has been completed by the WCTU to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The risk to participant safety in relation to the intervention
- All other risks related to the design and methods of the trial (including risks to participant safety and rights as well as data integrity)

The potential risks have been balanced against the level of risk that a trial participant would be exposed to outside of the trial. This trial has been categorised as a low risk trial where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the WCTU Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 11).

5.0 Participating site selection

All bowel screening units in the Bowel Screening Wales screening programme will be invited to participate in this study. 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.

The following documentation must be completed and received by the WCTU in order for a site to begin recruitment:

- Confirmation of local R&D approval
- Signed partnership agreement between the host care organisation and Sponsor
- All site SSPs and colonoscopists must have attended site initiation training
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- Completed Delegation Log (signature list and delegation of responsibilities)
- Full contact details for all host care organisation personnel involved, indicating preferred contact

Once all the documentation has been received at the WCTU, confirmation of site approval will be sent by the WCTU to the site PI.

All documentation must be stored in the Investigator Site File (ISF) at the site and in the Trial Site File (TSF) at the WCTU. The WCTU must be notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to-date information.

Occasionally during the trial, amendments may be made to the trial documentation listed above. WCTU will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the site to ensure that they obtain local R&D approval for the new documents, and that all relevant staff, are working to the current versions once R&D approval has been obtained.

Site initiation will be by attendance at a national CONSCOP launch meeting, or by teleconference or site visit if attendance of key personnel is unfeasible.

6.0 Participant eligibility

Any queries about whether a patient is eligible to enter the trial should be discussed with the WCTU **before** randomisation. Any issues will then be raised with the CI or one of the clinical Co-Investigators in the CI's absence.

Patients are eligible for the trial if all the inclusion criteria (Section 6.1) are met and none of the exclusion criteria (Section 6.2) apply.

The SSP should identify eligible patients prior to ringing patients to conduct the Telephone Assessment Clinic to discuss their colonoscopy.

6.1 Inclusion criteria

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

1. All participants testing positive on Faecal Occult Blood Test (FOBT) 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.

6.2 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 colorectal surgery will be excluded from the study though their standard management in the screening program will continue unchanged.
3. Anyone with a known allergy to a food colouring agent.
4. Previous inclusion in the trial

6.3 Informed consent

During the Telephone Assessment Clinic, the SSP should describe the study to the patient. A full explanation should be given of the investigative options, including the conventional and generally accepted methods of investigation. All patients must be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. The SSP should tell the patient that they will be sent more information about the study (the CONSCOP Patient Information Sheet (PIS)) through the post along with two consent forms:

- the standard colonoscopy consent form
- and the CONSCOP 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.

Following the phone call, the SSP should randomise all eligible patients (see section 7). This can be done before informed consent has been obtained.

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. The patient will then be seen by the SSP to confirm that they are happy to participate in the trial and written consent forms will be collected in accordance with the principles of Good Clinical Practice. **The site team must not tell the patient which trial arm they have been allocated to until consent has been obtained.** 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 sign both consent forms. One copy of the CONSCOP 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.

The right of the participant to refuse to participate in the trial without giving reasons at any time must be respected. Similarly, the participant must remain free to withdraw at any time from the protocol without giving reasons and without prejudicing his/her further treatment.

For all randomised patients (including those who have only signed the standard colonoscopy consent form), the following screening information should be returned to WCTU via the CONSCOP screening log

- BSW number
- CONSCOP trial ID
- Whether or not informed consent was obtained
- If not, reason:
    - Withdrew consent after discovering trial arm
    - Not interested in taking part in study
    - Patient ineligible (previous colorectal surgery)
    - Patient ineligible (unfit for colonoscopy)
    - Patient ineligible (allergy)
    - Patient ineligible (not index screening colonoscopy)
    - Patient ineligible (previous inclusion in the trial)
    - Other

7.0 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 using a computer-based algorithm. This is to ensure that the groups of participants receiving each of the different methods are similar.

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

Participant randomisation will be performed by the SSP using a central randomisation system.

Within 2 days prior to a colonoscopy list (after sending out the bowel preparation kit to those patients), the SSP should randomise the patients on that list to either an enhanced or non-enhanced colonoscopy. This can be done either by telephone or by the internet:

Telephone (Mon – Fri, 9am-5pm): 02920 64 5500

Internet (Anytime): http://www.wctu.org.uk/rando

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

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

8.0 Trial interventions

All participants will undergo a routine colonoscopy test as part of the National Bowel Cancer Screening programme in Wales (BSW).

An approved BSW 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 in the form of a benzodiazepine (midazolam) and or an opioid analgesic (Pethidine, fentanyl) is offered to the participant unless specifically declined by the patient as per routine 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 BSW list has an SSP who is present in the room and will collect data about the procedure. If there are any polyps detected then they will be removed in the standard manner. The process described above is standard practice in the Bowel Cancer Screening Programme.

8.1 Trial Arm A: Colonoscopy without enhanced dye:

Participants will undergo colonoscopy as per standard procedure described above.

8.2 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. 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 only an extra 12 minutes and no longer than 15 minutes. Overall procedure times may vary depending on therapy being required for polyp removal.

Indigo carmine is a blue contrast dye that pools in the crevices and valleys between the mucosal projections and highlights topography and it does not stain cells. It is a safe food colouring agent (Food standards agency-EU approved additive E number: E132) (27) and is already been used routinely in various endoscopy procedures in standard clinical practice. The technique of contrast enhanced colonoscopy (or chromoendoscopy) with the use of dye spray has been investigated in numerous studies in different settings and in almost all studies has been demonstrated to increase polyp detection. A Cochrane review on the topic of contrast enhanced colonoscopy has also analysed studies using the dye spray technique though not in the setting of screening and found a positive correlation between polyps detected and use of the technique (2). Pan colonic dye spray during colonoscopy already forms part of standard practice in other settings such as colonoscopic surveillance for neoplasia detection in high-risk cases of inflammatory bowel disease and is part of national guidelines in that setting. (25, 28)

8.2.1 Drug interactions

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.

8.2.2 Supply of dye

Indigo carmine dye spray *used for study patients will delivered to sites every 2 months. The amount will be based upon recruitment.* (see section 5).

9.0 Trial assessments

9.1 Data captured after colonoscopy list

For those patients who consented to participate in the trial, the following data should be recorded on the CONSCOP Colonoscopy Case Report Form (CRF) for each patient by the SSP:

1. Demographics: smoker/non-smoker (never smoked)/ex smoker
2. Was enhanced dye given
3. The presence of other factors that can cause a difficult colonoscopy: i.e.
   (a) previous abdominal surgery
   (b) presence of diverticular disease
4. Resource utilisation data (Llandough only):
   (a) amount of dye and dilutant used (b) was a scope guide used
   (c) any other resource use (additional accessory use including clips, sample pots etc)
5. Endoscopist assessment of procedural difficulty
6. Use of patient position change, adequate insufflation, repetitive examination of colonic segments, examination of flexures and proximal sides of folds, use of torque to flatten folds, and suctioning of liquid

The following information must be entered into BSIMS by the SSP (the SSP will be asked on the CONSCOP Colonoscopy CRF to confirm that they have entered this data) after the procedure:

1. Demographics: age, sex
2. Total Procedure time (a. start time and b. end of procedure)
3. Withdrawal time (a. time of reaching anus minus b. time of reaching caecum)
4. Caecal intubation
5. Whether the colonoscopy was complete or incomplete (extent of examination i.e. caecum, ileum etc.)
6. If colonoscopy incomplete then reason for this (e.g. difficult procedure, inadequate bowel preparation)
7. Adverse events (immediate complications) – see section 10 for further information for reporting these as SAEs to WCTU
8. Data on bowel preparation and quality
9. Participant comfort scores (during and after procedure)
10. Resource utilisation data:
    (a) How much sedation and antispasmodics used

The following histology data will be entered into BSIMS:

11. The histology report must be scanned and uploaded to BSIMS as soon as it becomes available

12. Total number of polyps (polyp detection rate)
13. Endoscopic and histological polyp characteristics (description of location, size and morphology)
14. Polyp retrieval rate
15. Total number of right sided polyps
16. Total number of adenomas

Public Health Wales will provide this BSIMS data to WCTU for analysis.

9.2 Central review of polyps found at the splenic flexure or above

After local reporting, all polyps found at the splenic flexure or above in all trial participants should be sent for central review (see section 13). Using data uploaded to BSIMS (see 9.1 above), the central study team will work out which patients had right sided polyps and will request these directly from the appropriate local pathology department. The local pathology department will send the requested paraffin blocks to the pathology laboratory in Cardiff following the instructions in the letter.

9.3 Follow up in routine datasets of all patients up to 30 days after colonoscopy

Public Health Wales will obtain the following data from routine datasets for each participant:

- 7 day and 30 day hospital re-admission rates (late complications)

Public Health Wales will provide this BSIMS data to WCTU for analysis.

9.4 Longer term follow up

Patients will be asked to optionally consent to longer term follow up by Public Health Wales to allow the following data to be obtained after the completion of this study protocol:

- Cancer incidence
- Mortality and causes of death

Public Health Wales will provide this BSIMS data to WCTU for analysis.

9.5 Completion of CRFs

The top copy of each completed CRF should be returned to the WCTU for data entry **at the end of each week**. The remaining copy is to be retained at the local site. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the WCTU in the CRFs.

CRF pages and data received by the WCTU from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

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 case report form 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 returned to the WCTU and a copy retained at the site along with the participants' CRFs.

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

10.0 Safety reporting and pharmacovigilance

The following definitions are in accordance with GCP. Screening unit staff will be trained by the Research Team in adverse event reporting at the same time as they are trained in trial methods (see section 5.0).

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. An AE can therefore be any unfavourable or unintended sign (including abnormal laboratory finding), symptom, or disease. Examples are:

- A patient is injured as a result of a medical device failure or misuse
- A patient's treatment is interrupted or compromised by medical device failure
- A patient's health deteriorates due to medical device failure or an allergic reaction to the dye

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an in-patient 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 adverse event.

*** Note: Other events that may not result in death or are not life-threatening may be considered as a serious AE 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.

Serious Adverse Event relating to colonoscopy and/or colonoscopy with enhanced dye: Any serious event occurring in a clinical trial participant for which there is reasonable possibility that it is related to either the colonoscopy procedure or the use of enhanced dye.

Suspected Unexpected Serious Adverse Event (SUSAE): These are any adverse events that are serious as defined above, thought to be related to either the colonoscopy procedure or the use of enhanced

dye but is 'unexpected' i.e. an adverse reaction, the nature and severity of which is not consistent with the currently known information about the medical procedure.

10.1 Causality Assessments

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship with the procedure, and will answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the SAE may have been caused by the procedure or the use of enhanced dye?".

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.

10.2 Expectedness Assessments

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 below 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

When to report:

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

For all adverse events, colonoscopy with or without enhanced dye complications occurring up to 60 days after the procedure:

- Grade 3-4 report on SAE form, only during procedure or if patient is admitted to hospital
- Deaths due to any cause

10.3 Participating screening unit SAE reporting responsibilities

All SAEs that a participating unit becomes aware of should be reported to WCTU using the trial specific SAE forms provided within 24 hours of knowledge of the event.

The PI should assess the SAE to see if it is related or not related to the trial intervention. In the PIs absence a medically qualified delegate on the delegation log should complete the assessments. A separate form must be used to report each event. SAE forms and SAE fax cover sheet should be faxed to the WCTU within 24 hours of knowledge of the SAE.

WCTU SAE Fax Number:
029 2064 4488

Please contact the WCTU immediately if you have a query about the classification of an AE or SAE.

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

- Full participant trial number
- An adverse event/reaction
- A completed assessment of the seriousness and causality as performed by the PI or an appropriately qualified delegated doctor registered on the delegation log. N.B. It is a requirement of GCP that a clinician provides this clinical assessment. SSPs, Nurses and other local trial staff should NOT complete this section of the SAE CRF, or authorise SAE CRFs. If they do so, the SAE form will be immediately queried by WCTU trial staff and a clinician review must be gained as soon as possible and the SAE form resubmitted with this information.

If any of these details are missing, you will be contacted by the WCTU and the information must be provided as soon as it becomes available.

Sites are required to follow up SAEs until resolution and respond to queries from WCTU regarding follow up information as soon as possible.

Serious adverse events should continue to be reported until 30 days after the participant has their colonoscopy.

10.4 WCTU responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible and further information may be requested by the WCTU. The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

Once an SAE is received at the WCTU, it will be evaluated by staff at the WCTU and the CI (or their delegate) for seriousness, expectedness and causality.

The causality assessment given by the PI cannot be overruled by the CI (or their delegate) and in the case of disagreement both opinions will be provided with the report.

The WCTU will report any SUSAEs to the main REC within 15 days of the date the SAE was transmitted to the WCTU.

The WCTU will report a list of all SAEs (expected and unexpected) and any other safety recommendations to the REC, every 12 months, throughout the course of the trial.

11.0 Trial management

11.1 Trial committees and trial management

The conduct of the trial is being overseen by the following committees:

- 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, other active trial investigators, WCTU representatives, and specialist advisors.
- 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.

11.2 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 trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

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

11.3 Participant 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.

CONSCOP Withdrawal CRF fax number: 02920 687501

Patients may:

Level 1: Withdraw from the translational study – participants continue follow-up but do not provide translational samples

Level 2: Completely withdraw from the trial – participants stop follow-up and any translational sample collection.

Withdrawal for any reason requires a completed CONSCOP Withdrawal CRF to be faxed to the WCTU 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 participant withdrawal at either of the two levels indicated above will be collected and used for trial analysis by the WCTU.

Patients who withdraw consent prior to the colonoscopy will be treated as having not given consent.

11.4 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the WCTU as soon as they become aware of it.

11.5 The End of the Trial

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 when the last patient has undergone their colonoscopy and had associated data collected.

11.6 Archiving

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

12.0 Statistical considerations

12.1 Randomisation

Randomisation will take place centrally at the WCTU using either an automated telephone or a secure online service (see section 7.0). Participants will be randomised using simple randomisation. Randomisation will have an allocation ratio of 1:1.

12.2 Outcome measures, sample size calculations and analyses

This is a feasibility study with the following objectives:

1. To assess whether enough participants can be recruited into the study (uptake by both participants and screeners) to suggest that it is feasible to run a future, larger scale trial investigating the impact of enhanced colonoscopy on polyp detection and rate of interval cancer detection on follow up.
2. To assess whether the enhanced colonoscopy takes an acceptable length of additional time to conduct
3. To estimate the proximal serrated polyp detection rate in the intervention arm to inform the sample size calculation of a future trial by allowing an assessment of the possible magnitude of improvement in cancer detection
4. To estimate the proportion of samples that are able to be collected as per protocol to inform the design of the translational element of the future trial
5. To assess the feasibility of incorporating an economic evaluation into a larger scale trial by exploring issues relating to collection of data on resource utilization, costs and outcome measures.

The following outcome measures will be used for each objective:

Objective 1: Based on current numbers of participants in the Bowel Cancer Screening Programme, if we were to open the study to recruitment in all centres involved in the Welsh colorectal screening programme for 1 year, we estimate that approximately 2200 patients would attend for colonoscopy following an abnormal faecal occult blood test (FOBT) and would be eligible for inclusion in the study. From experience in other trials in this area, we estimate that the proportion of eligible patients who give consent may be as high as 60%. With 2200 patients, we would be able to estimate this parameter with 95% confidence intervals of ±2%. If recruitment is below 50% then the external validity of the results would be in serious doubt and so we would not proceed to the full study.

Objective 2: will be assessed using a non-inferiority design. Current data from Bowel Screening Wales suggests that the procedure time in the standard colonoscopy control arm has a mean of 30 minutes (SD 15 minutes, normally distributed). Experience suggests that the intervention arm may take 12 minutes longer but should be no more than 15 minutes longer. This will require 1052 patients (power 90%, alpha=0.05 (one sided)) based on a two group t test.

Objective 3: If 60% of all patients were recruited (2200*0.6=1320) then we would be able to estimate the proximal serrated polyp detection rate in the intervention arm (which is estimated to possibly be as high as 9%) with 95% confidence intervals of ±2.2%.

Objective 4: If 60% of all patients were recruited (2200*0.6=1320) then we would be able to estimate the proportion of samples that are able to be collected as per protocol (which we would want to be higher than 50%) with 95% confidence intervals of ±2.7%.

Objective 5: A preliminary cost-effectiveness analysis will be undertaken alongside the feasibility study to assess whether detailed cost data can be generated and information relating to resource utilisation. Resource utilisation and differences in cost will be studied between the two groups with regard to staff time, consumables used during the procedures, use of sedation and other agents to improve patient comfort. We will however look to using this data input as the basis for a formal cost effectiveness analysis which would be best undertaken as a further study in correlation with the outcomes. A series of sensitivity analyses will be undertaken to determine the extent to which baseline findings are sensitive to parameter variation will inform numbers required to cost-effectiveness analysis within full scale trial.

Criteria for proceeding to a full trial: If objective 1 is passed then objective 2 will be assessed. If objective 2 is passed then results from objective 1 and 3 will be assessed to decide whether or not a full trial assessing impact on cancer rates is achievable in a reasonable time frame.

13.0 Translational research

Background

Colonic polyp removal lowers the incidence of colorectal cancer and hence saves lives (29). Colorectal polyps have been traditionally classified as either hyperplastic or adenomatous, with only the latter progressing to carcinoma via the adenoma-carcinoma sequence. It has been thought that most colorectal cancers (CRC) arise from conventional adenomas via the traditional tumour suppressor pathway initiated with a mutation of the APC gene, but it has been found that this pathway accounts for only approximately 70-80% of CRC cases (30-32). However has been recognised recently that hyperplastic polyps, i.e. certain subsets of serrated polyps, could predispose to cancer via an alternative pathway. These serrated polyps are a heterogeneous group of lesions with distinct morphologic, histologic and molecular genetics profiles. They are thought to be the likely predominant precursor lesion in the right colon and the alternative pathway of colorectal carcinogenesis that has been proposed is the serrated neoplasia pathway (18). It is hypothesized the progression of a subset of serrated adenomas or polyps to colorectal cancer may be responsible for 20% of all sporadic CRCs (33). Hence it would appear quite important to detect and remove these serrated polyps in order to prevent and reduce the incidence of right-sided colorectal cancer.

The alternative pathway or serrated pathway of colorectal carcinogenesis(30) leads to CpG island methylator phenotype (CIMP+) carcinoma with BRAF mutation and with or without microsatellite instability. They can follow two pathways i.e. BRAF mutation (mainly found in right sided polyps) and KRAS mutation (found in left sided polyps). The mechanism of carcinomas arising from this alternative pathway seems to begin with an activating mutation of the BRAF oncogene. This BRAF mutation provokes the development of serrated lesions that are mainly micro vesicular hyperplastic polyps or sessile serrated polyps (34). These lesions are prone to methylation of CpG islands in the promoter regions of genes resulting in their epigenetic silencing. The best-characterised gene silenced by this mechanism is MLH1. This gene is one of the mismatch repair genes and its epigenetic silencing results in sporadic tumours with microsatellite instability (MSI). However, other genes such as P16, MGMT, or IGFBP7 may also be epigenetically inactivated. SSAs have been associated with proximal CRCs, high level of CIMP, BRAF mutations and MSI-High(35, 36). Recently there has been identification of germ line and somatic POLE and POLD1 mutations (37) that can cause sporadic CRC as well.

Aim

To ensure serrated polyps found above the splenic flexure are histologically classified into high and low risk polyps by expert histopathologists and to subsequently perform molecular genetic studies on serrated polyps and to analyse for known and novel mutations in genes thought to be implicated in the development and progression of these polyps to cancer.

Methodology

In the bowel cancer-screening programme, polyp morphology data is routinely collected as a part of the specialist screening practitioners (SSP) colonoscopy pro-forma. This is subsequently checked and validated by screening colonoscopists as a part of standard practice. In addition to this histopathology data is also routinely collected as part of standard practice. After a polyp is removed it is routinely preserved in formalin and sent to the local pathology laboratory for further analysis. Once the

specimens obtained from the right side of the colon (i.e. the splenic flexure and above) are examined and reported by the histopathologists at the local assessment centres, the samples will then be paraffin embedded.

In the CONSCOP trial the SSPs should ensure that when management of a case is completed, i.e. once the local pathologist has completed a histology report, that the histology data requested in section 9.1 is entered into BSIMS **including scanning and uploading the histology report**. This usually takes a period of 1-2 weeks.

Using data uploaded to BSIMS (see 9.1 above), the central study team will work out which patients had right sided polyps and will request these directly from the appropriate local pathology department. The local pathology department will send the requested paraffin blocks to the pathology laboratory in Cardiff following the instructions in the letter for central view an genetics work.

Once the blocks arrive in Cardiff, they will be registered by the central pathology coordinator. A list of samples that arrive will be maintained and updated weekly to ensure timely review. These samples will be reviewed by three expert pathologists who will report and risk stratify serrated colonic lesions into the high and low risk categories based on the WHO criteria recorded onto a pro-forma. All samples will have a CONSCOP sticker attached by the coordinator.

After analysis these blocks will then be sent to the genetics department in Cardiff where samples will be received by a designated coordinator who will register and code samples ensuring lab codes are linked with BSW and trial numbers. These samples will then be banked and stored till further DNA extraction can be performed during the course of the study and subsequently be subjected to molecular genetic analysis at the end of the study.

Molecular Genetic Analysis

The Institute of Molecular Genetics is currently a designated CRUK centre for the Stratified Medicine Program (Experimental Cancer Medicine Network) and would look to analyse these serrated polyps as a multiplex analysis as part of its remit and capacity to undertake standardised high quality cost effective genetic testing of tumours.

These serrated polyps will be subject to current routine diagnostic molecular methods to analyse for mutations in genes, thought to be implicated in the development and progression of these polyps to cancer (i.e. CIMP status, MSI, K-ras, N-ras, PI3KCA, TP53, PTEN, BRAF), along with using more advanced methods of detection; including 'next generation' sequencing capable of detecting additional mutations or genes that were not known previously to be associated with serrated polyps. The team including a clinical research fellow at the Institute of Medical Genetics in Cardiff will undertake all research pertaining to the study.

The polyp tissue stored and for used for research in the institute of genetics would be covered under the realms of Cardiff University for HTA licence.

14.0 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.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial, as agreed by the CI and Director of WCTU. If there are no named authors then a writing committee will be identified.

15.0 Ethical and regulatory considerations, and Informed Consent

15.1 Ethical approval

This protocol will be submitted to a Multi-centre Research Ethics Committee (MREC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. The approval of the MREC must be obtained before the start of a clinical trial or any trial procedures are conducted.

15.2 Regulatory considerations

All substantial amendments to this Protocol must be approved by the MREC responsible for the study, before the implementation of the amendments. Minor amendments will not require prior approval by the MREC.

If the trial is temporarily halted it will not be recommenced without reference to the MREC responsible for the study.

The MREC will be notified within 90 days of trial completion. If the trial is terminated early, the MREC will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the MREC responsible for the study within one year of the end of trial.

15.3 Research governance approval

This trial protocol will be submitted through the Research Governance process of the host care organisation for review and approval. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

15.4 Sponsorship

The CONSCOP trial is being sponsored by Cardiff University. The Sponsor shall be responsible for ensuring that the trial is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005),
- the Data Protection Act 1998,

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

- Obtaining favourable ethics committee opinion and subsequent amendments
- Selection of investigators and ensuring each site has full trial documentation
- Giving notice to the MREC when the trial has ended or if the trial is suspended to recruitment or terminated early
- Keeping records of all AEs reported by PIs
- Ensuring recording and prompt reporting of SARs to the CI
- Reporting to the MREC any SUSARs within specified timeframes
- Ensuring PIs are informed of SUSARs
- Providing annual listing of all SARs to investigators and MREC using the Annual Safety Report, or Investigator Safety Report.
- Reporting urgent safety measures to MREC within 3 days of initial notification
- 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 WCTU 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 WCTU immediately and no later than 24 hours
- Report serious breaches of GCP or trial protocol to WCTU immediately and no later than 24 hours

The following responsibilities are delegated to Public Health Wales:

- Provision of data to WCTU in accordance with section 9 of the protocol

The following responsibilities are delegated to Julian Sampson in Medical genetics, Cardiff University:

- Analysis and storage of the tissue samples in accordance with section 13 of the protocol

15.5 Indemnity

Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient 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.

15.6 Data protection

The WCTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. All data leaving sites and Public Health Wales and going to WCTU will have had all identifiers (name, date of birth, postcode, NHS number etc). The BSW number (a reference number only meaningful to staff in the BCSP) will be provided to WCTU to allow linkage with data from CRFs.

Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. The data custodian for this trial is the Director of the WCTU. The sample custodian for the trial is Julian Sampson.

15.7 Finance

The CONSCOP trial is being funded by National Institute for Social Care and Health Research (NISCHR) Research for Patient and Public Benefit Wales and is thus part of the NIHR/NISCHR portfolio of clinical trials.

The WCTU is core funded by CR-UK and these core resources will be used to support this trial. The trial is in the National Cancer Research Institute (NCRI) and National Institute for Health (NIHR) portfolio. Local WCTN support should be available at each site taking part to support entry of participants into this trial.

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