# NIHR HTA Programme

# 10 June 2013

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# Is whole colon investigation (WCI) by colonoscopy, CT colonography (CTC) or barium enema (BE) necessary for all patients with colorectal cancer (CRC) symptoms, and for which patients would flexible sigmoidoscopy (FS) suffice?

**HTA Project No. 11/136/120**

**Short Project Name: SOCCER (Symptoms of Colorectal Cancer Evaluation Research)**

**Protocol**

**Version 1.0**
**25 February 2013**

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## 1 PROJECT TITLE

Is whole colon investigation (WCI) by colonoscopy, CT colonography (CTC) or barium enema (BE) necessary for all patients with colorectal cancer (CRC) symptoms, and for which patients would flexible sigmoidoscopy (FS) suffice?

## 2 PLANNED INVESTIGATION

### 2.1 Research objectives

The project is a retrospective analysis of data accrued from the SIGGAR Study Cohort: the group of patients who were registered as potentially eligible for the SIGGAR study (whether randomised or non-randomised), all of whom were referred to hospital with symptoms suggestive of colorectal cancer (CRC). *(SIGGAR1 original ethics approval, Northern and Yorkshire MREC/3/3/075, approved 15/01/04).*

*Primary objective*:

- To investigate the link between patients' symptoms at presentation and the risk of cancer in the proximal colon, to determine whether there are particular symptoms or symptom combinations which indicate that a patient could be adequately cared for by a distal colon exam (flexible sigmoidoscopy, FS) rather than more extensive whole-colon investigation (WCI). The aim of the study is to provide evidence that FS is a safe, effective alternative to WCI in patients whose symptoms do not suggest proximal disease.

*Secondary objectives*:

- To determine the miss rate of CRC after FS.
- To measure the prevalence of proximal and distal CRC in patients referred to hospital with symptoms suggestive of CRC.
- To assess the quality of FS performance at the time the study was in progress (2004-07).

### 2.2 Background and rationale for the study

Most symptoms suggestive of CRC (e.g. abdominal pain, change in bowel habit) are non-specific and common in the general population, with correspondingly low predictive values for the disease.[1] As a result, most patients who are investigated will not be found to have any significant abnormality. The annual NHS spend on diagnosis of CRC was estimated at £290.7m in 2007, with only 7% of this figure (£20.6m) spent on patients found to have CRC.[2] Any strategy that allows resources to be targeted more effectively toward patients with cancer would therefore be highly beneficial.

When patients present with symptoms suggestive of CRC, one possibility is to refer them for whole-colon investigation (WCI), involving either endoscopic examination of the colon (colonoscopy) or a radiological procedure such as barium enema (BE) or CT colonography

(CTC). The aim of the SIGGAR study was to compare the newer technology, CTC, with the other two standard investigations, BE and colonoscopy.

An alternative to WCI in some cases may be flexible sigmoidoscopy (FS); an endoscopic examination of the lower part of the colon (up to 60cm). Unlike colonoscopy, FS requires no sedation and only minimal bowel preparation. It can also be performed by appropriately trained nurses,[3] allowing increased availability of the exam. These factors potentially make FS quicker, more convenient for patients, and less expensive than WCI. Since FS provides an examination of only the distal colon, however, it is important to determine whether particular symptoms or clinical features reliably indicate the presence of proximal or distal cancer, and therefore whether a patient requires WCI or may be adequately investigated by FS.

A prospective study of 16,433 patients at a single site was published in 2008, with the aim of answering this question (the Lead Applicant and Statistician for the current proposal were collaborators on this study).[4] It was found that 86% of cancers were located in the distal colon (and therefore possible to detect at FS), but this proportion rose to 95% in patients whose presenting symptoms did not include iron deficiency anaemia (IDA) or a palpable abdominal mass. Patients without these symptoms could therefore be investigated adequately by FS.

The SIGGAR cohort is an ideal sample to test if these findings are generalizable. It provides a substantial group of consecutive symptomatic patients (8,484 in total) drawn from 21 NHS hospitals around the country.

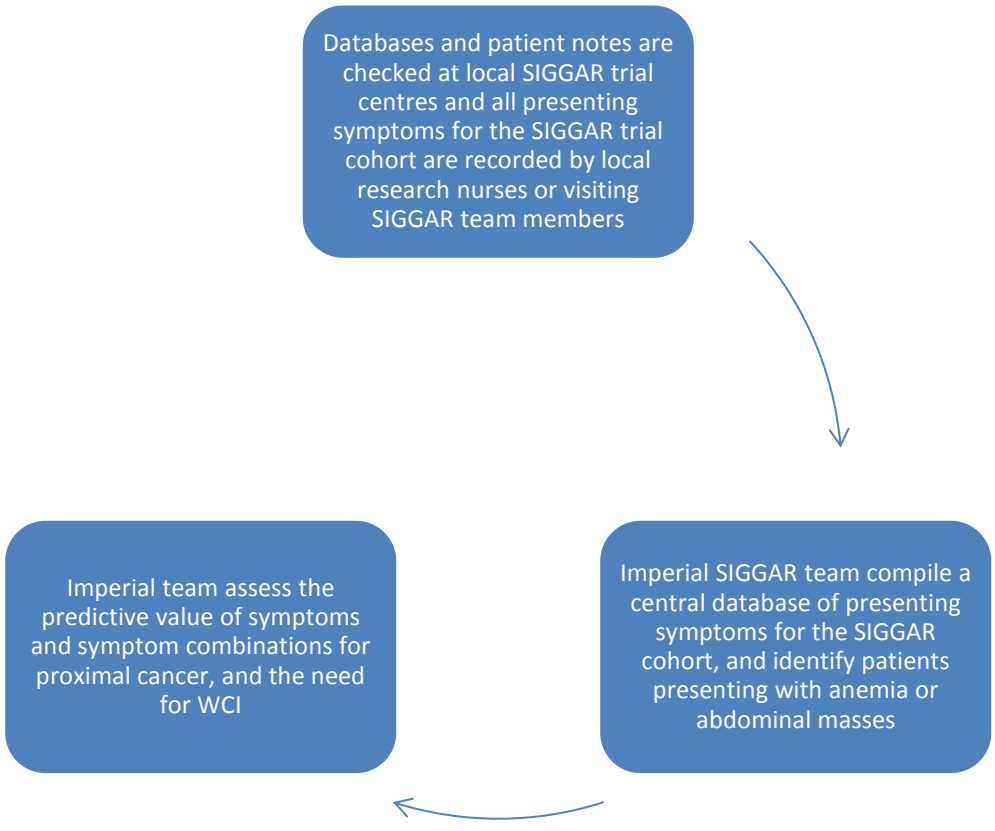
If we find convincing evidence that patients with certain symptoms can be adequately cared for by FS rather than WCI, this may have implications for clinical practice within the NHS and shape future guidelines on referral of patients with symptoms suggestive of colorectal cancer. If FS is to become more widely used as an alternative to WCI in appropriate cases, NHS guidelines for standardisation and quality assurance of FS will also be required, to ensure there is no fall in standards of patient care.

## 2.3 Research methods

We need to establish whether the dataset we have collected is complete, supplementing it with further data where necessary. There are two parts to the data collection process in this study:

1. Collecting data on presenting symptoms and signs of colorectal cancer, including details of colorectal exams, from patients' medical notes and hospital databases.
2. Obtaining nationally recorded data on cancers and deaths from the NHS Information Centre (NHSIC).

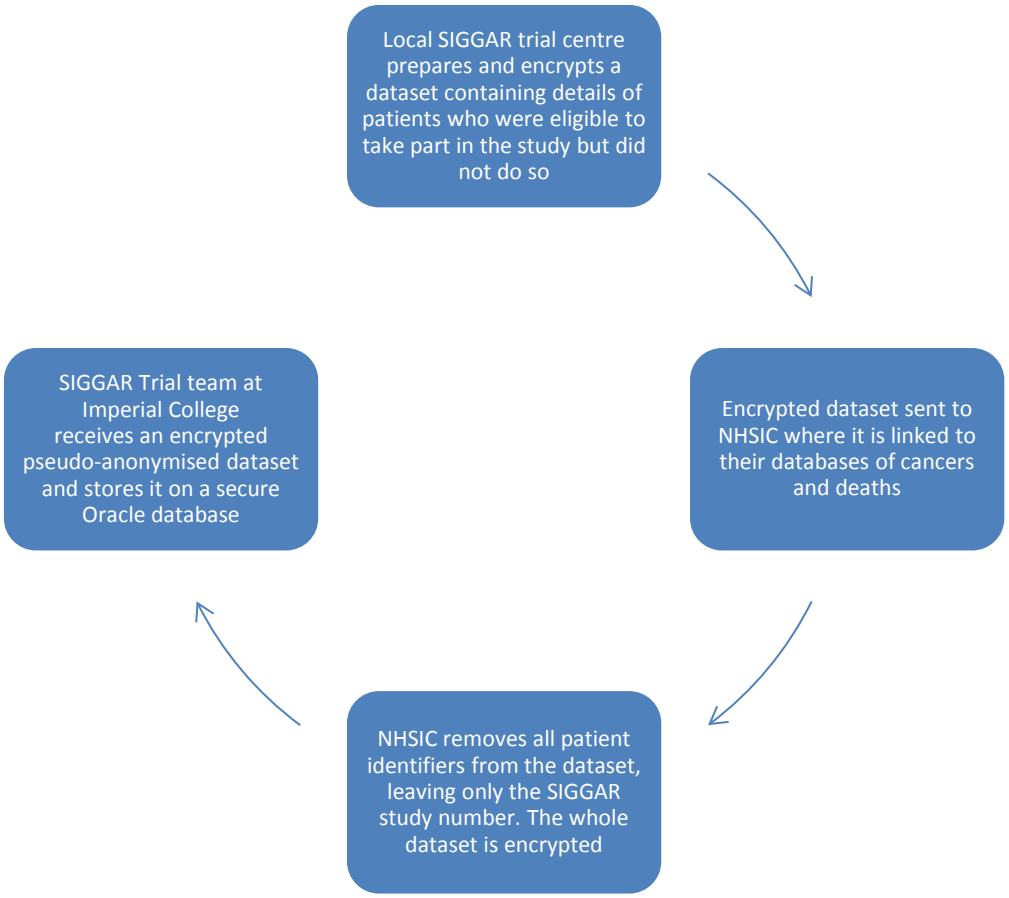
1. Data on patients' presenting symptoms were originally captured on a trial pro forma completed by a clinician or research nurse at the patient's initial outpatient appointment. The pro forma contained tick boxes to record rectal bleeding, a change in bowel habit, abdominal pain, anaemia, weight loss, or a positive faecal occult blood test result. There were also free text fields to record additional details or other presenting symptoms. Of particular interest for this project are symptoms of anaemia or a palpable abdominal mass, which the previous study showed are important indicators of proximal CRC.[4] Although a tick box was provided to record anaemia as a presenting symptom, we cannot be certain that this was always accurately completed, and it is also possible that patients could have been referred for a blood test after the trial pro forma was filled in. We have also coded any references to an abdominal mass which were recorded in the free text fields on the trial pro forma, but again we need to ensure that we are aware of all such cases.




Once we have complete data on presenting symptoms, we will assess the predictive value of symptoms and symptom combinations for proximal cancer, and the need for WCI.

A secondary objective is to assess the quality of the 1,576 baseline FS exams carried out in the SIGGAR study cohort. FS exams carried out in potentially eligible patients were recorded on specially designed pro formas, enabling us to capture information that is not routinely recorded in hospital reports. This information included room enter and exit times, procedure start and stop times, the endoscopist's overall assessment of the exam ('very easy', 'quite easy', 'quite difficult', 'very difficult'), the endoscopist's assessment of the quality of bowel preparation ('excellent', 'good', 'adequate', 'poor'), the segment of the colon reached, reasons (if any) why the exam could not be completed, overall findings, details of any polyps found, presence of diverticula in each segment of the colon and a rating of severity ('none', 'mild', 'moderate', 'severe'), and details of any adverse events during the exam. These measures provide us with a large amount of information on which to base assessments of FS technique. This will provide a detailed snapshot of nationwide FS practice at the time the study took place. Before we begin the analyses, we will check hospital databases to ensure that our dataset is complete.

2. We have already obtained data from NHSIC on CRC diagnoses and deaths in randomised patients, but we need to obtain this information for non-randomised patients as well, so that our analyses include all patients presenting to hospital with symptoms of CRC. This will ensure that our results are generalisable and not based on a selected sample. Each hospital will provide data to NHSIC to permit linkage of study patients with national databases. The data required are: forename, surname, date of birth, NHS number, and address. The spreadsheet of patient data will be encrypted and sent securely to NHSIC directly from the hospital. NHSIC will then link our study data to their patient databases and send details of CRC diagnoses and deaths to us, removing patient-identifiable information so that records are linked only to a study number.




## 2.4 Planned interventions

There are no interventions planned for this study as we are merely gathering additional data.

## 2.5 Planned inclusion/exclusion criteria

Patients were eligible for the SIGGAR study if they were:

- Experiencing symptoms suggestive of colorectal cancer.
- Aged 55 years or older.
- Clinically judged to need whole-colon investigation.
- Clinically judged fit to undergo full bowel preparation.
- Able to give fully informed consent.

Patients were excluded from the study if they had:

- A known genetic predisposition to cancer, e.g. familial adenomatous polyposis (FAP), or hereditary non-polyposis colorectal cancer (HNPCC).
- A known diagnosis of ulcerative colitis or Crohn's disease.
- Undergone a previous whole-colon examination in the past six months.

- Been referred for whole-colon examination to follow up a previously diagnosed colorectal cancer.

All patients meeting these criteria were registered as eligible for the study, regardless of whether they were ultimately randomised.

## 3 ETHICAL ARRANGEMENTS

### 3.1 Risks and anticipated benefits for trial participants and society

As this project only involves additional data collection on the existing SIGGAR cohort, it does not present any new risks to patients. The anticipated benefit of the project would be in providing corroborating evidence that patients with certain symptoms can be adequately investigated by FS rather than WCI. Patients referred for FS as a result of this work would benefit from having a test that is quicker and more acceptable than WCI, while any patients still requiring WCI would be no worse off than before. Increased use of FS would also be cost-saving for the NHS, since it is a quicker exam than colonoscopy, does not require sedation and therefore allows patients to leave hospital immediately, and can be performed by an appropriately trained nurse specialist. Increased use of FS will free up colonoscopy resources (which are currently oversubscribed) for diagnosis of patients with a high risk of proximal disease.

### 3.2 Informing potential trial participants of possible benefits and known risks

This project poses no new risks to patients.

### 3.3 Obtaining informed consent

We have been granted permission by the National Information Governance Board (*ECC 5-04(E)/2011)* to obtain the required data in the non-randomised group as it was not practical to retrospectively obtain consent from these individuals.

### 3.4 Proposed time period for retention of relevant trial documentation

All primary research data will be retained for a minimum period of ten years following completion of the project, as required by the Clinical Research Governance Office at Imperial College.

### 3.5 Proposed action to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'

We have obtained permission from the NIGB to collect data on non-randomised patients in the SIGGAR cohort and are now seeking an extension to the ethical permissions (main ethics and local ethics approval) granted for the original SIGGAR study (*MREC/3/3/075*). We will

also have a Trial Steering Committee, which will meet twice a year. For more information, see section 5, 'Research governance', below.

### 3.6 Involvement of service users

Involvement of service users was an important part of the SIGGAR study. As well as making an assessment of the clinical and cost effectiveness of CTC, BE, and colonoscopy, the study also aimed to determine the acceptability of each test to patients (*MREC/3/3/075, substantial amendment no. 1*). This was assessed by giving questionnaires to a sample of participants in the study, to be completed on the morning after their test, and at three months after the test. The design process for the questionnaires involved a series of qualitative interviews with patient groups.[5] The questionnaires gave patients in the study an opportunity to record their experiences, including items such as the least acceptable aspect of their test, post-procedural side effects, and how they felt about delivery of the results. Analyses of the questionnaire findings have now been published.[6,7]

Before applying to the NIGB for permission to obtain data on non-randomised patients, we approached a number of service users to identify issues that would concern them if their clinical data were to be used in medical research without their explicit consent. We explained the study design and the need to obtain data on both randomised and non-randomised patients, to ensure that our results apply to the whole patient group and not a selected sample. The questions we asked were:

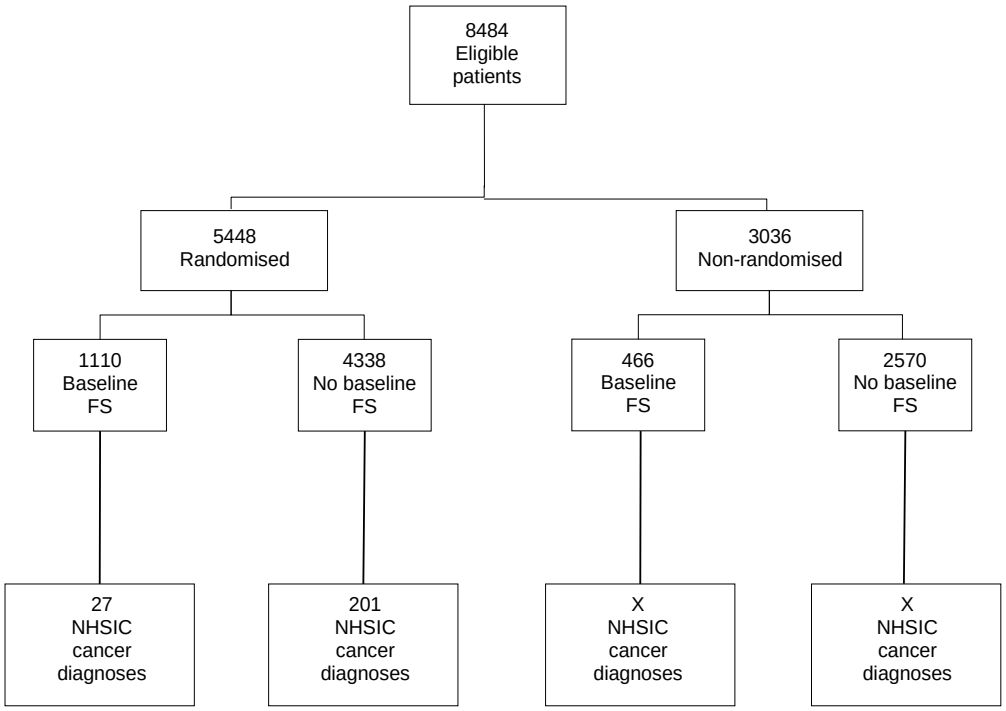
1. Would you have any objection to your clinical data being used in medical research without your prior consent, if it was in anonymised form? You as a person would not be identified from your clinical data.
2. If you have any objections, would you mind telling us what they are?

Most of those interviewed told us they had no objections, provided that their identity was protected and that their data was not misused. Those who had objections were worried mainly about their personal data being passed to third parties and used for financial gain. Once we explained the process they were reassured and agreed that anonymised clinical or demographic data could be collected without prior consent if used for public benefit only.

## 4 STATISTICAL ANALYSIS

### 4.1 Proposed sample size

The sample will consist of 8,484 patients from 21 UK NHS hospitals, comprising 5,448 who were originally randomised as part of the SIGGAR study and 3,036 who were considered eligible but ultimately not randomised (see flow diagram overleaf).




## 4.2 Analysis plan

The outcome variable will be detection of proximal or distal CRC within three years of presentation at clinic, according to symptoms or combinations of symptoms at presentation. The presence or absence of the following symptoms or signs of CRC will be analysed: rectal bleeding, change in bowel habit, abdominal pain, weight loss, IDA, or an abdominal mass.

The primary analysis will be to estimate the diagnostic yield of distal or proximal cancer by various categories of symptoms at presentation. Diagnostic yield will be examined to determine combinations of symptoms that define high and low risk of proximal cancer. We will estimate the sensitivity for detection of CRC if patients with symptoms conferring a low risk of proximal cancer are offered only FS, while those at higher risk are offered WCI. The distal colon will be defined as the rectum and sigmoid colon, as in the previous study.[4]

Secondary analyses will include estimation by symptom group of the number needed to screen to diagnose one CRC, hypothetical proximal CRC miss rates if only certain patients are sent for WCI, and the observed CRC miss rate in the subset of patients who had FS performed. These estimates will also be calculated separately in men and women, and in younger and older patients.

Results will be presented as percentages with binomial exact 95 per cent confidence intervals.

In the following calculations we apply the distribution of symptoms and cancers in the previous study by Thompson[4] to our cohort of 8,484 SIGGAR patients. We also assume that

FS detects 100% of distal cancers and that WCI detects 100% of both distal and proximal cancers. We would like to estimate the sensitivity for cancer (all sites) of a regime in which all patients with a specific set of symptoms are sent for WCI, while the remainder receive FS.

Under these assumptions we would expect a total of 489 cancers (68 proximal and 421 distal) in the SIGGAR cohort.

In the Thompson study,[4] the group of patients with IDA and/or abdominal mass were selected as having a high yield of proximal cancer and thus benefiting from WCI. One scenario would be to offer WCI in the presence of at least one of these symptoms and only FS in their absence. In this regime, 470 of the total 489 cancers would be detected, giving a sensitivity estimate of 96.1% (95% confidence interval 94.0% to 97.6%).

Patients in the Thompson study with abdominal pain were found to have an elevated yield of proximal cancer when compared to patients with only rectal bleeding and/or change in bowel habit, or only 'other' symptoms or signs. A second scenario would be to offer WCI in the presence of IDA, an abdominal mass, or abdominal pain, and only FS in their absence. This would result in 481 of the 489 cancers being detected, giving a sensitivity estimate of 98.4% (95% confidence interval 96.8% to 99.3%).

### 4.3 Proposed outcome measures

*Primary outcome*: Diagnostic yield of CRC (proximal or distal) within three years of presentation at clinic, by symptom category at presentation.

*Secondary outcomes*:

- The number needed to examine to diagnose one cancer, presented for various categories of symptoms at presentation.
- Hypothetical proximal CRC miss rates if only patients with certain symptoms or combinations of symptoms are sent for WCI.
- The actual miss rate of CRC at FS, in the subgroup of patients given FS at baseline.
- Prevalence of proximal and distal CRC in the study cohort.

## 5 RESEARCH GOVERNANCE

Imperial College is the nominated sponsor for this study. Approval for this project has been obtained from the College's Clinical Research Governance Office, which continues to oversee our research activities and ensures compliance with all relevant legislation.

Ethical approval for the SIGGAR study was obtained from the Northern and Yorkshire Multi-Centre Research Ethics Committee on 15 January 2004 (*MREC/3/3/075*), and subsequently

from individual trial centres. All randomised patients signed a consent form giving permission for their data to be used in future research. In addition, an application to the NIGB was made on 19 April 2011 to obtain data on CRC diagnoses and deaths among non-randomised patients. Permission to obtain data in this patient group (in pseudo-anonymised form) was granted on 1 June 2011 (*ECC 5-04(E)/2011*).

We are currently convening an advisory committee for this project and have invited a Colorectal Surgeon, a Gastroenterologist and two General Practitioners with special interests in Bowel Cancer to join the committee.

The research governance procedures in place at Imperial College ensure that all appropriate regulations and guidelines are followed. In addition, we utilise various resources for advice and guidance, including the Clinical Trials Toolkit (http://www.ct-toolkit.ac.uk/) for trial regulation and governance requirements, the website of the UK Clinical Research Collaboration (http://www.ukcrc.org/), and the MRC Regulatory Support Centre (http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/RegulatorySupportCentre/index.htm).

## 6 PROJECT TIMETABLE AND MILESTONES

**Obtaining approvals from trial centres (3 months)**

- Requesting approvals for the project from the Research and Development (R&D) offices at participating trial centres.
- Obtaining letters of access for research, from trial centres where data collection visits are required.

**Preparing data for NHSIC (3 months)**

- Contacting trial centres to obtain local assistance in preparing datasets of non-randomised patients (to include name, sex, date of birth, address, and NHS number).
- Advising trial centres on formatting requirements for NHSIC.
- Where necessary, arranging visits to trial centres to prepare datasets where local assistance is unavailable.

**Collecting data on patient symptoms (10 months)**

- Contacting trial centres to obtain local assistance in collecting data.
- Arranging with centres to check hospital databases and patients' medical notes for blood test results, references to IDA, abdominal mass or other tests that patients were referred for in order to reach a clinical decision prior to discharge.
- Where necessary, arranging visits by appropriate members of the research team to obtain data from trial centres where local assistance is unavailable.

**Preparing datasets for analysis (2 months)**

- Coding collected data.
- Obtaining details of CRC diagnoses and deaths from NHSIC.

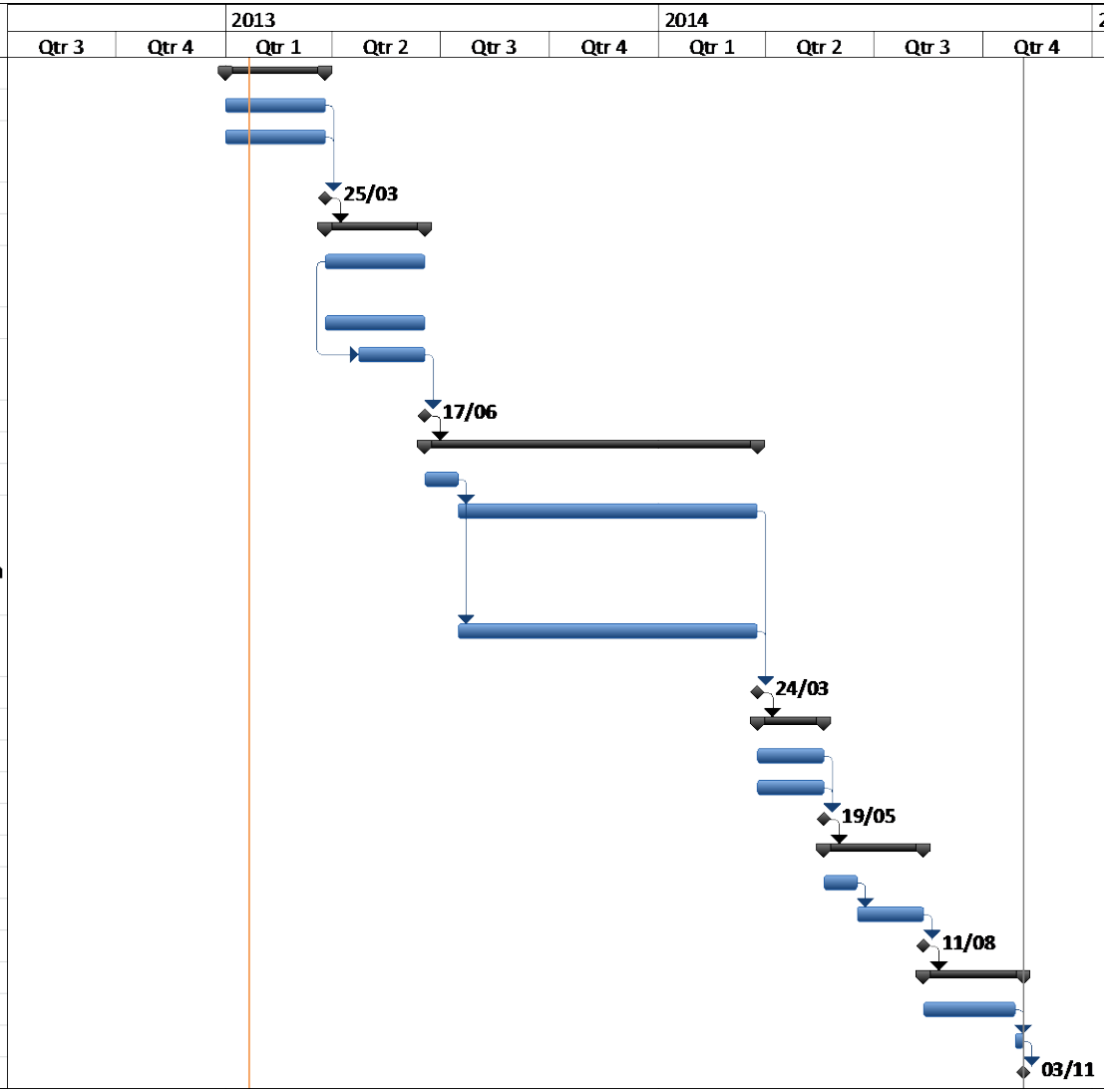
**Data cleaning and statistical analysis (3 months)**

- Preliminary analyses and data cleaning.
- Final analyses.

**Publication of results (3 months)**

- Preparation of manuscript.
- Submission for publication.

| Task Name |
|---|
| **Phase 0: Obtaining approvals from trial centres** |
| Obtain R&D approval from trial centres. |
| Obtain letters of access for research from trial centres requiring data collection visits. |
| End of Phase 0 |
| **Phase 1: Preparing data for NHSIC** |
| Contact trial centres - obtain local assistance in preparing datasets of non-randomised patients |
| Advise trial centres on formatting requirements for NHSIC |
| Arrange visits to trial centres to prepare datasets where local assistance is unavailable |
| End of Phase 0 |
| **Phase 2: Collecting data on patient symptoms** |
| Contact trial centres to obtain local assistance in collecting data |
| Arranging with trial centres to check hospital databases and patients' medical notes for blood test results, references to IDA, abdominal mass or other tests that patients were referred for in order to reach a clinical decision prior to discharge |
| Arrange visits to obtain data from trial centres where local assistance is unavailable |
| End of Phase 1 |
| **Phase 3: Preparing datasets for analysis** |
| Code collected data |
| Obtain details of CRC diagnoses and deaths from NHSIC |
| End of Phase 2 |
| **Phase 4: Data cleaning and statistical analysis** |
| Preliminary analyses and data cleaning |
| Final analyses |
| End of Phase 3 |
| **Phase 5: Publication of results** |
| Prepare manuscript(s) |
| Submit for publication |
| End of Phase 4 |



## 7 EXPERTISE

Our team has considerable experience of working on studies of diagnostic accuracy, including:

- The previous study of FS as a possible alternative to WCI,[4] on which the current proposal is based.
- The SIGGAR1 study (in the process of being published), comparing barium enema, CTC, and colonoscopy for diagnosis of CRC or large polyps in older symptomatic patients.
- The UK Flexible Sigmoidoscopy Screening Trial (UKFSST),[8] an 18-year (and ongoing) study in over 170,000 patients, examining the potential of a single FS exam to reduce CRC incidence and mortality. Part of the statistical analysis for this study involved modelling endoscopist performance and diagnostic accuracy.

The people involved in the proposed study are:

**Prof. Wendy Atkin**: Epidemiologist with expertise in CRC screening, endoscopy, and study design. Principal investigator on several grants from the National Institute for Health Research, Cancer Research UK, the Medical Research Council, and the Centers for Disease Control and Prevention in the US. She will have overall responsibility for delivery of the project outcomes and for the ethical, legal, and financial conduct of the study.

**Kate Wooldrage**: Medical statistician on several large studies including the UKFSST and SIGGAR. This has given her the expertise needed to provide methodological support for the current project, and to undertake the required statistical analyses.

**Edward Dadswell**: Data Manager and SIGGAR Trial Coordinator. He will be responsible for the timely collection of all data required for the project, and preparation of datasets for analysis.

**Prof. Stephen Duffy**: Director of the Policy Research Unit in Cancer Awareness, Screening and Early Diagnosis, funded by the Department of Health. Professor Duffy is a statistician and will provide external guidance on the analyses undertaken in this project.

**Mr Michael Thompson**: Consultant in Colorectal Surgery with expertise in national bowel cancer audit projects, GP referral guidelines, and the development of large databases of patient symptoms. Lead author of the 2008 study[4] investigating the use of FS and WCI for the diagnosis of CRC in symptomatic patients. He will provide clinical expertise and assistance with data analysis and interpretation.

**Mr Omar Faiz**: Consultant in Colorectal Surgery. He will provide clinical expertise and assistance with data analysis and interpretation.

**Karen Flashman**: Research Coordinator for the Gastrointestinal Surgery department at Queen Alexandra Hospital, Portsmouth, and co-author of the 2008 study[4] investigating the use of FS and WCI for the diagnosis of colorectal cancer in symptomatic patients. She has significant experience in data collection, analysis, and interpretation in this field, and will provide advice in these areas.

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