Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care

Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd. Assessment Group

Project lead: Marie Westwood
Second Contact: Shona Lang
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York YO19 6FD
Tel: 01904 727983
Email: marie@systematic-reviews.com; shona@systematic-reviews.com

Health economics lead: Isaac Corro Ramos
Second contact: Maiwenn Al
Institute of Health Policy and Management
Erasmus University
P.O. Box 1738
3000 DR Rotterdam
The Netherlands
Tel: +31 10 4088565
Email: corroramos@imta.eur.nl; al@bmg.eur.nl

Plain English Summary

Bowel (colorectal) cancer is the third most common cancer in the UK. There is a better chance that bowel cancer can be treated successfully if it is found early. Symptoms, such as rectal bleeding, unexplained weight loss, anaemia, abdominal pain and altered bowel habit can be early warnings of bowel cancer but, in most people, these symptoms will have another explanation. In order to be sure whether or not someone has bowel cancer or another serious bowel disease, one or more tests, usually done in hospitals, are needed. Such testing usually includes colonoscopy, (an internal examination of the bowel using a camera on a flexible tube which is passed through the anus). Because colonoscopy can be unpleasant and carries a small risk of heavy bleeding or tearing of the bowel, it is important to find tests which can help to select people who really need to have colonoscopy, i.e., those who are more likely to have bowel cancer and other serious lower gastrointestinal disease, including inflammatory bowel disease.

Blood in the faeces is a further sign of possible bowel cancer and tests are available which can detect the presence of small amounts of blood in the faeces which are not visible to the naked eye (often called occult blood). These tests for occult blood in faeces, traditionally called faecal occult blood tests (FOBTs) are currently used by the NHS Bowel Cancer Screening Programme in England, which offers screening every two years to all men and women aged between 60 and 74 years. Tests for occult blood in faeces have also been recently recommended for people reporting symptoms of bowel disease to their doctor, who are considered to be at low risk of having bowel cancer; in these people, a negative FOBT result may be used to rule-out bowel cancer and avoid the need for hospital tests. However, FOBT are not perfect tests. A positive FOBT result can sometimes be caused by things which are not connected to disease, e.g., eating red meat, medicines like aspirin that can irritate the gut, or bleeding from the gums; this is called a false positive test result. Also, people who do have bowel cancer can sometimes have a negative FOBT; this is called a false negative test result. These tests are called guaiac faecal occult blood tests (gFOBT) because of the chemical used as an indicator in the test.

There is a newer type of test for the presence of blood in faeces, called a faecal immunochemical test for haemoglobin (FIT). It is thought that this test produces fewer false negative results, meaning that fewer people with bowel cancer would be missed and may also produce fewer false positive results than gFOBT, meaning that fewer people would be referred for unnecessary invasive hospital tests. FIT has been approved for the Scottish Bowel Screening Programme and has been recommended for adoption in the NHS Bowel Cancer Screening Programme in England.

This assessment will consider whether FIT should replace gFOBT for people reporting bowel symptoms to their doctor.

1 Decision problem

1.1 Population

The primary indication for this assessment is the use of tests for the presence of occult blood as a triage step in the investigation of people presenting, in primary care settings, with lower abdominal symptoms who require investigation for possible colorectal cancer (CRC), commonly referred to as bowel cancer. NICE guidance on suspected cancer: recognition and referral (NG12) recommends the use of testing for occult blood in the faeces, as a triage step before referral for secondary care investigations, in specified symptomatic patient groups:

- people aged ≥50 years who have unexplained abdominal pain or weight loss
- people aged <60 years who have changes in their bowel habit or iron-deficiency anaemia
- people aged ≥60 years who have anaemia in the absence of iron deficiency

This assessment will consider the clinical and cost-effectiveness of using quantitative faecal immunochemical tests for haemoglobin (FIT) as a triage test. The clinical- and cost-effectiveness of triage testing using FIT will be considered for all people presenting, in primary care settings with lower abdominal symptoms who require investigation for possible colorectal cancer (CRC). The target population for this assessment is those with low risk symptoms as defined in NG12. However, in order to maximise the available evidence, our assessment will include any studies where the population is described as symptomatic, not limited to the specific groups as detailed in NG12. The committee will then be able to take a view on how applicable the estimates derived from the literature are to the population included in the scope.

CRC is the third most common cancer in the UK population overall and people aged 50 years and over, after breast cancer and lung cancer for females and prostate cancer and lung cancer for males. The most common cancers differ for younger age groups. Office of National Statistics (ONS) cancer registration data for 2013 showed approximately 35,000 new cases of CRC in England (18,839 males and 14,926 females).[1] The incidence of CRC was 87 cases per 100,000 males and 52 cases per 100,000 females; the age standardised incidence rate was 54.4% higher in males than in females and has increased for both males and females over the last 10 years.[1] CRC accounted for approximately 11.5% of all new cancers diagnosed in 2013 (12.6% in males and 10.4% in females) and increasing with age to 14.2% of cancers in males aged 80 years and over and 15.2% in females aged 80 years and over.[1] The age standardised one year survival rates for men and women diagnosed with CRC between 2009 and 2013 and followed up to 2014 were 77.5% and 75.8%.[2] The corresponding five year survival rates were 58.5% and 58.2%, respectively.[2] Survival rates for CRC have not changed substantively since the previous data collection period (2008 to 2012).

The NHS Bowel Cancer Screening Programme in England currently utilises gFOBT, but FIT has been recently recommended by the UK National Screening Committee, has been piloted for national roll-out and recommended by European Commission guidelines.[3] However, studies assessing the effectiveness of FIT or comparing the performance of FIT and gFOBT in asymptomatic population-based screening for CRC will not be included in this assessment. This is because the prevalence of CRC is likely to be higher in a population with even relatively low risk symptoms than in the general population without symptoms eligible for screening and FIT used for screening applications will generally use higher cut-off faecal haemoglobin concentrations than would be used for triage of people with symptoms. The cost-effectiveness modelling used to inform NG12 based its estimate of the prevalence of CRC in a low risk population on the positive predictive value (PPV) of symptoms in twenty-two studies identified as relevant.[4] The PPV of altered bowel habit in men and women aged <60 years ranged from 0.01 to 15.7 and the base case analysis used a CRC prevalence estimate at the lower end of this range (1.5%).[4] By comparison, estimating the prevalence of CRC in the general population of England based on ONS cancer registration and population data gives approximately 0.065% for the whole population and 0.226% for the screening eligible age group (60 to 74 years): i.e., those most likely to match the population included in screening studies. Furthermore, it has been shown that differences in disease prevalence can effect estimates of test performance; data from 23 meta-analyses, which covered a wide range of clinical conditions, showed changes in sensitivity and specificity estimates of between 0 and 40% from the lowest to the highest prevalence.[5] In relation to FIT testing, a recent meta-analysis of 19 studies conducted in average risk, asymptomatic screening populations reported summary estimates of sensitivity and specificity for CRC of 79% (95% CI: 69 to 86%) and 94% (95% CI: 92 to 95%), respectively,[6] whereas sensitivities of up to 100% have been reported in symptomatic patients.[7]

The 2015 National Bowel Cancer Audit Report stated that, of all patients diagnosed with CRC in 2014, 55% were diagnosed following a GP referral and 9% (20% of those in the eligible age range for screening, 60 to 74 years) were diagnosed through the NHS Bowel Cancer Screening Programme: however, 20% were only diagnosed following an emergency presentation (referral source data were missing for 16% of patients).[8] Treatment with curative intent was possible for more of those patients diagnosed through screening (90%) and following GP referral (70%) than those presenting as an emergency admission (52%).[8] Work to promote screening up-take and awareness of CRC symptoms is stated as a recommendation, with the aim of reducing the proportion of emergency presentations and improving outcomes. However, increased up-take of screening and increased awareness of and presentation in primary care of patients with low risk symptoms could result in more invasive investigations such as colonoscopy being conducted. Estimates from the charity 'Bowel Cancer UK' [9] have suggested that there will be a 10-15% year on year increase in demand for colonoscopies, which impacts on the two week suspected cancer referral time

and NHS capacity.[10] In addition, colonoscopy has associated risks which include bowel perforation, bleeding, infection and abdominal pain [11]. A recent review reported that most colonoscopies performed in symptomatic patients do not find either CRC or other serious bowel disease and do not yield changes to the therapeutic approach.[12] The identification of tests which can help to rule-out CRC and select people who are more likely to benefit from further investigation is therefore an important goal. It has been suggested that using quantitative immunochemical measurement of faecal haemoglobin concentration to select patients for referral has the potential to reduce unnecessary colonoscopies and provide more accurate classification of patients than traditional, symptoms-based guidelines.[7]

The majority of the evidence reviewed to inform recommendations on faecal occult blood testing in NG12 was about guaiac tests. This assessment will provide a comprehensive summary of the evidence about the performance of FIT as a triage test for people presenting, in primary care settings, with lower abdominal symptoms, who require investigation for possible CRC.

1.2 Intervention technologies

There are two major types of test for the presence of small amounts of blood in faeces, these are guaiac based (gFOBT) or immunochemical based (FIT). Guaiac-based methods detect the haem complex whilst immunochemical methods specifically detect the globin moiety of human haemoglobin. Quantitative FIT assays are the intervention for this assessment and gFOBT is a comparator.

gFOBT rely on the pseudo-peroxidase activity of haem. A faecal sample is placed onto a paper impregnated with guaiac to which hydrogen peroxide is applied as developer of the test. In the presence of haem, a chemical reaction occurs yielding a blue or green coloured product within seconds. Usually two faecal samples from each of three separate bowel motions are required.[13] The test is not specific for blood and will also respond to animal blood, muscle protein and iron supplements. In addition certain vegetables contain constituents with peroxidise activity which can lead to false positive results, although this can be minimised by waiting for 72 hours before development of the test. Bleeding gums or medicines which can cause gastrointestinal irritation or bleeding, e.g., aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), can also result in a false positive test result.[14] In addition, a high intake of vitamin C can cause a false negative result. In consequence, dietary and medicine restrictions are often imposed prior to testing.[13]

Faecal immunochemical tests (FIT) use antibodies that specifically recognise the globin of human haemoglobin. FIT has the potential to reduce false positives caused by upper gastrointestinal bleeding because globin is degraded in the upper gastrointestinal tract and therefore is not present in faecal samples for FIT to detect. However heam is resistant to degradation in the upper gastrointestinal tract and therefore this molecule remains in faecal samples and can be detected by gFOBT (false positive).. Usually, only one (or sometimes

two) faecal samples are collected and no dietary or medicine restriction is required.[15] FIT can be either qualitative or quantitative and both are available from many different manufacturers with variable designs. Qualitative tests have an endpoint which is read as positive or negative visually, usually they are of a lateral flow immunochromatographic design similar to home pregnancy tests. Faecal samples can be collected onto cards, similar to the traditional gFOBT, or more commonly into specimen collection devices that use probes attached to the lid of the device to transfer a very small amount of faeces into a small volume of stabilising buffer in the device. Each manufacturer sets their own cut-off faecal haemoglobin concentration for a positive test and available qualitative FIT are very different. The need for visual interpretation of the results can introduce inter-observer variation. Determination of the presence of a trace line in the test portion of the cassette is a subjective judgement, which can sometimes be difficult. It is difficult to introduce quality control and, if qualitative FIT are used outside laboratories, the stringent recommendations and guidelines for point-of-care tests must be followed. Quantitative FIT often uses immunoturbidimetric methods to measure the actual concentration of faecal haemoglobin. Analysis is usually automated, facilitating quality management procedures. Most quantitative FIT require 'wet' collection where samples collected with a probe attached to the lid of the specimen collection device and transferred into a small volume of buffer in the device. The sample may degrade between collection and analysis if not handled properly[13,15] Because faecal haemoglobin is very unstable: indeed, faecal samples for FIT must be collected into the specimen collection devices and cannot be collected by patients into traditional collection pots which are then returned to primary care for onward transport for FIT analysis.

A summary of the product properties of quantitative FIT assays available in the NHS in England and Wales and included in this assessment is provided in Table 1. Further tests, possibly including qualitative tests, may be included following the Assessment SubGroup meeting and issue of the final scope.

Table 1: Summary of Quantitative Faecal Immunochemical Tests*

Test	*Test system description*	*Sample size*	*Measurement range*	*Limit of detection (LoD)*	*Limit of quantitation (loQ)*	*Cut-off*	*Capacity*
HM-JACKarc system Kyowa Medex/Alpha Laboratories Ltd	mAb human Hb automated detection immunoturbidimetry	2 mg	7ng/mL to 400ng/ml (7 – 400 µg Hb/g faces)	NK	NK	10 µg Hb/g (10 ng/ml)	200 samples/ ho (maximum capa samples/ run)
FOB Gold system Sentinel/ Sysmex	automated detection immunoturbidimetry	10 mg	4.1-10 ng/ml to 700-840 ng/ml or highest calibrator concentration, depending on the analyser used	4.1 ng/ml to 19.5 ng/ml, depending on the analyser used	10 ng/ml to 28.5 ng/ml, depending on the analyser used	To be determined by each laboratory	Dependent on a used
OC-Sensor Eiken Chemical/MAST Diagnostics	pAb human Hb automated detection immunoturbidimetry	10 mg	10 ng/ml to 1000 ng/ml	10 ng/nl	NK	10 ng/ml	Dependent on a used
Ridascreen hameoglobin R-Biopharm	mAb human Hb manual sample preparation manual or automated detection ELISA	NK	NK	0.42 µg Hb/g	NK	2 µg Hb/g	NK
Ridascreen haemoglobin/ haptoglobin R-Biopharm	pAb human Hp manual sample preparation manual or automated detection ELISA	NK	NK	0.38 µg Hb/g	NK	2 µg Hb/g	NK

* Information supplied by companies or taken for the instructions for use if the test
Hb = haemoglobin; mAb = monoclonal antibodies; pAb = polyclonal antibodies; NK = information sought from companies, but not known at time of writing

HM-JACKarc system

The HM-JACKarc system is a fully automated quantitative faecal immunochemical test. A sample is obtained using the insertion of a probe attached to the cap of the specimen collection device, which is then inserted into a specialised collection tube containing buffer. The system picks up a small volume from the specimen collection devices and adds reagents including latex reagent pre-coated with antibodies specific to the globin moiety of human haemoglobin. Binding of the latex reagent to globin present in the faecal sample creates a complex which can be detected using turbidimetry. The system comprises an analyser, faecal sample collection devices (the Extel Hemo-auto MC A device), latex agglutination reagents (Extel Hemo-Auto HS) and buffer (Extel Hemo-auto). The test has a measuring range of 7- 400 µg Hb/g faeces. The HM JACKarc analyser can process up to 200 samples per hour, with a maximum capacity of 80 samples per run.[16]

FOB Gold

The FOB Gold system is an automated quantitative faecal immunochemical test. Faecal samples are collected on probes which are immersed immediately into solution within the specimen collection device. This ensures sample stability (14 days at 2-8 °C or 7 days at 15-30 °C). The devices are then placed into an automated analyser. A latex agglutination assay is used which is detected via turbidmetry.[17] The FOB Gold kit has CE marked applications for a range of clinical chemistry analysers including those supplied by Roche, Siemens, Beckman Coulter and Abbott. The test has a measuring range of 10 ng/ml to the highest calibrator concentration used, and instructions for use state that laboratories should establish their own population specific cut-offs. Test throughput is dependent on the analyser used to process samples.

OC Sensor

The OC Sensor is a quantitative faecal immunochemical test. A sample is collected on a probe and inserted immediately into a unique specimen collection device which contains buffer. Analysis is fully automated using the OC-Pledia analyser or the OC-Sensor IO analyser; both quantitatively determine the concentrating of haemoglobin present in faecal samples using polyclonal antibodies for human haemoglobin and latex agglutination turbidimetry.[18, 19]The OC-Pledia can process up to 320 samples per hour, with a capacity of 200 samples per run. The OC-Sensor IO analyser can process up to 88 samples per hour, with a maximum capacity of 20 samples per run.

RIDASCREEN haemo/haptoglobin complex

The Ridascreen hameoglobin test is a quantitative human haemoglobin/haptoglobin complex immunochemical test. Detection alone is automated. Samples are collected and kept in chilled storage media. Before analysis the samples are diluted with extraction buffer and mixed. This can be done manually or using the DSX automated ELISA system. The test is run on a 96 well microtitre plate which is precoated with polyclonal antibodies for human

haptoglobin. The sample solution is applied, followed by a wash step and then application of monoclonal antibody for anti-haemoglobin which is conjugated to peroxidise. In the presence of a haemoglobin/haptoglobin complex, a sandwich complex will forms between the polyclonal and monoclonal antibodies. After further washes a substrate is added which reacts with the peroxidase creating a colour change which can be detected by a plate reader. The values produced by the plate reader are interpreted with the RIDA-SOFT Win.net software. The company recommends a cut off value of >2µg/g to determine a positive sample. The test has a limit of detection of 0.42µg/g. The company suggest that the determination of the haemoglobin/haptoglobin complexes has a diagnostic advantage. Since the Hb/Hp complex is resistant to decomposition by acids or proteolytic enzymes, it will maintain in the stools after long periods in the intestine. Thus, blood admixtures from larger intestinal polyps and colon carcinomas located higher up in the intestine can also be recorded with high sensitivity.[20] However, discussion with clinical experts at the scoping stage of this assessment has suggested that this method may also result in an increased number of false positives.

Further quantitative FIT systems may be added following discussions with clinical experts at the assessment subgroup meeting.

It has been suggested that FIT may offer improved accuracy compared to gFOBT, particularly in relation to the rule-out of CRC. Although most studies do not provide evidence about the performance of the test in symptomatic populations, the idea that FIT may be associated with improved diagnostic performance relative to gFOIBT is supported by data from systematic reviews of studies conducted in screening populations.[21, 22] A meta-analysis of 17 studies demonstrated that FIT (OC-Sensor) had a higher sensitivity (0.87 vs 0.47) with similar specificity (0.93 vs 0.92) to gFOBT (Hemoccult) for screening for CRC.[22] More recent studies comparing FIT to gFOBT in screening populations have also reported increased sensitivity of FIT for the detection of CRC of between 31.7% and 61.5%, relative to gFOBT, with no change in associated specificity.[23-25] A recent study in symptomatic and asymptomatic patients scheduled for diagnostic colonoscopy reported a smaller difference in sensitivity (14.7%).[26] The results of these studies indicate that FIT may be associated with a decrease in the number of false negative (FN) results and potentially missed CRC, relative to gFOBT, but not a reduction in false positive (FP) results (inappropriate referrals).

This assessment will systematically review the evidence about the performance of FIT as a triage test for people presenting, in primary care settings, with lower abdominal symptoms, who require investigation for possible colorectal cancer (CRC). The assessment will preferentially include direct comparisons of FIT and gFOBT, to inform comparative cost-effectiveness modelling. The assessment will also include studies of the diagnostic accuracy of quantitative FIT assays alone (no comparison with gFOBT); if available, data will be collected on the use of different faecal haemoglobin concentration cut-offs and/or multiple

sampling strategies in order to determine the best way to operationalise FITuse. If no direct comparisons of FIT and gFOBT in assessment of patients with lower abdominal symptoms are identified, the information on gFOBT used in our cost-effectiveness modelling will be taken from the systematic review used to inform NG12.[4] This approach would provide the committee with an indicator of how systematically derived estimates of the cost-effectiveness of FIT compare to the estimate of the cost-effectiveness of gFOBT suggested in current guidance. Our cost-effectiveness modelling will also include a no triage testing comparator.

A meta-analysis of studies comparing FIT and gFOBT reported that FIT was associated with a small increase in participation in asymptomatic population-based screening (RR 1.16 (95% CI: 1.03 to 1.30)).[27] Initial reports from the NHS Bowel Cancer Screening Programme in England pilot of FIT also indicate that FIT may be associated with increased uptake compared to gFOBT (63.9% compared 54.4% in 60 year olds invited for screening for the first time).[28] We are not aware of any similar studies on testing uptake (or compliance) in symptomatic populations and the extent to which the acceptability of FIT sample collection would be an issue for people with symptoms is unclear. This assessment will consider any reported information on testing up-take and on acceptability or patient satisfaction outcomes reported in studies of symptomatic populations.

1.3 Care pathway

Testing for occult blood in faeces in patients presenting to primary care settings
The NHS Bowel Cancer Screening Programme in England offers screening every two years to all men and women aged between 60 and 74 years. People over the age of 74 years can request a screening kit by contacting the Programme. Screening is currently based on gFOBT, but FIT have been recommended by the UK Screening Committee for this purpose and a pilot evaluation has already been completed. FIT are currently recommended as the best non-invasive screening modality in all national and international guidelines.[29]

According to the 2015 NICE guideline 12,[10] patients should be referred for an appointment within 2 weeks if they have suspected CRC defined as:

- aged 40 years and over with unexplained weight loss and abdominal pain or
- aged 50 years and over with unexplained rectal bleeding or
- aged 60 years and over with iron-deficiency anaemia or changes in their bowel habit
- tests show occult blood in their faeces

A suspected cancer referral (for an appointment within two weeks should also be considered for:

- people with a rectal or abdominal mass

- adults aged under 50 years with rectal bleeding and abdominal pain or change in bowel habit or weight loss or iron-deficiency anaemia

According to NICE guideline 12,[10] testing for occult blood in faeces should be offered to adult patients who present with initial symptoms without rectal bleeding who are:

- aged 50 years and over with unexplained abdominal pain or weight loss
- aged under 60 years with changes in their bowel habit or iron-deficiency anaemia
- aged 60 years and over and have anaemia even in the absence of iron deficiency

Further testing following a positive test result for occult blood in faeces
Following a positive test result for occult blood in faeces, people in England are usually offered a secondary care appointment for suspected lower GI tract cancer within two weeks; further investigations (e.g. colonoscopy) may then be scheduled to establish a diagnosis.

The 2011 NICE Colorectal Cancer Diagnosis and Management Guidelines (CG131)[30] states that patients should be advised that one or more investigations may be necessary to confirm or exclude a diagnosis of CRC. Colonoscopy is offered to patients without significant comorbidity to confirm a diagnosis of CRC; if a suspicious lesion is detected a biopsy should be performed (unless contraindicated). For people with co-morbidities, CT colonography can be offered as an alternative to colonoscopy.

The SIGN 2011 guidance for CRC[31] patients over the age of 40 years who present with new onset, persistent or recurrent rectal bleeding should be referred for investigation. Review of the patient by a regional clinical genetics service is recommended for accurate risk assessment if family history of CRC is the principal indication for referral for investigation. General practitioners should perform an abdominal and rectal examination on all patients with symptoms indicative of CRC. A positive finding should expedite referral, but a negative rectal examination should not rule out the need to refer. All symptomatic patients should have a full blood count; in cases of anaemia the presence of iron deficiency should be determined. Where CRC is suspected clinically, the whole of the large bowel should be examined:

- Colonoscopy is recommended as a very sensitive method of diagnosing CRC, enabling biopsy and polypectomy.
- CT colonography can be used as a sensitive and safe alternative to colonoscopy.

Guidelines from clinical professional bodies follow a similar pattern: the Royal College of Radiologists recommends that symptomatic patients with suspected CRC should receive evaluation/diagnosis by imaging studies (colonoscopy, CT colonography or barium enema);[32]

the Association of Coloproctology of Great Britain and Ireland recommends that patients with higher-risk symptoms should be fast-tracked either in special clinics or with urgent appointments in routine clinics. Patients so referred should be investigated with sigmoidoscopy (flexible or rigid) plus a high quality double contrast barium enema, or colonoscopy, or CT colonography.[33]

Treatment of CRC

Following diagnosis and staging, CRC may be treated with surgery, chemotherapy and radiotherapy, or in some cases with biological agents such as cetuximab. Treatment is dependent upon the stage of the cancer and is described in more detail in NICE Clinical Guideline 131: Colorectal cancer diagnosis and management.[30]

2 Objectives

The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of testing for the presence of occult blood in faeces, using quantitative FIT, as a triage step in the investigation of people, presenting in primary care, with lower abdominal symptoms, who require investigation for possible CRC. Use of testing for occult blood in the faeces has been recently recommended for specific groups of people within this population who are considered to be at low risk of CRC; this assessment will consider the clinical- and cost-effectiveness of quantitative FIT as a replacement for guaiac testing. The following research questions have been defined to address the review objective. In symptomatic people who are at low risk of colorectal cancer:

- What is the clinical-effectiveness of FIT compared with gFOBT or no triage step (referral based on clinical assessment), for achieving appropriate referral for further investigation within the two week suspected cancer referral target?

- What is the comparative accuracy of different quantitative FIT assays and gFOBT, where CRC determined by colonoscopy (the reference standard method) is the target condition?

- What is the diagnostic accuracy of different quantitative FIT assays, where CRC determined by colonoscopy (the reference standard method) is the target condition?

- What is the cost-effectiveness of using FIT for the presence of occult blood as a triage step, compared to gFOBT and to no triage step (no testing for occult blood in faeces)?

The target population for this assessment is those with low risk symptoms as defined in NG12. However, in order to maximise the available evidence, our assessment will include any studies where the population is described as symptomatic, not limited to the specific groups as detailed in NG12. The committee will then be able to take a view on how applicable the estimates derived from the literature are to the population included in the scope.

3 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[34] and the NICE diagnostics assessment programme manual.[35]

3.1 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each of the clinical-effectiveness questions. These are summarised in Table 2.

Protocol Table 2: Inclusion criteria

Question	**What is the accuracy of different quantitative FIT assays, where the target condition is CRC determined by colonoscopy (the reference standard method)?**	**What is the clinical-effectiveness of FIT compared with gFOBT or no triage step, for achieving appropriate referral for further investigation within the two week suspected cancer referral target?**
Participants:	People presenting with lower abdominal symptoms who are being investigated for possible CRC[*]	
Setting:	Primary care	
Interventions (index test):	Quantitative FIT assays listed in Table 1	
Comparators:	Any other FIT method (including different faecal haemoglobin cut-offs or different numbers of samples), or gFOBT, or no comparator	gFOBT or no triage step
Reference standard:	Colonoscopy	Not applicable
Outcomes:	Diagnostic accuracy (the numbers of true positive, false negative, false positive and true negative test results), where the target condition is CRC determined by colonoscopy[**]	Appropriate referral for secondary care investigations with 2 weeks from presentation (proportion of patients referred for secondary care investigation in whom CRC was confirmed AND proportion of patients not referred for secondary care investigation in whom CRC was later diagnosed[$]), long term CRC mortality,[$$] any patient acceptability/satisfaction or HRQoL measures
Study design:	Diagnostic cohort studies	RCTs (CCTs will be considered if no RCTs are identified)

[*] Studies will be included if the participant selection criteria are unclear, but the population is described as symptomatic/suspected CRC and NOT asymptomatic population-based screening; study authors will be contacted for additional details, as needed. Studies conducted in people with pre-existing inflammatory bowel disease will be excluded. Studies of patients with high risk or 'red flag' symptoms will not be excluded as there is no consistent definition of 'red flag' symptoms; applicability to the review question will be assessed on an individual study basis

[**] If studies report diagnostic accuracy data for other target conditions, in addition to CRC, (e.g. adenoma, inflammatory bowel disease, organic bowel disease) these data will also be extracted. Studies where CT colonography is used as alternative reference standard in some patients will be included. Any reported data on test failure rates or measures of patient acceptability/satisfaction will also be extracted

[$] Patients not initially referred for secondary care investigation should be followed up for a minimum of one year, or until referral to secondary care.

[$$] Studies reporting CRC mortality should have a minimum follow-up for a specified period

3.2 Search strategy

Search strategies will be based on intervention (FIT assays) and target condition (CRC), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[34] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[36] Additional supplementary searches will be carried out as necessary. Searches for studies for costs and quality of life will be developed separately where required.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords associated with faecal immunochemical tests for occult blood will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations and Daily Update (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- International Network of Agencies for Health Technology Assessment (INAHTA) Publications (Internet) http://www.inahta.org/publications/
- NIHR Health Technology Assessment Programme (Internet)
- Aggressive Research Intelligence Facility (ARIF) database (Internet) http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and relevant systematic reviews will be checked.

No restrictions on language, publication status or date of publication will be applied Searches will take into account generic and other product names for the intervention. An example search strategy is presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.[37] Identified references will be downloaded in Endnote X6 software for further assessment and handling. References in retrieved articles will be checked for additional studies. The final list of included papers will also checked on PubMed for retractions, errata and related citations.[38-41]

3.3 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics, presenting symptoms, other risk factors, etc.), details of the FIT system evaluated (manufacturer, antibody, limit of quantitation, definition of cut-off, sampling procedure (including sample requirements), detection method (including analyser used), etc.), details of comparator gFOBT and other FIT test(s) if applicable (manufacturer, antibody, limit of quantitation, definition of cut-off, sampling procedure, detection method, etc.), details of reference standard, clinical outcomes (number of participants appropriately referred for secondary care investigation, i.e., the number of participants in whom the triage test correctly predicts final diagnosis, long term outcomes (e.g., CRC mortality), any patient satisfaction or HRQoL measures), and test performance outcome measures. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

3.4 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.[42] Diagnostic accuracy studies will be assessed using QUADAS-2.[43] The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of

recommendation for design of any future studies. Where sufficient data are available the results of quality assessment may be used to inform stratified meta-analyses in order to explore the impact if individual components of study quality upon the findings of the review. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

3.5 Methods of analysis/synthesis

If available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of different FIT methods compared to gFOBT, when used in a symptomatic population, will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[44-46] If more than one RCT evaluates the same clinical outcome in patients assessed with the same intervention (FIT assay method) and comparator (gFOBT or no triage), then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs. Any estimates of the relative accuracy/effectiveness of different FIT methods and gFOBT will be derived from direct, within study comparisons. Where sufficient data are available, clinically relevant subgroup analysis will be considered (e.g. age, gender, socioeconomic status, symptoms at presentation, current use of anti-coagulants or NSAIDs).

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed and by FIT method evaluated. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

4 Methods for synthesising evidence of cost-effectiveness

4.1 Identifying and reviewing published cost-effectiveness studies

Search strategy

Literature searches will be performed to identify published economic evaluations, cost studies and utility studies. A methodological study design filter to identify cost and economic studies in databases that are not health economic specific will be included in the search strategy for economic evaluations where appropriate. Relevant economic evaluations, utility studies and cost studies will be searched on the following databases and resources:

- NHS Economic Evaluation Database (NHS EED) (Internet)
- MEDLINE (Ovid)
- MEDLINE In-Process Citations and Daily Update (Ovid)
- EMBASE (Ovid)
- EconLit (EBSCO)
- CEA Registry (http://www.cearegistry.org/)
- Research Papers in Economics (RePEc) (http://repec.org/)

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses that study FIT assays or guaiac FOBT. Cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options, will be selected for our assessment. Clinical trials, modelling studies and cohort studies will be relevant within the scope of this assessment. The intention is to identify studies that can be used to support the development of a health economic model, and to estimate the model input parameters, that will aim to answer the research questions of this assessment, but not to perform a systematic review.

A summary with the results and the methodological quality of the selected studies will be reported. Methodological quality will be assessed following the criteria for economic evaluations in health care as described in the NICE methodological guidance.[47] Data extraction will focus on technologies compared, indicated population, main results in terms of costs, consequences and the incremental cost-effectiveness of the alternatives compared, but also on modelling methods used, the sources of input parameters and robustness of the study results.

4.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to assess the cost-effectiveness of using quantitative FIT for occult blood as a triage step in the investigation of symptomatic people who are at low risk of colorectal cancer, compared to guaiac faecal occult blood testing or to no triage step.

This assessment will evaluate the cost-effectiveness of the FIT assays described in Section 1.2 compared to guaiac FOBT and no FOBT. The perspective will be that of the NHS and a time horizon of lifetime will be used, as CRC is a condition where the relevant outcomes are spread through the lifetime. Any assumption used in the model and any parameter value will be based on the literature if possible and supplemented by clinical expert opinion as required. No health economic model will be developed for the cases where evidence is lacking (e.g. for a specific intervention, comparator, setting and/or sub-population). Future costs and benefits will be discounted at a rate of 3.5% per year as recommended by NICE.

Model structure

A combination of a decision tree and a Markov state-transition model will be used to capture the diagnosis and the progression of CRC, respectively. The structure of the model will be similar to that used in NG12[48]. A schematic representation of the model is shown in Appendix 3. The model begins with a cohort of symptomatic patients, presenting in primary care, who require investigation for possible CRC. A patient in the cohort is offered one of the following choices: FIT, gFOBT or no triage testing at all (referral straight to colonoscopy).

Testing branch (FIT or gFOBT)

If the gFOBT or FIT result is positive, patients are referred for either colonoscopy or CT colonography. For patients who test positive for CRC after colonoscopy or CTC, it is assumed that they receive a CT scan or MRI to establish the stage of the cancer and to determine the health state where they enter the Markov model used to simulate CRC progression. Patients who test negative for CRC after colonoscopy or CTC (people with a false positive FIT result) may require referral for further investigation where a clinician judges this to be necessary or may be discharged.

In line with the NICE suspected cancer guideline,[48] safety-netting (“active monitoring in primary care”) is recommended to reduce the impact of false negatives. Thus, for those patients with a negative test result, or for a selected group of those with a negative test result, (e.g. “people with any symptom that is associated with an increased risk of cancer, but who do not meet the criteria for referral or other investigative action"), it is assumed that additional investigation (e.g. repeat FIT testing or colonoscopy) will take place (within a time frame agreed with the patient) to determine whether the patient does in fact have CRC. It is assumed that the presence or absence of CRC will be established by an additional

colonoscopy. Patients who had false negative gFOBT or FIT results are assumed to persist in their symptoms and to have an increased probability of progressing to a worse cancer state.

No testing branch (colonoscopy)
Patients with a positive result will enter the Markov model for CRC progression, and patients with a negative result may require referral for further investigation where a clinician judges this to be necessary or may be discharged.

Markov model CRC progression
The structure of the Markov model may be similar to the one used in NG12, where cancer stages were defined based on the Duke's grading system for CRC and then mapped into the health states of the Markov model. The initial distribution of CRC patients through the model's health states will be determined by the probability of being in a certain Duke's stage. After the initial distribution is determined, it will be assumed that patients may stay in their current health state, progress to the health state representing the next worsening in the condition or die (from CRC or another cause). Furthermore, it will be assumed that a treatment depending on the health state will be offered and successful treatment (CRC is cured) will also be an option in the model. A one year cycle length will be used, in line with NG12,[48] and this is considered reasonable to capture the probability of progression for patients with CRC.

Sensitivity/scenario analyses
One way sensitivity analyses will be performed for all key parameters. Probabilistic sensitivity analyses will be performed using probability distributions for the input parameters of the model instead of fixed values. The sources of the assumptions made regarding the choices of the probability distributions will be reported. Cost-effectiveness planes and cost-effectiveness acceptability curves will be used to reflect decision uncertainty regarding mutually exclusive alternatives. Scenario analyses will be conducted to test the robustness of the model's results for different assumptions. This may include (depending upon data being available) the use of different cut-offs and/or multiple sampling strategies in order to determine the best way to operationalise FIT testing.

Health outcomes
Utility values, based on literature or other sources, will be incorporated in the economic model for the various health states. QALYs will be calculated from the economic modelling, by multiplying the life years that patients spend in each health state of the model by the associated utility, representing the valuation of the health state of the patient. Additionally, consequences may also be expressed in terms of e.g. the number of colonoscopies avoided. However, only QALYs will be used to calculate incremental cost-effectiveness ratios.

Costs

Resource utilisation will be estimated for the diagnostic tests. This may include: cost of equipment, reagents and consumables, cost of staff and associated training and medical costs arising from testing and care including further follow up and safety netting in primary care. Medical costs related to adverse events which arise from testing or further diagnostic work up (e.g. colonoscopy), including those associated with false test results, will also be considered. CRC treatment (if any) will also be included in the model. Cost data will be obtained from existing studies (if any), routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), and discussions with individual hospitals and/or with the manufacturers of the technologies included in the model.

5 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 21/06/2016. Data arriving after this date will be considered if practicable and at the discretion of the EAG. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

6 Competing interests of authors

None

7 Timetable/milestones

Milestones	Completion data
Draft protocol	23/02/2016
Final protocol	18/03/2016
Progress report	21/06/2016
Draft assessment report	16/08/2016
Final assessment report	14/09/2016

8 References

[1] Office for National Statistics. *Cancer registration statistics, England, 2013 [Internet]*. London: Office for National Statistics, 2015 [accessed 13.1.16]. 19p. Available from: http://www.ons.gov.uk/ons/dcp171778_409714.pdf

[2] Office for National Statistics. *Cancer Survival in England: adults diagnosed in 2009 to 2013, followed up to 2014 [Internet]*. London: Office for National Statistics, 2015 [accessed 13.1.16]. 13p. Available from: http://www.ons.gov.uk/ons/dcp171778_424443.pdf

[3] Halloran SP, Launoy G, Zappa M. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition - Faecal occult blood testing. *Endoscopy* 2012;44(Suppl 3):SE65-87.

[4] National Collaborating Centre for Cancer. *Suspected cancer: recognition and management of suspected cancer in children, young people and adults. Clinical guideline. Appendices A - E [Internet]*. London: National Collaborating Centre for Cancer, 2015 [accessed 13.1.16]. 64p. Available from: http://www.nice.org.uk/guidance/ng12/evidence/appendices-ae-74333342

[5] Leeflang MM, Rutjes AW, Reitsma JB, Hooft L, Bossuyt PM. Variation of a test's sensitivity and specificity with disease prevalence. *CMAJ* 2013;185(11):E537-44.

[6] Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014;160(3):171-181.

[7] McDonald PJ, Digby J, Innes C, Strachan JA, Carey FA, Steele RJ, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. *Colorectal Dis* 2013;15(3):e151-9.

[8] Health and Social Care Information Centre. *National bowel cancer audit report 2015 [Internet]*. Leeds: Health and Social Care Information Centre, 2015 [accessed 13.1.16]. 86p. Available from: http://www.hscic.gov.uk/catalogue/PUB19500/nati-clin-audi-supp-prog-bowe-canc-2015.pdf

[9] Bowel Cancer UK. *Improving capacity, saving lives: Endoscopy in the UK*. London: Bowel Cancer UK, 2012. 10p.

[10] National Collaborating Centre for Cancer. *Suspected cancer: recognition and referral. NICE guideline. Full guideline [Internet]*. London: National Collaborating Centre for Cancer, 2015 [accessed 13.1.16]. 378p. Available from: http://www.nice.org.uk/guidance/ng12/evidence/full-guidance-74333341

[11] Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. *Cancer Causes Control* 2012;23(2):289-96.

[12] Vega P, Valentin F, Cubiella J. Colorectal cancer diagnosis: pitfalls and opportunities. *World J Gastrointest Oncol* 2015;7(12):422-33.

[13] Beg M, Singh M, Saraswat MK, Rewari BB. Occult gastro-intestinal bleeding: detection, interpretation, and evaluation. *JIACM* 2002;3(2):153-8.

[14] Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med* 1999;341(1):38-46.

[15] Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. *Gut* 2015;64(8):1327-37.

[16] Alpha Laboratories Ltd. *Diagnostics for digestive health management [Internet]*. Eastleigh, Hampshire: Alpha Laboratories Ltd, 2015 [accessed 8.2.16]. 16p. Available from: http://www.alphalabs.co.uk/media/productfile/file/d/i/diagnostics-for-digestive-health-mngt_may15.pdf

[17] Sentinel Diagnostics. *FOB Gold(R): the universal system for fecal occult blood testing (FIT)*. Milan: Sentinel Diagnostics, [accessed 8.2.16]. 2p. Available from: http://www.sentinel.it/upload_doc/download/51-1-FOBGold.pdf

[18] Eiken Chemical Co Ltd. *OC-SENSOR PLEDIA. FIT (iFOBT) automation*. Toyko: Eiken Chemical Co Ltd, 2016 [accessed 8.2.16]. 2p. Available from: http://www.eiken.co.jp/en/product/images/OC-PLEDIA%20.pdf

[19] Eiken Chemical Co Ltd. *OC-SENSOR io*. Toyko: Eiken Chemical Co Ltd, 2010 [accessed 8.2.16]. 2p. Available from: http://www.palexmedical.com/file_download.cfm?ftid=1&fid=336

[20] R-Biopharm AG. *RIDASCREEN(R) Haemo-/Haptoglobin Complex. Article No: G0903*. Darmstadt: R-Biopharm AG, 2015 [accessed 8.2.16]. 16p. Available from: http://www.r-biopharm.com/wp-content/uploads/3983/G09031_RIDASCREEN_Haemo-HaptoglobinComplex_2015-05-06-gb1.pdf

[21] Launois R, Moine JG, Uzzan B, Fiestas Navarrete LI, Benamouzig R. Systematic review and bivariate/HSROC random-effect meta-analysis of immunochemical and guaiac-based fecal occult blood tests for colorectal cancer screening. *Eur J Gastroenterol Hepatol* 2014;26(9):978-989.

[22] Basu A, Smartt P. *Comparison of diagnostic accuracy between immunochemical and guaiac based faecal occult blood tests for colorectal cancer detection: a systematic review of the literature*. Christchurch: Health Services Assessment Collaboration (HSAC), 2009 Available from: http://www.healthsac.net/downloads/publications/HSAC16A%20FOBT-Part2%20220609%20FINAL.pdf

[23] Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;334(3):155-9.

[24] Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. *Eur J Cancer* 2013;49(14):3049-54.

[25] Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, Nicolas D, Moreno SG, Jimenez A, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol* 2010;45(7):703-12.

[26] Vasilyev S, Smirnova E, Popov D, Semenov A, Eklund C, Hendolin P, et al. A new-generation fecal immunochemical test (FIT) is superior to quaiac-based test in detecting colorectal neoplasia among colonoscopy referral patients. *Anticancer Res* 2015;35(5):2873-80.

[27] Hassan C, Giorgi Rossi P, Camilloni L, Rex DK, Jimenez-Cendales B, Ferroni E, et al. Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. *Aliment Pharmacol Ther* 2012;36(10):929-40.

[28] Cancer Research UK. *Major increase in bowel cancer screening uptake shown with new screening test (Press release: 27 March 2015) [Internet]*, 2015 [accessed 8.2.16] Available from: http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2015-03-27-major-increase-in-bowel-cancer-screening-uptake-shown-with-new-screening-test-0

[29] Young GP, Symonds EL, Allison JE, Cole SR, Fraser CG, Halloran SP, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. *Dig Dis Sci* 2015;60(3):609-22.

[30] National Institute for Health and Care Excellence. *Colorectal cancer: diagnosis and management. Clinical guideline 131 [Internet]*. London: NICE, 2011 [accessed 18.1.16]. 47p. Available from: http://www.nice.org.uk/guidance/cg131/resources/colorectal-cancer-diagnosis-and-management-35109505330117

[31] Scottish Intercollegiate Guidelines Network. *Diagnosis and management of colorectal cancer: a national clinical guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2011. 56p. Available from: http://www.sign.ac.uk/guidelines/fulltext/126/index.html

[32] The Royal College of Radiologists. Colon cancer: diagnosis. In: *iRefer: Making the best use of clinical radiology [Internet]*. London: The Royal College of Radiologists, 2012 [accessed 20.1.16]. Available from: http://irefer.org.uk/images/pdfs/cancer_ca23_abstract.pdf

[33] The Association of Coloproctology of Great Britain and Ireland. *Guidelines for the management of colorectal cancer. 3rd edition [Internet]*. London: The Association of Coloproctology of Great Britain and Ireland, 2007 [accessed 20.1.16]. 117p. Available from: http://www.acpgbi.org.uk/content/uploads/2007-CC-Management-Guidelines.pdf

[34] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[35] National Institute for Health and Care Excellence. *Diagnostics Assessment Programme manual [Internet]*. Manchester: NICE, 2011 [accessed 9.3.16]. 93p. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf

[36] Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews [Internet]*: The Cochrane Collaboration, 2009 [accessed 23.3.11] Available from: http://srdta.cochrane.org/handbook-dta-reviews

[37] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[38] Wright K, McDaid C. Is the retraction of journal articles in electronic journals and databases consistent and timely? A case study [Poster]. *Cochrane Colloquium 19-22 October*. Madrid: Cochrane Collaboration, 2011.

[39] Wright K, McDaid C. Reporting of article retractions in bibliographic databases and online journals. *J Med Libr Assoc* 2011;99(2):164-7.

[40] Royle P, Waugh N. Should systematic reviews include searches for published errata? *Health Info Libr J* 2004;21(1):14-20.

[41] Waffenschmidt S. Assessing the completeness of systematic reviews via the "related articles" function and/or a simple structured Boolean search in PubMed – a pilot study (B202) [Oral presentation]. *Cochrane Colloquium 19-22 October*. Madrid: Cochrane Collaboration, 2011.

[42] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

[43] Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36.

[44] Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PMM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58(10):982-90.

[45] Harbord RM, Whiting P, Sterne JA, Egger M, Deeks JJ, Shang A, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *J Clin Epidemiol* 2008;61(11):1095-103.

[46] Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;8(2):239-51.

[47] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed ????]. 93p. Available from: http://publications.nice.org.uk/pmg9

[48] Vernon SW. Participation in colorectal cancer screening: a review. *J Natl Cancer Inst* 1997;89(19):1406-1422.

Protocol Appendix 1: Clinical effectiveness search

Embase (Ovid): 1974 to 2016 March 07
Date searched: 8.3.16
Records found: 5053

1 Fecal Immunochemical Test/ [EMTREE candidate term 13.1.16] (132)
2 ((immunochem$ or immuno-chem$ or immunohistochem$ or immuno-histochem$ or immunol$ or immunochromatographic or immuno-chromatographic or immunoassay or immuno assay) adj4 (f?ecal or f?eces or stool or stools)).ti,ab,ot,hw. (1617)
3 iFOBT.ti,ab,ot,hw. (162)
4 1 or 2 or 3 (1658)
5 F?ecal h?emoglobin.ti,ab,ot,hw. (154)
6 H?emoccult.ti,ab,ot,hw. (865)
7 FOBT.ti,ab,ot,hw. (1849)
8 5 or 6 or 7 (2770)
9 (f?cal or f?eces or stool or stools).ti,ab,ot,hw. (345973)
10 occult blood/ or occult blood.ti,ab,ot,hw. (11125)
11 (test$ or measur$ or screen$ or exam$).ti,ab,ot,hw. (9075537)
12 9 and 10 and 11 (5095)
13 4 or 8 or 12 (7119)
14 exp colon tumor/ (238696)
15 exp rectum tumor/ (181430)
16 exp colon cancer/ (190541)
17 exp rectum cancer/ (147548)
18 ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (316473)
19 CRC.ti,ab,ot. (26955)
20 ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (2631)
21 (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1924)
22 (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (29)
23 or/14-22 (328214)
24 13 and 23 (5058)
25 (FOB gold$ or FOBgold$).ti,ab. (27)
26 (jack-arc$ or jackarc$ or HM-JACKarc$).ti,ab. (7)
27 (RIDASCREEN$ H?emo$ or RIDASCREEN$ Hapto$).ti,ab. (2)
28 (OC Sensor$ or OC-Sensor$ or OC Pledia$ or OC-Pledia$).ti,ab. (150)
29 or/25-28 (168)
30 24 or 29 (5069)
31 animal/ (1720979)
32 animal experiment/ (1913973)

33 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6154262)
34 or/31-33 (6154262)
35 exp human/ (16877184)
36 human experiment/ (349350)
37 or/35-36 (16878630)
38 34 not (34 and 37) (4845304)
39 30 not 38 (5053)

Protocol Appendix 2: Related NICE guidance

Published NICE guidance

Suspected cancer: recognition and referral. NICE guideline 12 (2015). Available from: www.nice.org.uk/guidance/ng12

Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011). Available from: www.nice.org.uk/guidance/cg131. Date for review: December 2015.

Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. NICE clinical guideline 118 (2011). Available from: www.nice.org.uk/guidance/cg118. Date for review: TBC.

Improving outcomes in colorectal cancer. NICE clinical guideline CSGCC (2004). Available from: www.nice.org.uk/guidance/csgcc . Date for review: December 2015.

Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 531 (2015). Available from: www.nice.org.uk/guidance/ipg531.

Transanal total mesorectal excision of the rectum. NICE interventional procedure guidance 514 (2015). Available from: www.nice.org.uk/guidance/ipg514.

Combined endoscopic and laparoscopic removal of colonic polyps. NICE interventional procedure guidance 503 (2014). Available from: www.nice.org.uk/guidance/ipg503.

Fluorouracil chemotherapy: The My5‑FU assay for guiding dose adjustment. NICE diagnostic guidance 16 (2014). Available from: www.nice.org.uk/guidance/dg16.

Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. NICE technology appraisal guidance 307 (2014). Available from: www.nice.org.uk/guidance/ta307.

Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118). NICE technology appraisal guidance 242 (2012). Available from: www.nice.org.uk/guidance/ta242.

Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedure guidance 401 (2011). Available from: www.nice.org.uk/guidance/ipg401.

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 212 (2012). Available from: www.nice.org.uk/guidance/ta212.

Endoscopic submucosal dissection of lower gastrointestinal lesions. NICE interventional procedure guidance 335 (2010). Available from: www.nice.org.uk/guidance/ipg335.

Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. NICE interventional procedure guidance 331 (2010). Available from: www.nice.org.uk/guidance/ipg331.

Cetuximab for the first-line treatment of metastatic colorectal cancer. NICE technology appraisal guidance 176 (2009). Available from: www.nice.org.uk/guidance/ta176.

Radiofrequency ablation for colorectal liver metastases. NICE interventional procedure guidance 327 (2009). Available from: www.nice.org.uk/guidance/ipg327.

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007). Available from: www.nice.org.uk/guidance/ta118.

Laparoscopic surgery for colorectal cancer. NICE technology appraisal guidance 105 (2006). Available from: www.nice.org.uk/guidance/ta105.

Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal guidance 100 (2006). Available from: www.nice.org.uk/guidance/ta100.

Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006). Available from: www.nice.org.uk/guidance/ipg201.

Computed tomographic colonography (virtual colonoscopy). NICE interventional procedure guidance 129 (2005). Available from: www.nice.org.uk/guidance/ipg129.

Wireless capsule endoscopy for investigation of the small bowel. NICE interventional procedure guidance 101 (2004). Available from: www.nice.org.uk/guidance/ipg101.

Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. NICE technology appraisal guidance 61 (2003). Available from: www.nice.org.uk/guidance/ta61.

NICE guidance under development

Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line) ID794. NICE technology appraisal guidance. Publication expected: April 2016.

Colon cancer (adjuvant) - irinotecan [ID379]. NICE technology appraisals guidance. Publication expected: TBC.

Low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer. NICE interventional procedure guidance. Publication expected: TBC.

Protocol Appendix 3: Draft model structure