HTA20/140 - NIHR133852

1. Full title of project

COLOFIT – Optimal use of Faecal Immunochemical Testing for patients with features of possible colorectal cancer.

2. Summary of research (abstract)

Colorectal Cancer (CRC) is the third commonest cancer in the UK and second commonest cause of cancer death. Around 42,300 new cases are diagnosed in the UK each year, with 16,300 deaths. Around 700,000 English patients are referred from primary to secondary care annually for investigation of possible CRC symptoms, though less than 5% have CRC. Symptoms associated with CRC include rectal bleeding, altered bowel habit, weight loss, iron deficiency anaemia, abdominal or rectal mass. Lower GI symptoms are common in the general population so are poorly discriminatory for CRC. Once referred to hospital, most patients undergo colonoscopy or Computerised Tomographic Colonography (CTC). Both investigations are invasive, with associated risks: requiring attendance at secondary care and pre-procedural bowel preparation.

The NHS is struggling with colonoscopy and CTC capacity, with only 55% of English units meeting urgent cancer wait targets. This has worsened during the Covid-19 pandemic with a significant backlog of patients awaiting cancer investigations. Improved strategies to define patients by CRC risk are needed so that invasive investigations can be targeted at those most at risk. Enhanced triage will also reduce overtreatment and overdiagnosis. Faecal immunochemical testing (FIT) measures the level of haemoglobin within the stool. It is now the basis of population-based screening programmes and has an evolving role in symptomatic patients.

COLOFIT will evaluate the evidence and develop a risk-based algorithm for implementation of a FIT-based strategy for patients with possible CRC symptoms presenting to primary care. This will be achieved through four Work Packages (WP 1-4). WP1 will undertake systematic reviews of published evidence on FIT and include other potential CRC risk factors such as age, sex, family history, Body Mass Index or blood markers. WP2 will develop a mathematical model of risk and test the model to see if it works in available datasets. WP3 will study patient, clinician and stakeholder views on FIT-based assessment of risk covering a wide range of issues including acceptability of stool-based testing, not being referred with symptoms when FIT was negative, safety netting and non-CRC diagnoses. WP4 will study health economics using results of WPs1-3, examining cost of investigations, savings from fewer investigations and how resources might be better used.

Overall, COLOFIT will establish the optimal use of FIT for patients with possible CRC. It will develop an algorithm based on best available evidence, will validate it, will explore patient and clinician acceptability, and will assess value for money. The benefits of this research will be a patient pathway that allows those at highest risk to be investigated quickly and correctly and reduce unpleasant investigations for those who do not need them. It will additionally study the health economics of such a pathway.

3. Background and rationale

3.1 The importance of Colorectal Cancer.

Colorectal cancer (CRC) is the third most common cancer in the United Kingdom (UK) with around 42,300 new cases diagnosed per year, leading to 16,300 deaths.[1] Although there is some evidence for improved survival with expedited diagnosis of symptomatic cancer for many cancer sites,[2,3] the evidence is strongest for CRC.[4] The survival benefit from expedited diagnosis is postulated to arise from stage-shift (or within-stage shift) plus avoidance of emergency presentation, where the complication precipitating the emergency brings additional mortality. A recent modelling study of the harms of delayed diagnosis or treatment of CRC estimated 6.4-10.7% worse 10-year survival for an 8-week delay (the range of estimates being across age groups).[5] Extrapolated to the UK, if all symptomatic CRCs were to have diagnosis advanced by 8 weeks, approximately 3000 colorectal cancer deaths could be prevented annually.

3.2 Presentation of CRC.

Symptomatic presentation. Most CRCs (>90%) are diagnosed after symptoms develop. Bowel symptoms are, however, poorly discriminatory for CRC, and until recently, there was no triage test in primary care. Features of possible CRC underpinned the National Institute for Health and Care Excellence (NICE) guidance on Suspected Cancer: recognition and referral, NG12, in 2015.[6] This guidance used a risk of 3% to define high-risk patients requiring urgent secondary care investigation (via 2 Week Wait (2WW)). Low-risk patients were to be offered testing for faecal occult blood, with urgent investigation for those testing positive. Subsequent NICE guidance, DG30, recommended FIT for these primary care low-risk patients.[7] However, these guidelines have been variably implemented with significant resistance from many clinicians. There remains considerable variation in use of diagnostic services and 2WW across the NHS. Crucially – and the subject of this application – the optimum role of FIT has yet to be determined. The different potential presenting features of CRC were collated in the NICE NG12 guidance and separated into two groups based on the risk of cancer.

High risk, equating to a risk of cancer of 3% or more. Symptoms in primary care considered high risk are:

- Weight loss **with** abdominal pain in over 40s
- Rectal bleeding in over 50s
- Iron-deficiency anaemia or change in bowel habit in over 60s
- Rectal or abdominal mass
- Rectal bleeding in under 50s **if accompanied by** abdominal pain, change in bowel habit, weight loss or iron-deficiency anaemia

Low risk symptoms, equating to a risk between 1 and 3% are:

- Abdominal pain or weight loss in over 50s
- Iron-deficiency anaemia or change in bowel habit in under 60s
- Anaemia without iron deficiency in over 60s

We will use the terms high-risk and low-risk throughout the application, and introduce the term, **pan-risk**, to cover both of these populations i.e., all patients in primary care presenting with features of possible colorectal cancer equating to a risk of cancer of 1% or more.

Population based screening. Screening for CRC is effective, but a combination of moderate sensitivity, moderate uptake and limited age range in national programmes, means that fewer than 10% of CRCs are diagnosed by this route. Screening also uses FIT,

which can be a source of confusion (raised in PPI meetings), so throughout the COLOFIT programme we will endeavour to keep the distinction between the two uses very clear.

Emergency presentation. In 2017, 22% of CRC patients presented as an emergency,[8] and these patients have poor outcomes, over and above that expected from the generally worse staging at diagnosis in this emergency admission group.[9]

3.3 Definitive investigations.

Colonoscopy and Computerised Tomography Colonography. Colonoscopy is the gold standard investigation of the colon, providing direct visualisation of the colonic mucosa to identify abnormalities, take biopsies and perform therapeutic and preventative procedures including polypectomy, to remove dysplastic lesions. In addition to diagnosing and preventing CRC, colonoscopy also plays a vital role in diagnosing and assessing non-neoplastic conditions, which often share symptoms with CRC.[10] Colonoscopy, however, is an invasive procedure and has associated risks both from the bowel preparation taken pre-procedure and from the procedure itself. The risks related to the procedure include bleeding and perforation.[11] It is therefore imperative that the benefits of the procedure outweigh any risks. Computed Tomographic Colonography (CTC) is used as an alternative to colonoscopy, when a colonoscopy is incomplete or if the patient is medically unfit.[12,13] However, a major disadvantage is that histology cannot be obtained, and therapeutics cannot be performed via this investigation. Both procedures, and the associated bowel preparation, are unpleasant for patients.

Current service provision. In England, approximately 700,000 adults per year are investigated for symptoms of possible CRC, most receiving colonoscopy.[11,14] Unfortunately, possible CRC symptoms are poorly discriminatory, with colonoscopy CRC yield of only 4.1%.[15] Over 2 million endoscopies are performed in the UK annually and the NHS is struggling to meet demand with only 55% of English units meeting 2WW target times.[16] The Joint Advisory Group on GI Endoscopy accredits English endoscopy units and pre-pandemic one third of units were failing accreditation due to long waiting times. This picture of demand exceeding capacity was consistently worsening even before the Covid-19 pandemic which has reduced capacity further. The impact of Covid-19 on diagnostic delays is widely reported.[5]

3.4 Faecal Immunochemical Testing.

The health technology being assessed - FIT is a method of detecting and quantifying haemoglobin levels within faeces. FIT utilises antibodies to the globin portion and is specific to human blood.[17] A single sample is required, with a purpose-made collection device containing buffer. All UK tests are now quantitative, giving a haemoglobin value in units of micrograms of haemoglobin/gram of faeces. Various cut-offs to define a 'positive' test are in use, with population-based screening thresholds much higher than the 10 µg Hb/g faeces threshold generally used in the symptomatic population. Several assays exist.

FIT has replaced the traditional guaiac faecal occult blood test (gFOBT) within the NHS Bowel Cancer Screening Programme (BCSP). It provides CRC screening based upon FIT results in individuals aged 60-74 years. gFOBT required 3 separate stool samples, whereas FIT only requires one. The uptake of screening with the BCSP has increased by around 10% since the change from gFOBT to FIT, suggesting the method of sampling used in FIT may be more acceptable to patients – which is also relevant in the symptomatic population.[18,19] Most use of FIT has been in population-based screening programmes: however, since DG30 it is also recommended in low-risk symptomatic primary care patients.[20] Two large, published UK cohorts (from co-applicants) report effective diagnostic performance of FIT in low-risk

patients in primary care.[15,19] In secondary care, several English areas now offer FIT to 2WW patients, aimed at identifying lower risk patients within this overall high-risk population. Because the Covid-19 pandemic has significantly reduced availability of LGI services, FIT has been used to prioritise patients for definitive LGI investigation. Several secondary care cohort studies have been established; with two (also from co-applicants) published.[15,19,21,22] Use of FIT varies hugely nationally with resistance to use from some stakeholders.

Benefits and harms from FIT as currently used in the symptomatic population. Improved symptomatic CRC diagnosis with FIT could yield the following benefits: improvement in CRC survival;[23] reduction in emergency presentation of CRC and associated mortality; diagnosis at less-advanced stage, with less need for extensive treatment; improved patient experience; reduction in need for LGI investigations (with reduced waits for those requiring investigation); reduction of complications of investigations and reduced 'costs' for patients in terms of time and anxiety; cost benefits.

Potential harms of a FIT-based strategy include missed or delayed cancer diagnosis, failure to identify, and thus treat, individuals with advanced colorectal neoplasia (ACN), failure to diagnose other serious conditions and to address patient symptoms; lost opportunistic cancer prevention by adenoma removal (including ACN).

A broader system risk could be that FIT simply introduces delay. In this scenario, patients avoid a cancer pathway initially, but are eventually referred for colonoscopy or CTC. This helps no-one. It is therefore crucial that a FIT-based strategy incorporates robust plans for those individuals who test FIT negative and for those where the pathway indicates they do not require FIT. Symptomatic non-cancer patients still need to be helped: being FIT-negative indicates that an individual is unlikely to have CRC, but some will have another condition such as inflammatory bowel disease, irritable bowel syndrome or diverticular disease that requires management. Defining these pathways goes beyond the scope of this research; however, we will work with stakeholder groups to ensure that pathways for management of non-CRC patients are robust. Safety netting to ensure that patients whose symptoms change or persist will be required. These potential harms could lead to failure of patients or clinicians to 'buy in' to a FIT-based strategy. This issue bedevilled the introduction of faecal calprotectin for assessment inflammatory bowel disease; lessons have been learned. These risks, along with feasibility and acceptability of a FIT-based approach, will be addressed by COLOFIT.

Future use of FIT. Currently an artificial divide exists between NG12/DG30 high-risk patients – who are referred using the 2WW pathway – and those considered low risk, who may be offered a FIT test in primary care (and are 2WW referred if FIT is positive). We propose simplifying the FIT pathway whilst still basing selection for referral upon evidence-based criteria. This is fundamental to NHS delivery of efficient CRC services.

This application is underpinned by two significant advances in the use of FIT:

Wider population use of FIT. Since the Covid-19 pandemic FIT has been used to triage low-risk patients in primary care (as recommended by NG12 and DG30); a new addition was to use FIT for triage urgency of timing of investigation in high-risk patients in secondary care. COLOFIT will develop and validate algorithms separately for three groups: low-risk, high-risk, and pan-risk, the last of these being where all relevant primary care patients with features of possible CRC receive a FIT as part of their initial assessment.

Whilst the evidence review (see below) supports FIT as having predictive power for CRC, it is likely other variables will add to the predictive power. A small systematic review suggested this was the case for the screening population. Age is almost certainly one variable, and sex

a likely second. Other factors may contribute, including haemoglobin, mean corpuscular volume, ferritin, platelet count, and potentially symptoms, or family history. All of these have been shown in studies before the FIT era to predict CRC. None has been studied in a multivariable analysis including FIT, nor in the symptomatic population. The algorithm COLOFIT develops will report on the probability of CRC, guiding investigations and their urgency.

3.5 The wider context. This application is underpinned by the recent vision for NIHR research with COLOFIT:

- embedded in the NHS, using existing data, and generating new data
- patient-centred, responding to patient need, and guided by patients with strong PPI input.
- efficient (in using existing data where possible) and innovative (studying optimum place for FIT in the patient pathway, and conducting the research with a forward-thinking aspect)
- enabled by NHS data, and the end-product designed to be easily digitised within existing NHS structures
- sustaining and fostering the research workforce, by merging experienced researchers with mid-career researchers, and having the latter to co-lead where appropriate.

3.6 Evidence explaining why this research is needed now

The position before Covid-19 pandemic. The UK remains in an unenviable position for cancer survival compared to other high-income countries, despite improvements in diagnosis and treatment. CRC is no exception. Much of the UK's poor outcomes are considered to originate from diagnostic delay. FIT has brought a paradigm-shift, allowing for the first time the possibility of primary care triage testing in patients with possible CRC. However, the evidence base for FIT in symptomatic patients remains patchy, and no research has examined FIT in combination with other possible variables. We are now in a position whereby the initial barriers to FIT are falling away – but FIT is still seen as a binary test. Using FIT as a component of a multivariable algorithm is likely to improve it considerably, allowing more precise targeting of definitive investigation to those who need it most. In effect, this brings a personalised medicine approach, providing an individual FIT cut-off, using age, sex and other relevant variables.

Attempts have been made to develop UK guidance on use of FIT for symptomatic patients but have failed due to lack of consensus and lack of synthesis of the evidence (BSG / ACPGBI 2020). Lack of consensus across societies has led to an inconsistent application and piecemeal approach with widespread geographical variation. NHSE have prioritised the importance of implementation of FIT into symptomatic pathways but have been unable to do this given the gaps in evidence.[24]

The position now. The Covid -19 pandemic has led to a significant reduction in diagnostic capacity. Endoscopy services in 2020 were reduced to around 50% of pre-pandemic levels. Whilst significant recovery has taken place, a reduction in capacity persists caused by need for testing, enhanced PPE and longer room turnaround times.[25–27] The backlog of referrals due to the pandemic adds to this capacity problem. CTC services are similarly affected. The Covid-19 pandemic has also significantly affected patient behaviour leading to delays to diagnoses, compounding the problem.

4. Aims and objectives

COLOFIT will address the utilisation of FIT alongside other variables in primary care as a tool for determining which patients with defined LGI features require referral for secondary care investigation. Questions will be addressed through a series of interlinked work packages, overseen by lead applicants – Rees and Hamilton. Questions to be addressed will include:

- What other variables (e.g. age, personal characteristics, family history, other biomarkers) can be used to aid selection for definitive investigation in patients whose FIT value is known? Addressed by **WP1, systematic reviews and horizon scanning.**
- Are there diagnostic algorithms including FIT and other variables to aid prediction? If so, have they been validated? If not, can one/more be created and validated? Addressed by **WP2, using WP1 outputs.**
- What is the feasibility and patient and clinician acceptability of such algorithms, and how can they be implemented into CRC diagnostic pathway (including safety netting)? Addressed by **WP3 primarily, using qualitative methods, though all WPs contribute.**
- If a preferred algorithm can be found (or derived) what is its clinical and cost-effectiveness at different algorithm thresholds? What would be the impact on cancer diagnostic services and resources? Addressed by **WP4 economic analysis.**
- What other serious conditions are identified or missed in any new pathway? Addressed by **WPs 1 and 2.**

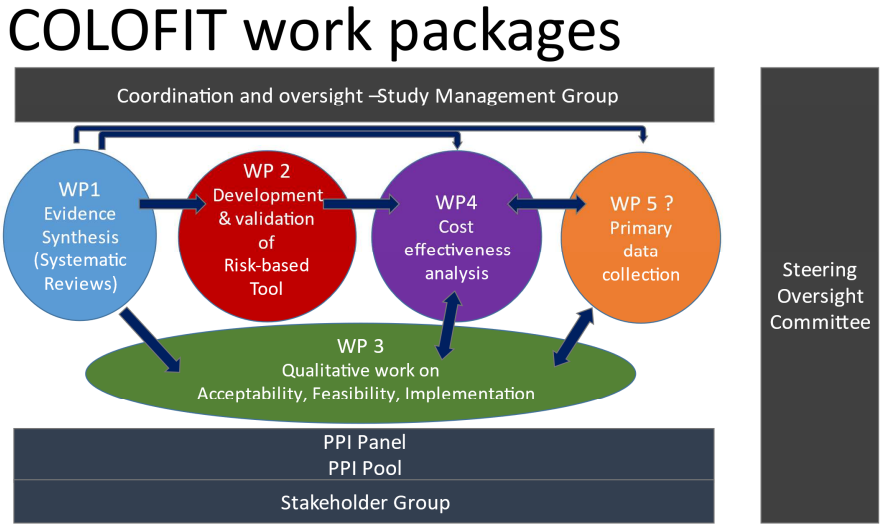
A possible patient flow chart is uploaded alongside the application. It emphasises the importance of the cancer pathway (including those who should bypass FIT and go straight to LGI investigations, those who do not need FIT (those with very low risk)) and of developing management plans for non-cancer patients. This will be modified throughout COLOFIT.

5. Research plan / methods

Health technologies being assessed

COLOFIT will establish the role of FIT within the pathway of patients with lower GI features which may be indicative of CRC, through a series of interlined and interdependent work packages using the structure in Figure 1.

Figure 1



In this application have given detailed science and finances for WPs 1-4, and this is what we are requesting. However, we intend to make a later researcher-led application for WP5, an implementation cohort when the WPs1-4 programme ends.

5.1 WP1: Systematic reviews. Leads: Sharp, Craig, Rees

Review aims. Two systematic reviews will be undertaken to identify and synthesise:

1. Quantitative data on the contributions of FIT, and other variables (e.g. age, personal characteristics, family history, haemoglobin and other blood variables) in addition to FIT, to the prediction of CRC and ACN. This will inform the development of the algorithm (WP2, WP4) and, specifically, decisions on which variables could be used in combination with FIT to identify patients who should be referred for definitive investigation.
2. Qualitative evidence on patient and health care professional views and experiences of FIT as a diagnostic tool in symptomatic patients. This will inform WP3.

Search strategies. Both reviews will be conducted and reported following PRISMA guidelines,[28] and protocols will be registered on PROSPERO.

For Review 1, we will search Medline/Embase, Cochrane Libraries and PubMed to identify papers published in English which develop or validate risk prediction models for either CRC or ACN, and which include: 'FIT'; 'FIT Plus' (Plus: symptoms and/or other risk factors) or 'Plus' (symptom and / or other risk factors) alone. Studies from any health care setting internationally, and where definitive LGI investigation is offered to FIT positive patients, will be eligible; those of FIT use in population-based screening settings or surveillance will be excluded. Conference abstracts will also be excluded as these usually contain insufficient data to extraction and synthesise. As this is a rapidly moving area, it is likely that some relevant work will not yet be published in scientific journals. Therefore, we will also search grey literature sources (e.g., OpenGrey, GoogleScholar), registers of trials/protocols (e.g., Clincialtrials.gov) and repositories for preprints (e.g., Open Science Framework) and consult with experts in the area (e.g., via the networks of the research team, professional bodies (BSG, RCGP)) supported by the NIHR innovation observatory. In addition, algorithms including FIT, such as the Faecal Haemoglobin Concentration, Age and Sex Test (FAST) score, will be identified and collated, along with any validation studies.[29,30] Backward and forward citation searching of eligible papers/reports will be conducted and we will review reference lists of any relevent systematic reviews.

For Review 2, we will search Medline/Embase, PubMed, PsycInfo, CINAHL and Scopus to identify papers or dissertations published in English which report qualitative research on patient or health professional views and experiences of FIT. Studies will be eligible if they report qualitative data: (i) collected from patients or members of the general population who have undergone FIT, or are asked hypothetically about undergoing FIT, in settings other than CRC screening or surveillance, or (ii) collected from health professionals on their attitudes, views or experiences of using FIT in symptomatic populations. Conference abstracts will be excluded. Backward and forward citation searching of eligible papers/dissertations will be conducted and reference lists of any relevent systematic reviews checked to identify any papers that have been missed.

For both reviews, titles and abstracts will be screened independently by two members of the research team. Full text of any citations considered potentially eligible by either or both reviewers will be obtained and reviewed (by two members of the research team) against the inclusion criteria. Disagreements on eligibility will be discussed and, if required, a third member fo the team consulted. Authors of original papers will be contacted to confirm eligibility where required.

Data extraction, quality appraisal & synthesis. For both reviews, data will be extracted by one member of the research team and checked by another. For Review 1, study settings/populations will be categorised as primary, secondary or pan-care (where FIT is offered irrespective of CRC risk). Contributions of FIT (and other variables) to models will be assessed and model validation (including discriminatory power, calibration accuracy) evaluated. Data extraction will be informed by the TRIPOD statement,[31] and risk of bias and applicability assessed using the PROBAST tool.[32] Where appropriate, meta-analysis will be undertaken in RevMan. Studies will only be combined if ≥5 relevant studies are available.[33] Statistical heterogeneity will be quantified using I^2 values and Tau (T).[34] In meta-analyses containing >10 studies, funnel plots will be used to assess potential publication bias.[35] Robustness of effect estimates will be explored through pre-specified subgroup (e.g. by setting, risk of bias, outcome) and sensitivity analyses (e.g. by study design). To determine whether effect estimates are due to particularly influential studies, a leave-one-out sensitivity analysis will be performed by iteratively removing one study at a time.[36]

For Review 2, data will be abstracted on characteristics such as setting, study population, method of data collection, and approach to analysis. The quality of eligible studies will be appraised using the Critical Appraisal Skills Programme (CASP) qualitative research checklist, which considers study rigour and credibility.[37] A meta-ethnography approach, based on the methods described by Noblit & Hare, will be used to synthesize the findings, constructing a new overarching interpretation that applies across studies, and integrates their similarities and differences.[38,39] This approach has been recommended for synthesizing smaller numbers of papers and has been suggested to be particularly suited to exploring patient experiences.[40,41] The Enhancing Transparency of Reporting the Synthesis of Qualitative Research (ENTREQ) statement will be followed.[41]

Co-app Craig leads the NHS National Innovation Observatory, making the team uniquely positioned to horizon scan research within this field. We will horizon scan all available evidence, unpublished datasets and the pipeline for relevant research providing a full picture of FIT based research globally to further inform WPs2&4.

Outputs:

- Evidence on predictors of CRC risk (FIT, FIT Plus, Plus) with weightings, will inform algorithm development in WP2.
- Report on previous qualitative findings on patients' and professionals' views and experiences of FIT will inform all WPs and act as a basis for WP3.

5.2 WP2: Algorithm development and validation. Leads: Humes, Bailey, Hamilton

Available cohorts: We have agreement for at least four cohorts to be used, two each in primary and secondary care. Several other secondary care cohorts are available from collaborators and can be included if required. Existing algorithms, such as FAST, will be validated externally.

Sampling. Humes, **Nottinghamshire.** General Practices have had unrestricted access to FIT in primary care since 2017 within the 2WW pathway.[42] At 2-year evaluation, 13,361 completed FITs with 227 CRCs diagnosed were available. By January 2021, this was 22,561 primary care FIT patients with 436 CRCs diagnosed with a minimum of one year follow up, by commencement of the award.[43] Bailey, **Exeter** have evaluated FIT in primary care across SW England, since roll out for the low-risk symptomatic population in 2017. Data are available on 3890 patients with 51 CRCs, with a minimum of 1 year of follow up.[15] This cohort could be expanded. Nicholson, **Oxford** have undertaken evaluation of FIT in primary care of 9896 patients, of whom 105 were diagnosed with CRC with at least 6 months follow

up. This cohort included those with rectal bleeding.[19] The dataset is ongoing, with currently 11,801 patients having at least 6 months follow up data. Turvill, **York** has completed a diagnostic accuracy study across 13 Yorkshire sites of FIT in 5040 patients meeting NG12 criteria for a 2WW referral, with CRC in 151 of those evaluated. Data collection, including non-cancer outcomes, continues. The Exeter, Oxford, and York data are based on the HM-JACKarc analyser and the Nottingham data are based on the OC-Sensor analyser. Nottingham have previously published data on 732 paired samples which compared the use of both analysers on the same stool sample. This reported variations in sensitivity and specificity at different cut offs for the two tests.[44] This variation in diagnostic accuracy has been previously noted in a systematic review of FIT in primary care.[45] Using these data from Nottingham we will therefore aim to develop a weighting or transformation factor to allow the risk stratification tool to be used with both tests.

Outcomes

CRC will be identified from local electronic cancer data for the first year following FIT along with electronic histopathology, endoscopy, and radiology reports. ACN and inflammatory bowel disease (IBD) will also be identified, where available. Although the primary outcome is CRC, we wish to identify ACN and IBD where possible, as the final algorithm may lead to fewer colonoscopies and thus potentially delay these other diagnoses. Predictor variables, identified from WP1, are likely to include at least age, sex, haemoglobin, mean corpuscular volume, ferritin and platelet count in addition to FIT result. Strategic decisions will be made regarding variables to be included, ensuring they are easily available from electronic health records.

Analysis

We will construct multivariable models in derivation datasets using logistic regression primarily, and all variables identified as relevant by WP1. Variables with missing data will be imputed using multiple imputation with chained equations to obtain the final estimates. We will examine a small number of clinically-plausible interaction terms, such as 'raised FIT'*low haemoglobin'. Non-linear associations will be considered for strong predictors (particularly FIT result) and modelled using fractional polynomials if required, although this did not improve goodness of fit in the Exeter evaluation.[15] Various f-Hb cut-offs will be examined, and sensitivity and specificity values calculated in model development to assess if these provide a comparable but simpler model to using a continuous linear or fractional polynomial variable. Contribution of the selected individual variables to the model fit and discrimination will be examined using forward and backward elimination whereby discarded variables are reassessed at each step. During development, the model's performance will be internally validated in the derivation dataset, using ten-fold cross validation. Calibration and over optimism will be assessed using bootstrapping to estimate a uniform shrinkage factor from the derivation cohort, and through testing and refining the score within the testing cohort. Sensitivity analyses of the score's performance will be assessed in different age and referral pathway strata to identify where a generalised score might not be appropriate and stratification of the model through further interactions is required. The appropriateness of simplifying the final score into categories to ease real world calculations will also be assessed in the testing cohort. We are focussing on 'traditional' statistical methods for risk prediction in preference to AI-based approaches: with relatively few simple variables there is limited scope for improvement with AI, and the more direct interpretability of a statistical model will be of greater benefit within the clinical/implementation context.

External validation will use the second dataset for the health care setting, producing a receiver-operating characteristic (ROC) curve. This validation will be stratified as per the previous sensitivity analyses in the testing cohort, and involve assessment of discrimination, calibration, sensitivity, specificity, positive and negative predictive values of the score. These will be fed into WP3 (qualitative) and WP4 (health-economic). ROC curves will be produced

for FIT and FIT Plus for high- and low- risk populations. Finally, a 'pan-FIT' multivariable model and ROC curve will be created, spanning both risk categories.

No testing strategy is perfect. One to three in 1000 patients tested with FIT will be false negative for CRC at a threshold of 10µg/g, depending on the healthcare setting. False negatives should be reduced by our algorithm, but some will remain. Additionally, colonoscopy yields other serious diagnoses, most notably IBD. A safety netting approach will be included in the final proposed algorithm and guidelines to ensure patients with additional concerns outside of the risk stratification can still be referred via an appropriate pathway. We expect the data from WP2 to inform a lower age threshold (below which CRC risk is very low) for the algorithm.

Power To assess an expected model's performance, we used the minimum sample size approach of Riley et al.[46] We have observed a cancer outcome prevalence of 1.9% (436 cancers within 22,561 patients) in the Nottingham derivation cohort, and a conservative adjusted r^2 of 4% (derived from previously published FIT prediction model performance from Cubiella *et al*.). This estimates a minimum sample size of 22,300 people if we set the desired over fitting of the model parameters to be less than 5% (shrinkage = 0.95); have precision in the estimate of the average outcome risk of +/-0.05; assume a 0.05 difference between apparent and adjusted r^2=; and allow up to 45 candidate predictors in the model building (although we expect the final model to include no more than 10). We will therefore have ample power to derive this model within the existing Nottingham cohort alone and assess the full range of blood tests and f-Hb in a multivariate model, whilst also allowing for additional parameters that are required to assess categorical variables, possible non-linear fractional polynomials, and interactions for the selected parameters.

Ethical and data sharing considerations. Cohorts identified currently have approval under service evaluation. We will apply for HRA approval to use the anonymised data without consent (undertaken in Nottingham as part of on-going work) to develop the risk prediction tool and will arrange relevant data sharing agreements to use the data. The requirement for individual patient data for use within this study meets the criteria set out in section 6 of the General Data Protection Regulation: Guidance on Lawful Processing. The processing of data is based upon GDPR Article 6 (1)(e) - 'exercise of official authority' and article 9(2)(h) 'management of health and care services'. Enabling legislation is NHS Act 2006 section 13E, including the duty on NHS England to 'secure continuous improvement in the quality of services'.

Outputs: Algorithm will be tested qualitatively (WP3) and inform WP4.

5.3 WP3: Qualitative. Leads: Sharp, Rees

Design. WP3 will involve two elements:

1. A cross-sectional qualitative multi-site study will be undertaken to develop rich and detailed understanding of feasibility and acceptability of FIT for triage of potential CRC patients, including those considered low and those considered high risk.
2. PPI and stakeholder workshops will be conducted to understand and articulate the context and complexity of the FIT algorithm to inform its implementation across the NHS.

Interview participants & recruitment. Two sets of semi-structured interviews will be conducted with: (1) patients and (2) healthcare professionals (HCP) from primary and secondary care. Patients will be eligible if they have had a LGI investigation between 3 and 12 months previously, following referral from primary care with bowel symptoms. Several groups will be eligible: those referred with high-risk symptoms (i.e., through the TWW pathway); those with low-risk symptoms referred on the basis of a positive FIT in primary care; and those without experience of FIT. The time window has been chosen to ensure that

the experience of symptoms, referral and hospital investigation is sufficiently fresh in the interviewee's mind that they can recall it but is not so recent that additional procedures or results are awaited.

Patients will be recruited from the following sites, chosen because they cover socio-economically and ethnically diverse catchment populations including: South Tyneside & Sunderland NHS Foundation Trust; Nottingham University Hospitals NHS Trust, Oxford University Hospitals NHS Foundation Trust, Yorkshire NHS Trusts. Purposive sampling strata will include basis of referral (low/high-risk symptoms); referral based on FIT (yes/no); and LGI outcome (CRC/polyps/other conditions/negative). Diversity in the sample will be sought by age-group, gender, ethnicity and socio-economic status. Health professionals in the clinical centres will identify potentially eligible patients from their records and provide them with a study information sheet (either face-of-face at a clinic visit, or by post). Interested patients will return a reply slip to the research team, who will contact them to answer any questions and arrange an interview.

Healthcare professionals involved in delivery of care to patients with low and high-risk bowel symptoms, and who would be anticipated to be involved in the delivery of FIT-based triage will be eligible to be interviewed (i.e., GPs, gastroenterologists). Secondary care professionals will be recruited via the collaborating clinical sites (named above). GPs will be recruited via the Macmillan GP network (to provide access to GPs with an interest in cancer) and by working in partnership with local CRNs in diverse parts of the country. Purposive sampling will be by discipline, and diversity will be sought in other characteristics (e.g., years in practice, gender). As recruitment proceeds, unfilled sampling strata will be targeted.

Data collection. Interviews will be organised at a time convenient for the interviewee, and may use telephone, video-conference software (e.g., Zoom, MS Teams) or face-to-face, if social distancing recommendations allow. Flexibility in recruitment and data collection can support recruitment of harder to reach patient groups[47] and offering telephone and online interviews can ease participant discomfort and the perception of greater anonymity can lead to greater disclosure.[48,49]

Interviews will be informed by topic guides, which will be used flexibly to allow interviewees to raise issues they consider important and allowed to evolve as interviews progress to ensure sufficient depth is reached. Patient interviews will explore experience, acceptability (including undertaking stool FIT) and perceived advantages and disadvantages of FIT triage; any additional information or practical needs relating to either FIT or FIT triage; and whether there are concerns about FIT triage and, if so, how these could be addressed. Amongst patients who have undertaken FIT prior to referral, interviews will explore experience, understanding and acceptability of the test.

HCP and stakeholder interviews will explore feasibility and implementation. Health service issues influencing implementation of FIT triage will be identified using core concepts of Normalisation Process Theory (NPT).[50] To inform HCP interviews, patient vignettes of different FIT scenarios will be used. Vignettes will be based on the team's research and clinical experience, informed by literature and will present varied scenarios around patient characteristics, symptoms, FIT result, and referral. HCP views on risks of missing cancers, safety netting and the proposed algorithm will be explored.

Interviews will be audio-recorded and transcribed verbatim. Analysis will take place in parallel with data collection to ensure any new issues raised are explored in subsequent interviews. The first few interviews in each set will be independently coded by two team members, with discussion and agreement of emerging codes and themes. These will be

applied to the remainder of the interview set. Coding will be facilitated by NVivo software. Inductive thematic analysis will be undertaken,[51] supported by standard approaches to rigorous analysis of qualitative data (e.g., open and focused coding, constant comparison, deviant case analysis).[52] Members of the wider co-applicant and collaborator team, including PPI representatives, (Including co-applicant John Whelpton and PPI panel recruited at May 4th PPI meeting) will contribute to the development of the qualitative analysis and interpretation of findings. The two interview sets will be analysed separately initially, with patient and professional views subsequently compared and contrasted. Recruitment will continue until reasonable data saturation is reached;[53] most likely 20-30 interviews per set.

PPI and Stakeholder Workshops. There are two major challenges to the implementation of evidence-based practices: the context into which that practice is implemented and the complexity of the practice/ intervention itself.[54] To understand these challenges, we will complement our empirical qualitative research with a series of PPI and stakeholder workshops seeking to understand and articulate the context and complexity of the algorithm to inform its implementation. Specifically, these workshops will seek to build a framework of issues key to successful implementation of FIT-based triage across the NHS. Workshop 1 participants will include NHS England, professional bodies (RCGP, BSG, ACPGBI), Cancer Alliances and commissioners. Workshop 2 will include staff working in laboratories which analyse, and report FIT results. Workshop 3 will include public and patients (from the PPI pool and those who participated in interviews) and representatives of bowel cancer charities (e.g., Bowel Cancer UK, Guts UK). At the workshops, the proposed algorithm (WP2) and possible pathways will be presented, together with a summary of qualitative findings. Discussions will explore system complexity, enabling us to identify problems or opportunities which could act as barriers or facilitators to implementation and sustainability of the algorithm. They will also seek to identify any additional issues of importance to patients and professionals relevant to implementation. Findings will inform the development of an implementation plan for the algorithm which will report to the funder and NHS England, and will inform the proposed later WP5 application.

Outputs

- Report on qualitative findings on acceptability and feasibility of FIT triage to patients and healthcare professionals
- Implementation plan for the algorithm to be delivered to NHS England and stakeholders.

Findings will ensure that a FIT-based pathway is co-designed with patients and stakeholders feeding into final recommendations and dissemination event.

WP4: Health-economics Leads: Chilcott, Thomas, Mandrik

An individual patient level health economic model will be developed to assess cost-effectiveness of FIT-based risk algorithms for different levels of risk. This new model will be built in the R programming language and will include elements of existing Sheffield School of Health and Related Research (ScHARR) models for CRC natural history, in particular our new Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel) developed in screening context. [55–57]

Population. A synthetic model baseline population will be developed based upon characteristics of individuals in symptomatic primary care cohorts used for WP2 (for instance, sex, age, socioeconomic deprivation, relevant symptoms) and will include both a FIT measurement and a personalised score for each individual from the FIT-based risk algorithm. Sensitivity and specificity obtained from validation of the algorithm will be included

in the model to randomly assign individual's underlying health states at baseline and their probability of being eligible for further investigations and having CRC or adenomas/ACN detected.

Diagnostic Pathways: Routes to diagnosis following symptomatic presentation will be incorporated in the model, together with costs and harms of diagnostic procedures.[58] The costs of administering the FIT-based risk algorithm will be estimated based on expert opinion and included in the model together with the costs of FIT. Individuals with CRC will incur costs and utility decrements associated with CRC treatment,[59,60] and will be subject to a risk of death from CRC, dependent upon their age, sex, CRC stage and time since diagnosis.[61] All individuals will be at risk of death from other causes.

Progression of CRC and adenomas/ACN in individuals with scores under the risk threshold, or those with scores over the risk threshold but found not to have CRC upon further investigation, will be modelled using a pre-existing CRC natural history model (MiMiC-Bowel).[55,56] Individuals whose CRC is missed at initial presentation to the GP will have the opportunity to be diagnosed at a later date. If data is available to inform this, subsequent rounds of GP presentation will be explicitly modelled, whilst if no data is available, a general symptomatic diagnosis procedure based on existing calibrated parameters for MiMiC-Bowel will be used.[62] Individuals may also be diagnosed through routine screening in the Bowel Cancer Screening Programme (already included in MiMiC-Bowel). Depending upon data availability and feasibility, a small number of additional conditions may be incorporated in the modelling (e.g., inflammatory bowel disease).

Analysis and Outputs. A series of analyses will be carried out investigating the impact of setting different thresholds for the FIT-based risk algorithm, compared to using FIT threshold alone or basing referral on GP opinion only. Two subgroup analyses will be performed, firstly focussing on use of FIT in patients who currently meet NG12 criteria (irrespective of FIT result) plus a more holistic analysis examining the pan-FIT concept spanning NG12/DG30. Probabilistic sensitivity analysis will explore parameter uncertainty. Modelled outcomes will include incremental CRC cases, advanced CRC cases, CRC mortality, colonoscopy resource impacts, costs, quality-adjusted life years (QALYs), and cost-effectiveness (costs per QALYs). Costs and QALYs will be discounted at 3.5%.[63] The model will take a lifetime horizon and NHS perspective.

6. **Design and theoretical/conceptual framework.** The design of the COLOFIT programme includes multiple methods, each appropriate to the knowledge required. Thus, it includes systematic reviews, algorithm creation and validation, qualitative work examining patient and clinician aspects, and health-economic analyses. Each of these methods has well-recognised frameworks with which we are familiar.

   The conceptual framework of the whole programme is predicated on a vision of different CRC investigative pathways post-pandemic. These pathways should be patient-centred, ensured by patient input both as research participants and in the programme oversight. The artificial divide between low-risk and high-risk patients is abandoned (though we will be able to produce a low-risk algorithm and a high-risk algorithm on the small chance the pan-risk strategy is not adopted). Furthermore, all initial testing is performed in primary care – so closer to the patient and quicker. The programme also includes a recognition that patients with symptoms need both diagnosis (which may not be CRC), and management so captures non-CRC diagnoses, and any delay in identifying them.

7. **Target population.** The HTA brief focusses on 2WW patients. However, given the artificial NG12/DG30 divide within primary care, wide geographical variation in 2WW referral rates,

and similarities in CRC detection rates across referral routes we believe that we should include 'low-risk' patients within any referral algorithm. This 'pan-risk' pathway, whereby all patients with defined possible CRC features (using NG12, both high- and low-risk) are offered a primary care FIT using the same algorithm, will reduce the risk of missing patients with CRC in the low-risk group and bring consistency across pathways. A small number of patients will present with defined higher risk features (e.g., rectal mass, perhaps severe iron-deficiency anaemia). These presentations will be identified from WPs 1 and 2, and modelling will assume they bypass the algorithm and receive definitive investigation.

8. **Summary of Patients / service users / carers / public as research participants.** COLOFIT has extensive support from patients and service users; however, the only direct recruitment of patients will be in WP3 qualitative work. In WP3, Individuals who have undergone LGI investigations following primary care referral will be identified from primary and secondary care and invited to participate. Purposive sampling will ensure inclusion of those with/without experience of FIT and different LGI outcomes. Patients will be given participant information leaflets in advance and full informed consent will be obtained. Methodology of interviews is outlined under WP3 details. Patients will be able to drop out at any time. They will be asked if they wish to receive the results of the study and will be offered access to the lay report. The study will ensure that a range of ages, ethnicities and socioeconomic backgrounds are covered, and will follow INCLUDE guidance.

   Clinicians and stakeholders will be invited to contribute to interviews. A range of views will be sought including clinicians from primary and secondary care, endoscopy staff ensuring that a mix of age, experience, gender and ethnicities are represented.

9. **Inclusion/Exclusion Criteria / Setting/context/ Data collection/Data analysis/ Measurement of costs and outcomes.** These sections have been covered in WP sections.

10. **Dissemination, outputs and anticipated impact.** This research has been commissioned by HTA at the request of NHSE. Primarily the researchers will work with NHSE to ensure that all of the appropriate questions on delivery of a FIT-based programme are addressed. The COLOFIT team span primary and secondary care from medical and surgical positions and thus are ideally placed to ensure that dissemination and implementation are optimised. The team will work with implementation scientists to ensure valid implementation approaches are used. The BSG, ACPGBI, PCSG are represented in this application meaning that key stakeholders are involved.

    The work will form the basis of a report to HTA and will be presented at national and international meetings and published in high impact peer review journals. The research will be presented to PPI groups and disseminated through BCUK and formal patient groups. Additionally, it will be spread through COLO-SPEED forum / website (https://colospeed.uk)

11. **Project management.** COLOFIT will be led by co-lead applicants Rees and Hamilton. Each work package has a named leadership team with Rees or Hamilton a member of all work packages. A COLOFIT management group will be established consisting of Rees, Hamilton, all work package leads and our PPI lead. The periodicity will vary over time, but initially will be: Joint lead applicants meeting – fortnightly; management group – monthly; all applicants and collaborators – quarterly. The PPI panel will meet every two months and will receive reports from the management team. The wider PPI group will additionally be available for email advice and input as needed.

12. **Summary of patients/service users/carers/public as research participants.** COLOFIT has been developed with strong PPI input. Mr John Whelpton is a named co-applicant and has reviewed and contributed to the application. Patients and public will be involved as

partners throughout this work including Yorkshire 'Bottom's up' and Cancer Partnership groups, Newcastle Cancer Perspectives group, the DISCOVERY group in Exeter, and BCUK patient groups. This proposal was informed by a PPI workshop on 4th May and following this workshop individuals have agreed to be part of the PPI panel and PPI pool. Further details are provided in the application form.

13. What do you intend to produce from your research?

13.1 Change in practice. The most important consequence of this research should be an evidence-based algorithm for better identification of CRC in patients presenting with symptoms. This should result in patients at highest risk of CRC receiving prompt definitive investigation, and those at lowest risk avoiding definitive investigation, whilst still receiving any necessary specialist input for non-cancer problems. Crucially, the algorithm should be fit for adoption. We have very strong records in implementation, and with the support of policymakers, patients and professional groupings (Letters of support are attached to the application.) have good reason to expect rapid adoption.

13.2 Conventional outputs. In addition, the programme will produce the following traditional outputs: a report for HTA and NHS England; peer-reviewed publications from each WP. Presentations at conferences in line with above publications. Social media will be used as well as reports on websites.

How will you inform and engage patients/service users, carers, NHS, social care organisations and the wider population about your work? We already have very strong patient/service user and charity input embedded in the programme. Our PPI workshop held on May 4th, 2021 had representatives from the main charities. All participants were committed to the concept of co-creation of research, and – in particular – to appropriate implementation and dissemination of research findings. We will continue in this spirit, and expect the charities (letter of support from BCUK) will also endorse and support wide dissemination. Implementation into the wider NHS has already been facilitated by the use of FIT in primary care, and the more recent use in secondary care. Therefore we expect 'bottom-up' support from health care staff, and from their professional organisations. We have received endorsement from the many professional bodies in this field spanning both primary and secondary care. Letters of support are attached to the application.

How will your outputs enter our health and care system or society as a whole? The outputs of COLOFIT will inform NHSE policy on implementation of FIT for symptomatic patients. As well as the bottom-up approach in the previous section, we are encouraged by the fact that the call for this research followed a specific request from NHSE. We have strong links with the relevant senior policy individuals in this area, and expect the results to be endorsed rapidly. It is realistic to assume this combined bottom up and top down desire to use FIT optimally will lead to rapid NHS adoption. This behoves us to produce the science accurately and rapidly – which we intend to.

What further funding or support will be required if this research is successful (e.g., From NIHR, other Government departments, charity or industry)? It is unlikely further research funding will be required, other than a formal separate application for WP5 at a later date. NHSE will need to support introduction of the algorithm into its host environment. Currently, this is likely to be through the laboratories though other possibilities such as individual primary care practices are possible. The latter is more complex and expensive (we have considerable experience in exactly this) which is why our current preference is a laboratory environment. Furthermore, if the algorithm is successful, the demand for urgent CRC-diagnostic colonoscopy should fall, decreasing overall NHS costs.

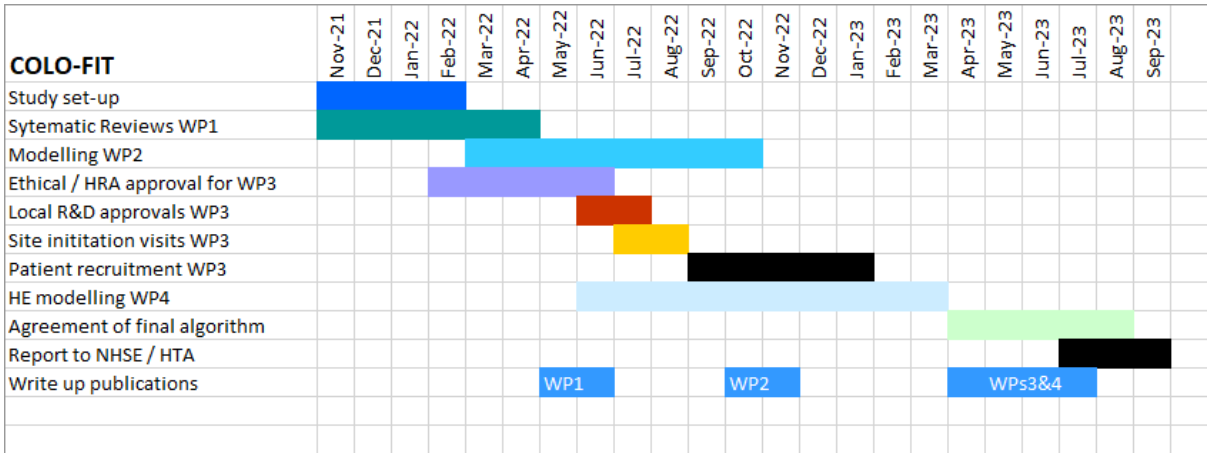
What are the possible barriers for further research, development, adoption and implementation? Acceptability of FIT-based approach is a potential barrier to implementation, and this could well affect uptake; we will seek to address potential barriers in WP3. There is also potential that behaviour changes around a FIT based approach lead to over- or under-referral. This is a particular issue as Covid-19 is likely to change behaviour and the algorithm is being based upon pre Covid-19 data.

What do you think the impact of your research will be and for whom? COLOFIT will redefine the NHS CRC referral pathway, allowing delivery of resources to individuals at most risk of CRC. This will allow more rapid access to those requiring investigation and should allow earlier diagnosis and improved outcomes. It will reduce unnecessary investigations in low-risk individuals. This will have significant impact for patients and additionally release endoscopy resources to allow expansion of the population-based screening programme and other services.

How will you share with study participants the progress and findings of your research? A user-friendly final report will be developed in partnership with PPI panel and pool. This will be available to all participants and will be reported at dissemination events. The results of the research will be made available on the COLO-SPEED website.

14. **Project / research timetable.** Timelines are mapped out on the GANTT chart below.

Figure 2 GANTT chart



15. **Ethics.** WP3 will be subject to IRAS applications. WP1 and WP4 ethical approval not required. WP2 Data sharing agreements and Caldicott guardian approval will be required (see WP2 section)

16. **Project / research expertise.** COLOFIT has world leading clinical and methodological expertise with the ability to both deliver this research and lead implementation of outputs into clinical practice. **Colin Rees** is Professor of Gastroenterology at Newcastle University. He is Chief Investigator for multi-site practice changing research recruiting 15000 patients to his studies over the last 5 years and holds multiple research grants. He leads COLOCOHORT and COLO-SPEED research platforms and is past chair of BSG endoscopy and currently chair of BSG endoscopy research. He will lead the COLOFIT study and co-lead WPs 1,3 and 5. **Willie Hamilton** is professor of primary care diagnostics at the University of Exeter. His main research focus is in improving cancer diagnosis, especially in the selection and testing of symptomatic patients. He has attracted over £60m in research funding from diverse sources and had seen his work heavily implemented into NHS practice (for instance 100 of the 210 NG12 recommendations can be traced back to work from his team. He

received a CBE for improving early cancer diagnosis in 2019. He will co-lead COLOFIT and WP2. **Linda Sharp** is Professor of Cancer Epidemiology at Newcastle University. She has a long-standing interest in early detection and screening in CRC, and expertise in systematic reviews and qualitative and quantitative methodologies. She has led many qualitative studies involving semi-structured interviews with patients and health professionals. She will co-lead WPs 1 and 3. **John Whelpton** is PPI lead. He is NIHR National and Regional Research Champion, PPI lead for Mid Yorkshire NHS Trust. Co-Applicant on several CRC related studies. He will lead PPI work. **David Humes** is Associate Professor of Epidemiology and Honorary Consultant Colorectal Surgeon. He has implemented FIT in the Nottingham CRC pathway and uses routinely collected healthcare data to study the epidemiology of surgical disease, quantifying outcomes and improving quality of care. He will co-lead WP2. **Colin Crooks** is an Associate Professor of Epidemiology, registered graduate Statistician and Honorary Consultant Gastroenterologist. His research focuses on using routinely collected health care data to study gastrointestinal diseases. He has extensive epidemiological, data science and statistical experience especially around deriving, testing and validating individual risk prediction models. He will support WP2. **Joe West** is a Professor of Epidemiology and Consultant Gastroenterologist and Clinical Lead of the Academic Health Sciences Network. He has helped with the evaluation of the Nottingham FIT pathway and has extensive experience in using large datasets from primary care, secondary care, Public Health England, cancer registries in both the UK and abroad. He will support WP2. **Sarah Bailey** is a senior post-doctoral researcher who led the South West evaluation of FIT for the low-risk population. She will co-lead WP2. **Brian Nicholson** is an NIHR Academic Clinical Lecturer who works to develop efficient cancer diagnostic pathways for symptomatic patients attending primary care. He will support WP2. **Lena Mandrik** is a cancer modeller and has been previously involved in development, calibration, and validation of the microsimulation colorectal cancer model of ScHARR. She will bring an expertise in mathematical disease modelling to WP4. **Chloe Thomas** is a mathematical modeller with experience in developing health economic models and leading modelling projects, with a focus on bowel cancer screening. She will co-lead WP4. **Jim Chilcott** is Professor of Healthcare Decision Modelling at ScHARR. Jim's research on cancer screening and early diagnosis includes health economic advice on the establishment and evolution of the NHS Bowel Cancer Screening Programme. He will lead WP4. **James Turvill** is a consultant gastroenterologist with a research interest in faecal biomarkers and the implementation of clinical pathways to support early diagnosis of bowel disease. He will support WP2. **Gary Abel** is a statistician and health services researcher specialising in the use of routine data. He has published extensively in the field of early cancer diagnosis. He will provide statistical input across the project, with particular input into WP2. **Dawn Craig** is head of the NHS Innovation Observatory with expertise in evidence synthesis. She will co-lead WP1.

In addition to the named co-applicants we have a strong team of collaborators: Professors Ramesh Arasaradnam (British Society of Gastroenterology (BSG) Research Chair), Mark Hull (NIHR GI CRN lead), Matt Rutter (Bowel Cancer Screening Research Chair), Bob Steele (Chair of NHS Cancer Screening Advisory Committee), Amanda Cross (expertise in FIT based screening) Drs Sally Benton (Director Southern Screening Hub Laboratory), Ed Seward (London FIT cohort), Ayan Banerjea (Nottingham FIT cohort), Craig Mowat (Dundee FIT Cohort), Ian Penman, (BSG Endoscopy Chair), Kevin Barrett (Primary Care Society of Gastroenterology (PCSG) Chair), Christina Dobson and Christian Von Wagner (qualitative research methodology) Mr Muti Abulafi (Croydon FIT cohort). We have formal support from BSG, PCSG, Association of Coloproctology and Bowel Cancer UK (BCUK), all of whom will be pivotal in implementation of a FIT strategy.

17. **Success criteria and barriers to proposed work.** Success will be determined by development of a robust model which has PPI, stakeholder and clinician buy in that is ready for implementation into clinical pathways. Ideally this should then be road tested in WP5,

following a later application. Long term success will be based upon widespread implementation with consequent better distribution of resources and ultimately earlier diagnosis of CRC and consequent improvement in CRC outcomes.