

REDESIGNING A FASTER PATHWAY TO IBD DIAGNOSIS: CAN DIRECT-TO-PUBLIC STOOL BIOMARKER TESTING REDUCE THE TIME TO DIAGNOSIS OF IBD?

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

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

For and on behalf of the Study Sponsor:

Signature:

Date: 07/04/25



.....
Dr Alison Kerridge
Royal Devon University Healthcare NHS Foundation Trust

Chief Investigator:

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Date: 8/04/2024

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FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
Mast Group	Provision of test kits and reagents to assess Faecal calprotectin and FIT
Crohn's and Colitis UK	£98,017
Royal Devon University Healthcare NHS Foundation Trust	2 x Gastroenterology clinical research fellows 12 months 0.5 WTE
National Institute for Health and Care Research	£325, 643

ROLE OF STUDY SPONSOR

The study Sponsor is the Royal Devon University Healthcare NHS Foundation Trust (RD&E). The Sponsor has no direct role in trial design, data analysis and interpretation, manuscript writing or dissemination of results. In terms of study conduct, the RD&E will fulfil its role of research sponsor as set out in the UK Policy Framework for Health and Social Care Research. Any delegation of duties will be formally documented but the Sponsor retains overall responsibility. A Sponsor representative will be invited to study management group meetings as an observer. The Sponsor will be responsible for financial oversight of the study.

ROLES AND RESPONSIBILITIES OF THE LIVED EXPERIENCE PANEL (LEP)

The LEP will comprise a group of people with lived experience of IBD including a research champion affiliated with Crohn's and Colitis UK.

Specific roles of the LEP will include:

- Review of study documents including patient information sheets and consent forms.
- Review of the interview guide, used for semi-structured interviews.
- Advising on barriers to recruitment.
- Advising on the validity of the themes and barriers identified in qualitative research work.
- Advising on the suitability of the marketing strategy.
- Advising on the acceptability and useability of the online portal.
- Advising on the acceptability and useability of the testing kits.
- Advising on the suitability of proposed care pathways.
- Helping in the interpretation of feedback from users of the RAPID pathway, and whether the pathway should be altered as a result.
- Dissemination of study findings

KEYWORDS: Direct-to-consumer, faecal calprotectin, faecal immunochemical testing, inflammatory bowel disease, Crohn's disease, ulcerative colitis, diagnosis, diagnostic delay

ABSTRACT

One-quarter of patients report symptoms for more than a year before the diagnosis of IBD is made. Why people with IBD wait so long to present with gastrointestinal symptoms is unclear. Embarrassment and the apprehension of invasive tests are common. Recent reports in patients with sexually transmitted infections suggest that this barrier may be overcome by the anonymity of direct-to-public stool testing.

We will define the time-to-diagnosis of IBD in incident cases over the course of 1-year and identify factors associated with a delayed diagnosis. We will then pilot direct-to-public stool testing. Stool samples will be assayed and patients with positive tests will be offered secondary care investigations. We will define the accuracy of direct-to-public FIT and calprotectin tests and investigate whether their use reduces the proportion of patients who wait more than 4 months for a diagnosis of IBD.

STUDY SUMMARY

Delay in the diagnosis of inflammatory bowel disease (IBD), is common: one-quarter of patients report symptoms for more than a year before the diagnosis is made. Timely diagnosis is important because earlier use of drug therapies leads to a reduction in hospitalisations, surgeries, and improvements in quality of life.

Distinguishing between irritable bowel syndrome (IBS) and IBD is difficult, and misdiagnosis is common. Calprotectin, a stool biomarker that detects inflammation in the bowel, reliably discriminates IBD from IBS and is used by GPs to determine who to refer for colonoscopy. The Faecal Immunochemical Test (FIT) detects blood in stool and is used to identify adults with bowel symptoms suspicious of a diagnosis of colorectal cancer (CRC), irrespective of age. Previous studies suggest that FIT could be used like calprotectin to test for IBD. This would have several advantages: it would unify primary care stool testing across all age-ranges and indications and because it is easier to automate, the costs associated with laboratory analysis is considerably cheaper.

The longest component of the time-to-diagnosis is the interval between symptom onset and an individual seeking help. Why people wait so long to present with gastrointestinal symptoms is unclear. Embarrassment and the apprehension of invasive tests are common. Recent reports in patients with sexually transmitted infections and hepatitis C, where a similar challenge presents itself, suggest that this barrier may be overcome by the anonymity of direct-to-consumer testing.

Direct-to-consumer tests require the consumer to collect a specimen, such as stool, and send it to the laboratory for testing without the involvement of a health care professional. Whether using calprotectin or FIT to identify people at risk of IBD in this way is acceptable or effective is unknown: but it could, reduce patient-delay and its implementation is worthy of investigation.

We propose a two-stage approach to answer this question:

RAPID-1: In a prospective cohort of about 200 patients newly diagnosed with IBD, we will define the time to diagnosis, split into the time from symptom onset to first GP contact, and by the time taken to move through primary and secondary care services.

Patients will complete a series of questionnaires and a subset will be asked to take part in a semi-structured interview. This interview will be conducted by a qualitative researcher and will be used to identify barriers to presentation with gastrointestinal symptoms and how best to market and distribute direct-to-public stool tests.

RAPID-2: We will then pilot direct-to-public stool testing in 5,000 people aged 16-49 who are experiencing lower gastrointestinal symptoms. We will define the positivity rate of FIT and calprotectin tests in this group.

Finally, by comparing the proportion of patients who wait more than 4 months to be diagnosed with IBD in this cohort to that reported in Study 1, we will test if stool biomarkers used in this ambitious way, reduces the time to diagnosis of IBD.

	RAPID-1	RAPID -2
Exposure	Primary care requests for stool tests Calprotectin and FIT (OC sensor)	Direct-to-public calprotectin testing and primary care requests for stool tests Calprotectin and FIT (OC sensor)
Timeframe	1 st June 2024 to 1 st October 2025 Follow up to 1 st October 2026	1 st September 2025 to 1 st September 2026 Follow up to 1 st September 2027
Primary outcome	Proportion of patients diagnosed with IBD > 4 months from symptom onset	Proportion of patients diagnosed with IBD > 4 months from symptom onset
Secondary outcomes	• Number of new IBD diagnoses • Proportion of patients who underwent a screening stool test and the positivity rate • Time to diagnosis stratified by patient, primary and secondary care intervals • Factors associated with diagnostic delay • Diagnostic accuracy of calprotectin and FIT • Emergency presentations for possible and/or probable IBD in year before and after testing • Surgeries for stricturing and penetrating complications of Crohn's disease and colectomy rate for UC • Qualitative analysis of barriers to IBD presentation	• Number of new IBD diagnoses • Proportion of patients who underwent a screening stool test and the positivity rate • Time to diagnosis stratified by patient, primary and secondary care intervals • Factors associated with diagnostic delay • Diagnostic accuracy of calprotectin and FIT • Emergency presentations for possible and/or probable IBD in year before and after testing • Surgeries for stricturing and penetrating complications of Crohn's disease and colectomy rate for UC
Variables	• Demographics (age, sex, ethnicity, household income, highest educational attainment, occupational group, comorbidities, height and weight, smoking status and postcode) • Mode of presentation (emergent vs elective, dates and numbers of primary and secondary care contacts) • IBD type (family history, disease activity [PRO2], phenotype according to Montreal classification)	• Demographics (age, sex, ethnicity, household income, highest educational attainment, occupational group, comorbidities, height and weight, smoking status and postcode) • Mode of presentation (emergent vs elective, dates and numbers of primary and secondary care contacts) • IBD type (family history, disease activity [PRO2], phenotype according to Montreal classification)
Co-variables	Patients will be asked to complete the following questionnaires using validated measures: - • fatigue (IBD-F) • psychological well-being (PHQ-8 and GAD-7) • quality of life (EQ-5D-5L) Work productivity and activity index WPAI:IBD	Patients will be asked to complete the following questionnaires using validated measures: - • fatigue (IBD-F) • psychological well-being (PHQ-8 and GAD-7) • quality of life (EQ-5D-5L) • Work productivity and activity index WPAI:IBD

STUDY PROTOCOL

REDESIGNING A FASTER PATHWAY TO IBD DIAGNOSIS: CAN DIRECT-TO-PUBLIC STOOL BIOMARKER TESTING REDUCE THE TIME TO DIAGNOSIS OF IBD?

BACKGROUND

Delay in the diagnosis of inflammatory bowel disease (IBD), is common: about one-quarter of patients report symptoms for more than a year before the diagnosis is made¹. The median time to diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) are reportedly 7.0 (95% CI: 3.0–26.4) and 4.6 (95% CI: 1.0–96.0) months, respectively². Timely diagnosis of IBD is important because earlier use of biologic therapies leads to mucosal healing, a reduction in hospitalisations and surgeries and improvements in quality of life^{2,3}. Pooled data confirm that a delayed diagnosis of Crohn's disease is associated with a two-fold increased risk of stricturing and/or penetrating complications and intestinal surgery². In patients with UC, a delayed diagnosis is associated with a four-fold increased risk of colectomy².

Distinguishing between irritable bowel syndrome (IBS) and IBD, even in the presence of red-flag symptoms, is difficult and misdiagnosis is common⁴. Contemporary studies of the time to diagnosis of IBD from the UK, where healthcare is free at the point-of-access and general practitioners (GPs) act as gatekeepers to secondary care services, are scarce. Faecal calprotectin is a stool biomarker that reliably discriminates IBD from functional gut disorders⁵.

We have shown that even in patients presenting with red-flag symptoms, calprotectin testing of adults and children with suspected IBD in primary care effectively identifies patients with IBD and reduces secondary care referrals and diagnostic healthcare costs^{6,7}. However, few studies have been adequately powered to evaluate the impact of primary care faecal calprotectin testing on time to diagnosis. The Faecal Immunochemical Test (FIT) detects blood in stool and is used to stratify adults with bowel symptoms suspicious of a diagnosis of colorectal carcinoma (CRC) for referral⁸. Previous studies suggest that FIT could be used like calprotectin to screen for IBD⁹⁻¹². This would unify primary care stool testing across all indications.

There is considerable interest from charities and healthcare providers in how to reduce the time-to-diagnosis of IBD¹³. Whilst streamlining primary and secondary pathways is important¹⁴, arguably because the interval between symptom onset and seeking help is the longest component of the time-to-diagnosis, novel interventions should be aimed at reducing patient-delay¹. Symptom awareness campaigns are being actively pursued, for example by Crohn's & Colitis UK with their 'cut the crap' programme¹⁵, but whether they change self-referral behaviour, is unknown. The UK governments 'Be Clear on Cancer' awareness campaigns¹⁶, which highlighted the importance of presenting to primary care with rectal bleeding to exclude bowel cancer, were well-funded but ultimately ineffective. An alternative, but more contentious approach, would be to use these campaigns to promote not only disease awareness but also direct-to-public stool biomarker testing. Recent reports in patients with sexually transmitted infections and hepatitis C, where similar stigmas

exist, suggest that embarrassment and the apprehension of invasive tests may be overcome by the anonymity of direct-to-public testing^{17,18}.

We have shown recently that in the UK online direct-to-public calprotectin testing is already available from multiple providers with turnaround times typically under 14 days. Consumers can choose between home-based lateral flow tests or send stool samples for gold-standard laboratory testing. Whilst the laboratory tests are considerably more expensive and take longer to return a result, they are reportedly more accurate. In a subsequent public and patient involvement survey of 132 patients with IBD, less than half had undergone a stool calprotectin prior to the diagnosis of their IBD and most patients wished that this had been available. Moreover, one of the barriers to conventional calprotectin testing is the collection, handling and return of whole stool specimens. To try to overcome this barrier we have worked with 20 people living with IBD to assess the acceptability and usability of an alternative method of stool calprotectin sample collection. Like in the bowel cancer screening programme, this uses a comb-picker to transfer a sample of stool into a diluent ready for testing: 85% patients found the picker more acceptable or more hygienic than using a standard universal container.

NICE has endorsed primary care faecal immunochemical testing (FIT) in people under the age of 50 years (NICE DG56). They highlight the need for further research to determine the clinical impact of dual (FIT and calprotectin) testing in people under 40 years who are more likely to have IBD than colorectal cancer. Previous studies suggest that FIT could be used like calprotectin to test for IBD. This would have several advantages: it would unify primary care stool testing across all indications and because it is easier to automate, the costs associated with laboratory analysis are considerably cheaper. In RAPID-1 and RAPID-2 we will test FIT and calprotectin in parallel.

Whether direct-to-public stool testing to identify people at risk of IBD is acceptable or effective in the general population is unknown, but it will involve people in decisions about their health, and could, conceivably reduce delay and create value for the taxpayer. For these reasons, its use is worthy of investigation.

AIM

To determine if a direct-to-consumer stool biomarker testing pathway can reduce time-to-diagnosis of IBD.

In two consecutive studies (RAPID-1 and 2) we aim to define:-

1. the barriers to IBD diagnosis and why people wait longer to present with gastrointestinal symptoms
2. the optimal marketing/dissemination strategy for a new direct-to-public stool test
3. the uptake, positivity rates, diagnostic accuracy, cost-effectiveness and resource-utilisation of calprotectin and/or FIT direct-to-public testing
4. if direct-to-public stool testing reduces the time to diagnosis of IBD

RAPID 1: STUDY OVERVIEW

RAPID 1: STUDY DESIGN

Prospective study at IBD diagnosis to identify modifiable factors associated with a longer time to diagnosis

RAPID 1: RECRUITMENT

Participant Identification

We will invite all patients diagnosed with IBD over the course of 1 year, at Royal Devon University Healthcare NHSFT (Exeter and Barnstaple sites), to participate. These patients will be identified via structured searches of referrals to gastroenterology and endoscopy reports. These search queries will be reviewed by members of the clinical team only.

Inclusion criteria

- Aged over 16 years old
- Able to give informed consent
- Diagnosed with inflammatory bowel disease (IBD) within 90 days of study recruitment.

Exclusion criteria

- Patients who are unable or unwilling to consent

Withdrawal of Participants

Participants may choose to withdraw from the study at any time. If they choose to withdraw prior to data analysis then their data will be destroyed, however, after analysis has commenced this may not be possible. Because of the nature of qualitative research, it will not be possible to exclude interview data from the point of entry. The reason for withdrawal must be documented in the electronic CRF and a withdrawal log should be completed.

RAPID 1: OUTCOME MEASURES

Primary outcome: The proportion of patients who wait more than 4 months to be diagnosed with IBD

Secondary outcomes:

1. The interval from symptom onset to diagnosis of IBD stratified by three subintervals: the time from symptom onset to first GP presentation (patient delay); the time from first GP

- presentation to GP referral (primary care delay); and the time from GP referral to IBD diagnosis (secondary care delay).
2. Identification of the barriers and facilitators to early diagnosis of IBD, using an in-depth semi-structured interviews with people with recent lived experience of IBD diagnosis.
 3. The impact of IBD on patient reported outcome measures at the time of diagnosis; including, quality of life, mood and fatigue.
 4. Rates of IBD related complications including; emergency admission and surgery in the 12 months following diagnosis.

RAPID 1: DATA COLLECTION

RAPID 1.1: Questionnaire and Follow up

We will ask participants to give informed consent. Following this they will be asked to complete a questionnaire using validated measures of fatigue (IBD-F), psychological well-being (PHQ-8 and GAD-7), quality of life (EQ-5D-5L), and work productivity and activity (WPAI:IBD). This questionnaire will also ask questions related to health, lifestyle, diagnostic delay and preferred method of communication.

We will collect data related to demographics (age, sex, ethnicity, household income, highest educational attainment, occupational group, comorbidities, height and weight, smoking status and postcode), mode of presentation (emergent vs elective, dates and numbers of primary and secondary care contacts) and IBD type (family history, disease activity [PRO2], stool testing [calprotectin vs. FIT], phenotype according to Montreal classification).

We will follow up participants over 12 months from diagnosis. This will involve researchers accessing participant's electronic health record and collecting data related to IBD treatment, hospitalisations, complications and surgeries. This review of the electronic health record will be supplemented with a follow-up questionnaire sent 12-months after diagnosis to patients using their specified preferred communication method.

Data Storage

All clinical data and questionnaire data will be entered onto a purpose designed electronic database designed using REDCap software, hosted at the Royal Devon University Healthcare NHS Foundation Trust. All analyses will be conducted in R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Authorised users will have access, via a high-grade-security dual factor authentication process. All access to and modifications of the database are logged, so user errors can be easily tracked if needed. Whenever possible study data will be collected on an electronic device to reduce the errors associated with data input from paper. Data submitted will be reviewed and if ambiguous or incomplete data clarification forms (DCFs) will be issued.

RAPID 1.2: Semi-structured Interview

We will sample a subset of patients using a semi-structured qualitative interview conducted within 4 weeks of IBD diagnosis. This will assess opinions regarding barriers to presentation with gastrointestinal symptoms and the acceptability and distribution of a direct-to-public stool test. This

patient and public involvement and engagement exercise will inform how best to market our stool testing service in RAPID-2.

Sampling

We will use a purposive sampling strategy, to achieve the maximum variation of participant characteristics (eg, age, sex, disease type), but also ensure that participants from important sub-groups that are known to experience diagnostic delay (those without rectal bleeding, and with depression) are represented. This will mean that we will invite the first 10 participants to be recruited to RAPID1 to be interviewed, and following this, invitations for interview will be issued to those with an under-represented demographic or important sub-group, as above.

We will aim to interview around 20 participants, however the exact sample size will be determined through interim analysis of qualitative data to determine whether a point of thematic saturation has been achieved. If thematic saturation has not been achieved after 20 participants then further will participant will be invited to interview.

Semi-Structured Interviews

The semi-structured interviews will centre around perceived barriers to IBD diagnosis and potential strategies to mitigate these. The interviews will be conducted utilising a topic guide, that will be circulated to participants prior to the interview.

Interviews will be conducted via Microsoft Teams, or face-to-face in a private room at the Royal Devon and Exeter Hospital site, depending on the preference of the participant.

If conducted via Teams an audio-visual audio-visual recording will be made. If conducted face-to-face then an audio recording only will be made.

The audio recording will be transcribed and once the transcript has been reviewed all the audio recordings (audio and audio-visual) will be destroyed.

RAPID 1: DATA ANALYSIS

RAPID 1.1: Questionnaire and Follow up

We will determine the distribution of diagnostic delay within the sample, both in terms of overall delay, and stratified by; time from symptom onset to first GP presentation (patient delay); the time from first GP presentation to GP referral (primary care delay); and the time from GP referral to IBD diagnosis (secondary care delay).

We will use multivariable linear regression models to identify factors associated with time to diagnosis.

We will determine the likelihood of an individual waiting more than 4 months for a diagnosis, and will use this as an estimate of diagnostic delay in the population diagnosed via routine care pathways. We will then be able to use this and the questionnaire data on participant reported outcomes as a comparator in the RAPID 2 analysis.

RAPID 1.2: Semi-structured Interview

The data will be thematically analysed utilizing Braun and Clarke method. The investigators will then use qualitative data analysis software (NVivo) to manage the data and undertake the thematic coding of the transcripts.

The themes that have been identified will be presented to the RAPID Lived Experience Panel as a check of interpretative fidelity, validity and generalisability.

RAPID 2: STUDY OVERVIEW

RAPID 2: STUDY DESIGN

Prospective pilot cohort study to assess if direct-to-public stool testing reduces time to diagnosis of IBD

RAPID 2: RECRUITMENT

Participant Identification and consenting

Participants will self-identify in response to a local advertising campaign. This will direct potential participants to an online portal that displays the electronic patient information sheet and study contact information, should potential participants have further questions related to the study. The online portal will link through to the study RedCAP held securely on the Royal Devon University Healthcare NHSFT servers, a confirmation that the potential participant meets the eligibility criteria and an electronic consent form. Following the completion of the consent form participants will be asked a few further questions related to their symptoms, demographics and contact details and details for postage of their kit.

Community Pharmacy Promotional sites.

Interested community pharmacies within the EX postcode region will operate as promotional sites. They will undergo remote training with the study team in order to help sign post participants to the QR for further information. They will be asked to highlight the study to people presenting to their services who fulfil the eligibility criteria, in addition to any other advice they would offer to such people as standard care. The role of the staff at these studies will be to promote the study and direct people to the study website and phoneline. They will not be taking consent and will not be on the delegation log. Beyond the quoting the eligibility criteria, pharmacy staff will not be expected to answer questions about the study. If a participant has questions about the study they will be directed to contact the study team directly via phone or email.

This pharmacy engagement is managed through the Community Pharmacy Devon and the NIHR South West Peninsula Regional Research Delivery Network. The pharmacies will be reimbursed for each consent participant.

Sample Size: 5000

Inclusion criteria

- Aged greater than 16
- Willing and able to give informed consent.
- Residing within the population served by the Royal Devon University Healthcare NHSFT.

Advised criteria for direct-to-public testing

- Aged 16 to 49 years
- Lower abdominal pain below the umbilicus, and/or diarrhoea and/or rectal bleeding for more than 4 weeks
- No flexible sigmoidoscopy or colonoscopy in the 2 years preceding stool testing.

Exclusion criteria

- Those who are unwilling to consent to the study accepting that researchers will have ongoing access to their primary and secondary care medical record for 1-year after the test for the purpose of follow up.

Withdrawal of Participants

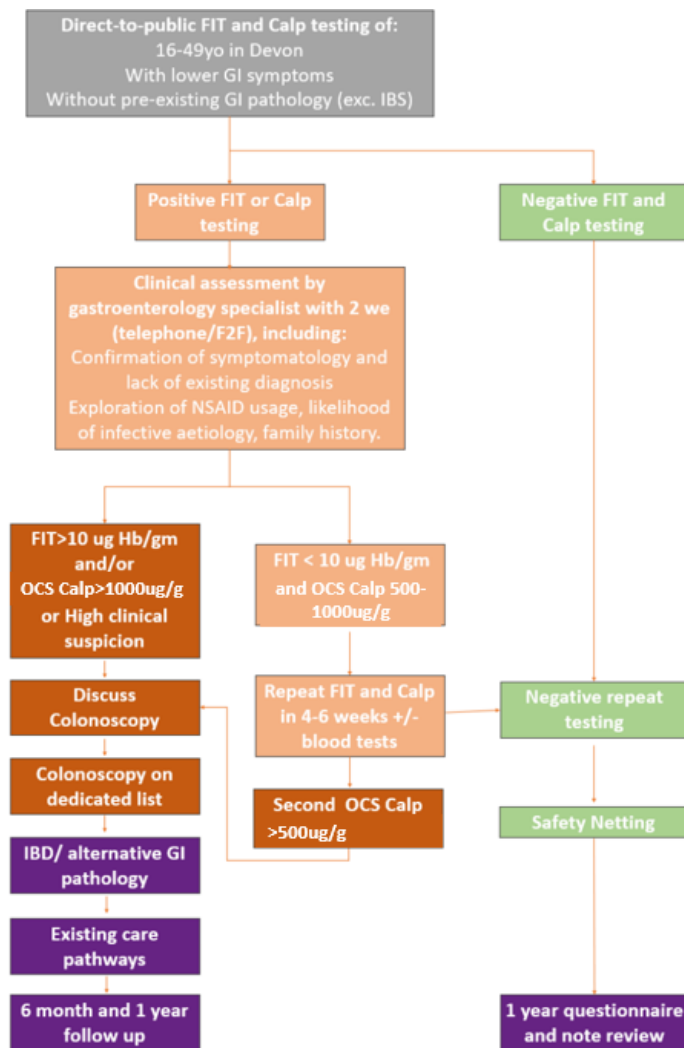
Participants may choose to withdraw from the study at any time. The reason for withdrawal must be documented in the electronic CRF and a withdrawal log should be completed, provided participants freely share this information.

RAPID 2: INTERVENTION

Individuals will complete e-consent and a purpose designed e-case record form.

Eligible individuals will be sent a stool collection pack, asked to collect a stool sample using a picker stick to transfer a small amount into a pre-labelled testing tube, which is then returned by Royal Mail pre-paid post. Both calprotectin and FIT samples will be tested.

Previous work suggests that dual FIT and calprotectin testing, even in patients who report GI alarm symptoms reduces false negative calprotectin testing alone. Those patients whose stool test is positive for calprotectin and/or FIT will be invited to a clinic appointment within four weeks and a history taken. Patients with calprotectin samples $>1000\text{ug/g}$ and/or FIT samples of $>10\text{ug/Hb/g}$ stool will be referred for a colonoscopy and/or axial imaging. To reduce the number of false positives patients whose stool calprotectin is $>500\text{ug/g}$ and $<1000\text{ug/g}$ will be re-tested if their FIT test is $<10\text{ug Hb/g}$. If the repeat test is $>500\text{ug/g}$ patients will be referred clinic consultation. In line with our current primary care pathway, patients with negative stool test results will be signposted to our IBS seminar which is co-delivered by our psychology and dietician teams and offered referrals to Talkworks and our community dieticians. We will be able to report the number of people who register for a test who do not complete it and if this relates to a lack of GI symptoms. We will use secondary care records and electronically follow participants for 12 months to determine if they were subsequently diagnosed with IBD. There is very little we can do to prevent individuals subverting the testing procedure.



Our patient information sheet will include information about the possible need for colonoscopy following a positive test. All patients with a positive test will be offered an appointment with a gastroenterology specialist at which the risks, benefits and alternatives to colonoscopy will be discussed. This is a service that is often not afforded in routine care where patients follow a 'straight-to-test' pathway. Participants deemed to have possible colorectal cancer will be upgraded to a conventional two week wait pathway, although we anticipate a similar short waiting time for all patients with positive stool tests.

Rapid 2 – GP informed of results

If the patients consent, the GP will be informed of the results of the dual tests provided the participant has undergone an appropriate process to authenticate their identity against their medical record.

Marketing

Direct-to-public stool testing will be advertised using a targeted digital and traditional media marketing strategy (see attached document from Denhams's digital - '*Know Your Sh*t*') and by advertising in community pharmacies. This will be informed by the Patient and Public Involvement and Engagement exercise in RAPID-1.

Identity Authentication and Validation

In order to hold the stool test result information against a participant's medical record, we must undertake a process of identity authentication and validation. This process will involve an automated dual factor authentication process to ascertain that a participant has access to the phone number listed against their medical record. If a participant's identity cannot be confirmed in this manner, then the study team will make contact and will undertake verbal identity checks against the medical record, without divulging any medical information. As is in keeping with healthcare policy for identification verification in primary and secondary care.

We will also authenticate a participant's email address using an automated personalised link at the end of the initial participant questionnaire. If their email address is authenticated this will be used as the means of providing them with a copy of their consent form and testing results.

If we are unable to authenticate their email address then we will provide a copy of their consent via post, and use their phone number alone to update them as to their sample testing results.

If a participant's identity cannot be authenticated with either of these processes then they will still be able to participate, however, their stool test result data will be held against their study ID and not their identity. In these cases we will not be able to share result data with their GP.

The study data for this authentication process will be held alongside other study data in a purpose-built RedCAP database on the secure servers of the Royal Devon University NHSFT,

Ordering and despatch of stool testing kits

Kits will be ordered and distributed through an online portal. Individuals will complete e-consent and a purpose designed e-case record form. Eligible individuals will be sent a stool collection pack, asked to collect a stool sample using a picker stick to transfer a small amount into a pre-labelled testing tube, which is then returned by pre-paid post. Both calprotectin and FIT samples will be assayed from the resulting solution.

Laboratory analysis

In a collaboration with MAST diagnostics, we will use the OC Sensor quantitative faecal immunochemical [NICE DG30 and DG56] and faecal calprotectin tests. These tests use a single collection tube containing buffer and a latex reagent, coated with polyclonal antibodies for human haemoglobin and calprotectin. This stabilises the sample. The tests will be run on the OC Sensor PLEDIA which can process up to 320 samples per hour. Calprotectin levels will be reported in the range 20 to 2720µg/g, with results lower than this reported as <20µg/g and results above the upper analytical limits not diluted and re-assayed but reported as >2720µg/g. FIT is reported between 2-200 µg Hb/g, with dilution extending the range to 50,000 µg Hb/g.

RAPID 2: OUTCOME MEASURES

Primary outcome: The proportion of patients who wait more than 4 months to be diagnosed with IBD.

Secondary outcomes:

1. The uptake, positivity rates, diagnostic accuracy, cost-effectiveness and resource-utilisation of calprotectin and/or FIT direct-to-public testing.
2. The interval from symptom onset to diagnosis of IBD stratified by three subintervals: the time from symptom onset to first GP presentation (patient delay); the time from first GP presentation to GP referral (primary care delay); and the time from GP referral to IBD diagnosis (secondary care delay)
3. The impact of IBD on patient reported outcome measures at the time of diagnosis; including, quality of life, mood and fatigue.
4. Rates of emergency admission and surgery in the 12 months following diagnosis.

Reference standard: The diagnosis of IBD and other organic intestinal disease usually requires ileocolonoscopy with or without gastroscopy and small bowel imaging. This burden of investigation is impractical and inappropriate for the diagnosis of functional gut disorders. Therefore, and in common with previous literature, we will record diagnoses after a 12-month period of follow-up to allow any missed cases of IBD and organic intestinal disease to be correctly diagnosed. This will permit the diagnostic accuracy analyses of FIT and calprotectin above.

RAPID 2: DATA COLLECTION

The following data will be gathered from all participants who use the direct-to-public pathway: demographics (age, sex ethnicity, household income, highest educational attainment and postcode) with height, weight and smoking status. We will also collect a clinical history, (symptoms, comorbidities and timing of previous gastrointestinal investigations) and well as concomitant medications like NSAIDs.

Further data collection will depend whether a participant tests positive on stool biomarker testing and whether they are diagnosed with inflammatory bowel disease or serious lower gastrointestinal pathology following secondary care assessment.

Participants Diagnosed with IBD via the Direct-to-Consumer Testing Pathway

The following data will be gathered from these participants via questionnaires and electronic health record review:

- IBD phenotype according to the Montreal classification, disease activity (PRO-2), family history stool testing [calprotectin vs. FIT]. Data on participants seeking-behaviours, prior IBD knowledge and health literacy.

Participant reported outcome data including; validated scores of fatigue (IBD-F), psychological well-being (PHQ-8 and GAD-7), quality of life (EQ-5D-5L), work productivity and activity (WPAI:IBD).

Data related to participants clinical IBD outcomes will be gathered prospectively in the 12 months following participants diagnosis. This will include data relating to:

Hospital admissions relating to IBD

Surgeries and complications of IBD

Prescriptions of advanced therapies and steroids to treat IBD Participants with positive direct-to-consumer testing but not diagnosed with IBD or serious gastrointestinal pathology following secondary care assessment.

The following data will be gathered from these participants via questionnaires and electronic health record review:

- Levels of reassurance felt by participants in relation to negative testing
- Subsequent diagnoses of IBD and other serious lower gastrointestinal pathology made over the subsequent 24 months.
- If a subsequent diagnosis of IBD is made then data will be collected on:
 - The mode of presentation, including subsequent stool biomarker testing results
 - Endoscopic and symptomatic severity at presentation
 - Hospital admissions relating to IBD
 - Surgeries and complications of IBD
 - Prescriptions of advanced therapies and steroids for IBD

Participants with negative direct-to consumer testing

The following data will be gathered from these participants via 6 monthly and electronic health record review:

- Levels of reassurance felt by participants in relation to negative testing
- Subsequent diagnoses of IBD and other serious lower gastrointestinal pathology made over the subsequent 24 months.
- If a subsequent diagnosis of IBD is made then data will be collected on:
 - o The mode of presentation, including subsequent stool biomarker testing results
 - o Endoscopic and symptomatic severity at presentation
 - o Hospital admissions relating to IBD
 - o Surgeries and complications of IBD
 - o Prescriptions of advanced therapies and steroids for IBD

Participants who have registered for testing but do not meet the advisable eligibility criteria

We understand that open-access to stool tests, may allow for subversion of testing. This in itself is a helpful measure of viability of a direct-to-public testing pathway. We will collect data on the number of participants who falsely self-certify that they meet the advisable eligibility criteria. These cases will be handled according to which question/response has been incorrectly reported. If a participant's date of birth suggests they are older than 50 years old then they will receive an automatic reply saying that a kit will not be sent out. If an NHS number cannot be linked to a

patient's name, postcode and date of birth, then they will be asked to provide this, to allow for corroboration of the correct date of birth.

The testing platform may attract people with known diagnoses of IBD, these people will receive testing kits. The existence of a previous diagnosis of IBD will be clarified in all participants, and further clinical investigation/treatment arranged as per routine care. This will be true for both those testing positive and negative.

Participants who do not return the testing kit

We will record the number of participants who register for testing kits but fail to return these. Automated reminders will be generated after the participant has consented to the study, if a kit has not yet been received by the laboratory, Participants will be asked whether they are experiencing any barriers to using the kit, if they require a further kit, or whether their symptoms have resolved. Provided the participants have no objections to continuing in the study, their follow-up will continue as planned regardless of whether they return a kit after the above discussions.

Patients diagnosed with IBD through standard care pathway

We will also identify patients diagnosed with IBD related to the number of IBD diagnoses made by ongoing standard care during the study period will also be collected, to capture any impact the advertising campaign may have on presentations through standard care pathways.

Broader service level data will be collected looking at the number of consultations and endoscopies utilised because of the pathway

Data Storage

All clinical data and questionnaire data will be entered onto a purpose designed electronic database designed using REDCap software, hosted at the Royal Devon University Healthcare NHS Foundation Trust. All analyses will be conducted in R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Authorised users will have access, via high-grade-security dual factor authentication process. All access to and modifications of the database are logged, so user errors can be easily tracked if needed. Whenever possible study data will be collected on an electronic device to reduce the handling of paper. Data submitted will be reviewed and if ambiguous or incomplete data clarification forms will be issued.

RAPID 2: DATA ANALYSIS

We will exclude participants from individual analyses where relevant data is missing and specify the denominator for each variable. Continuous variables will be reported as median [interquartile range] and compared with either Mann Whitney U or Kruskal-Wallis tests. Categorical variables will be summarised as frequencies and compared with chi-squared tests.

We will compare the number of participants waiting longer than 4 months for a diagnosis between the RAPID 1 and RAPID 2 groups using a Chi squared test. We will compare the time-to-diagnosis between the groups as a continuous variable using a Mann Whitney U test.

We will use a multivariate analysis to look at factors associated with diagnostic delay of greater than 4 months (as a binary variable), including demographics and all known risk factors, as well as pathway to diagnosis.

We will compare validated questionnaire scores between groups diagnosed via routine care versus direct-to-consumer pathways, using a Mann-Whitney I test.

We will also compare rates of IBD related complications using a multivariate analysis using both the populations diagnosed with IBD via the RAPID pathway and those diagnosed via the direct-to-public pathway. We will use this to determine if route to diagnosis is associated with IBD related complications, although we expect this study to be underpowered to detect this.

Sample size determination

In RAPID-2, we plan to study our direct-to-consumer intervention. The novelty of the pathway limits meaningful sample size calculations. The uptake and change in the positivity rate of FIT and calprotectin tests when switching from primary care use to direct-to-consumer testing are unknown. However, we calculate we would require 108 individuals to detect a reduction in the proportion of people whose diagnosis is delayed for >4 months from 30% to 14% with an odds ratio of 2.6 and 80% power at the 0.05 significance level.

The current positivity rate of our primary care calprotectin pathway is about 12% (262/2105 tests over last 12 months), of whom about 40% have IBD. We anticipate that the positivity rate will decrease. We have factored in a fall to 5%, and anticipate that we would need to undertake about 5000 tests to identify 200 new patients per year

Decision points

We will monitor our uptake and positivity rates monthly with a formal analysis at four months to ensure the study remains feasible. If the uptake is low and/or positivity rate <2.5%, then we will discontinue the study. If the uptake is adequate but the positivity rate <10% and >2.5% then we will extend the number of tests.

Stopping rules

Recruitment will close when 5000 tests have been dispatched, or 18 months after the launch of the pathway, whichever occurs earlier. Premature closure will occur if the decision point thresholds mentioned above are not reached.

Procedure for accounting for missing, unused, and spurious data

Patients who exited the study because of loss to follow-up or patient withdrawal of consent, will be censored at the time of study exit.

Procedures for reporting any deviation(s) from the original statistical plan

Deviations from the original statistical plan may be made prior to data analysis. These changes will be discussed with the study management committee and described in an amended protocol.

Additional analysis conducted after the start of data analysis will be reported as exploratory analyses in the protocol.

RAPID 1&2: STUDY CONCLUSION

The study will conclude 12 months after the final follow up data has been collected on RAPID 2 participants. At this point all stool sample analysis will be complete and all samples will have been destroyed.

STUDY TIMELINE

	3	6	9	12	15	18	21	24	27	30	33	36
Stages of Grant												
RAPID-1 and 12 month follow-up												
Development of marketing strategy												
RAPID-2 and 12 month follow-up												
Analyses												
Qualitative Researcher												
MTO												
Study Coordinator 0.5WTE												
Denhams												
Postage												

ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and GDPR, and in accordance with all applicable regulatory requirements including, but not limited to, the UK policy framework for health and social care research 2017.

The project proposal and study protocol have been reviewed by the Sponsor, the Royal Devon University Healthcare NHS Foundation Trust.

The Exeter IBD research team will ensure that the NHS Research Ethics Committee, Health Research Authority and NHS Trust approvals are in place prior to starting both RAPID 1 and RAPID 2. In addition, the Exeter research team will coordinate the distribution of the electronic site file, collating of CV's, GCP's and delegation logs. The CI will ensure that all study reporting is conducted, including annual and end of study reporting to the REC.

Assessment and management of risk

We will attempt to minimise the following risks:

1. False reassurance following false negative biomarker tests

False negative stool tests could lead to a delay in diagnosis of serious lower gastrointestinal pathology. However, stool testing prior to primary care referral is already imbedded in clinical practice supported by DG56 and DG11 NICE guidelines. To mitigate this risk we will utilise dual testing with both FIT and FC, to screen for both IBD and other major gastrointestinal pathology. In addition, we will utilise buffered calprotectin and FIT testing with an aim to improving sensitivity. Finally, the study will provide safety-netting recommendations to participants who have negative

tests, detailing the importance of seeking further help if symptoms persist. The false negative rate will be carefully monitored during the course of the study, although it may not be possible to confidently determine this until the follow-up period has been completed.

2. False alarm from false positive stool tests

A positive test might be alarming for people, which is why we will invite these participants to a specialist clinic appointment within 2 weeks of a positive test. Compared to routine clinical care this represents a much shorter waiting time. The greatest concern for patients is that they might have cancer rather than IBD. With input from the LEP, we will ensure the invitation letter provides some reassurance by providing some estimation of the risks of finding serious pathology. We will iteratively refine this risk during the course of the study.

The testing used in this study conforms to NICE DG56 and DG11 and therefore, the diagnostic accuracy, including the false positive rate, has national acceptability. We understand that widening access to testing may have an impact on diagnostic accuracy, which is why all participants with a positive test will have a rapid clinic-based assessment rather than being directed straight to colonoscopy.

3. Risks of colonoscopy

Colonoscopy is an invasive test and is associated with rare but serious complications of bleeding and perforation. The risks, benefits and alternatives of a colonoscopy will be discussed with participants who have a positive test at the clinic appointment. The benefits of early discovery of polyps, colorectal cancer and IBD will be weighed up against the risks of colonoscopy. Participants will consent separately for endoscopic intervention as they would in standard care pathways. All colonoscopies will be carried out by competent independent endoscopists.

Amendments

Any amendments that are required after study approval will be delegated by the CI to the Exeter Research Team. The Exeter Research Team will discuss the amendment with the Sponsor, and they will then be processed as a non-substantial or substantial amendment. The Exeter Research Team will follow the HRA guidance <https://www.hra.nhs.uk/approvals-amendments/amending-approval/>

INDEMNITY

NHS Indemnity will apply.

PEER REVIEW

The study protocol has been independently reviewed by the IBD clinical research group of the British Society of Gastroenterology, by the sponsor's scientific committee and the external funders.

PATIENT & PUBLIC INVOLVEMENT

We have shown that multiple UK providers already offer online direct-to-public calprotectin testing with turnaround times typically under 14 days. Consumers can choose between home-based lateral flow tests or send stool samples for gold-standard laboratory testing. Whilst the laboratory tests are considerably more expensive and take longer to return a result, they are reportedly more accurate.

In a subsequent public and patient involvement survey of 132 patients with IBD, less than half had undergone a stool calprotectin prior to the diagnosis of their IBD and most patients wished that this had been available. Regarding use of direct-to-public stool tests: 71% of respondents stated that if a stool test had been available to order online, in a pharmacy, or at a supermarket, then they would have used one. Prior to diagnosis, 71% of people would have clicked on an NHS endorsed social media advert and ordered a stool test. Of the media platforms, Facebook, Instagram, YouTube and the national radio were most viewed by patients aged 16-50.

Moreover, one of the barriers to conventional calprotectin testing is the collection, handling and return of whole stool specimens. To try to overcome this barrier we have worked with 20 people living with IBD to assess the acceptability and usability of an alternative method of stool sample collection which we have adopted for this study. Like in the bowel cancer screening programme, this uses a comb-picker to transfer a sample of stool into a diluent ready for testing: 85% patients found the picker more acceptable or more hygienic than using a standard universal container.

We will establish a Lived Experience Panel advisory group comprising people living with IBD including a research champion appointed by Crohn's & Colitis UK. This group will meet every 3-months to advise on the delivery of the study and to support dissemination and implementation of our findings.

Our lay summary was written with members of the Exeter patient panel and reviewed by a patient group from Crohn's & Colitis UK.

DISSEMINATION PLAN

Communications with clinical and academic communities will be through peer reviewed open access publications and presentations at scientific conferences, including the annual British Society of Gastroenterology and European Crohn's and Colitis Organisation meetings. Our current publication plan in relation to this current program of research includes three publications in high impact journals over the course of this 3-year period of work.

Clinically relevant findings will be disseminated by newsletter to patients and individuals participating in the RAPID studies and posted on our website

<https://medicine.exeter.ac.uk/research/biomedicalclinical/ibdandpharmacogenetics/>

Findings will be written up and submitted to a peer-reviewed scientific journal. Findings will be presented by the study team at national and international conferences including the British Society of Gastroenterology annual meeting and the European Crohn's and Colitis meeting. The study team will prepare a lay summary of the study findings for dissemination to members of Crohn's and colitis UK.

BENEFIT TO THE NHS

This protocol addresses clinically relevant priority research questions relating to the utility of direct-to-consumer testing within the NHS, at a time of rapid expansion of the private direct-to-consumer market. Understanding how the removal of primary care gatekeeping of testing might impact the utility of biomarker tests is key to determining whether direct-to-consumer testing can be employed to reduce diagnostic delay. A greater understanding of the resource implications required for such a diagnostic pathway will be important for considering whether such a pathway might be cost-effective and inform future service planning.

AUTHORSHIP ELIGIBILITY GUIDELINES

Author-contribution statements will be mandatory in all publications arising from this study. Authorship will be contingent on substantial contributions to the design, performance, analysis, intellectual content and reporting (and revising) of the work. Authors will agree to be accountable for all aspects of the work and will provide approval for the final version to be published.

APPENDICIES

Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	V3			- Addition of another Co-Principal Investigator (Dr Rebecca Smith) - PIC sites for pharmacy-based recruitment - Updated thresholds for calprotectin testing in line with recent laboratory validation studies and routine clinical care thresholds. - Addition study documents including media campaign and website text - Changing of inclusion criteria (In RAPID1 the diagnosis to recruitment window (30d to 90d), In RAPID2 the number of weeks that participants have been experiencing symptoms from 2 weeks to 4 weeks) -Changing of the timeframe for clinical consultation following a positive test from 2 weeks to 4 weeks, in line with Urgent Care waiting times. -Further detail about the process of participant identity authentication to hold data against their medical record.