THerapy personAlisation using Multiomic analysES in Inflammatory Bowel Disease – THAMES-IBD

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St Mark's Hospital Foundation
Crohn's and Colitis UK
NIHR Imperial Biomedical Research Centre, Imperial College

This protocol describes the THAMES-IBD study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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:
..../...../.....
Name (please print):
.....
Position:
.....

Chief Investigator:

Signature: Date:
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Sponsor	Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at: Research Governance and Integrity Team Imperial College London and Imperial College Healthcare NHS Trust Room 215, Level 2, Medical School Building Norfolk Place London, W2 1PG Tel: 0207 594 1862 https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/
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STUDY SUMMARY

Inflammatory bowel disease (IBD) affects approximately 400,000 people in the United Kingdom. The main subtypes are ulcerative colitis (UC) and Crohn's disease, which affect children and adults of all ages. They cause debilitating symptoms, including diarrhoea, rectal bleeding, abdominal pain and fatigue. The need for surgical intervention is common and many have an increased risk of colorectal cancer. Whilst treatment options continue to increase, particularly with anti-immune biologic medications and small molecules that inhibit intracellular signalling pathways, there is a high rate of primary and secondary loss of response. This suggests large heterogeneity in IBD pathophysiology in different patients. Evidence is increasing that inflammation and disease progression in IBD is driven by the interaction between a variety of biological factors. This includes the local microbiome, the metabolome and the transcriptome, along with systemic features such as psychological health and nutrition.

This study aims to characterise these multiomic features in IBD patients with active disease who are likely to switch to a new therapy. We plan to link these findings with patients' outcomes from their new treatment to determine if certain factors are associated with treatment response or treatment resistance. This could ultimately lead to predictive medicine approaches in IBD, which would reduce rates of loss of response and should improve patients' quality of life and disease course.

Study Title	Therapy Personalisation using Multiomic Analyses in Inflammatory Bowel Disease – THAMES-IBD
Internal ref. no. (or short title)	THAMES-IBD
Study Design	Observational cohort study
Study Participants	Adult patients ≥ 18 years-old with ulcerative colitis, Crohn's disease or IBD-unspecified, starting a new biologic or small molecule medication Adult patients ≥ 18 years-old without inflammatory bowel disease who will act as controls
Follow up duration	30 weeks
Planned Study Period	April 2022 to December 2026
Research Question/Aim(s)	Can multiomic analyses generate biomarkers that can predict response to treatment in IBD?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
St Mark's Hospital Foundation	Unrestricted project funds
Crohn's and Colitis UK	Project grant – £119,400
NIHR Imperial Biomedical Research Centre (BRC), Imperial College London	£1,157,829

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Crohn's and Colitis UK

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Table of Contents

1. INTRODUCTION

1.1 BACKGROUND

The prevalence of inflammatory bowel disease (IBD) is increasing internationally, especially in countries with higher socioeconomic status such as the UK and USA.(1) Between 1990 and 2017, there was an increase of 80 cases of IBD per 100,000 of the population in the UK, more so than most other countries. Recent estimates suggest over 400,000 patients suffer from IBD nationally. Biologic therapy is being used earlier than before to attempt to change the natural course of disease, particularly given the reduction in expenditure afforded by biosimilar medication. Nevertheless, annual patient care still costs on average over £3000 for Crohn's disease and nearly £2000 for ulcerative colitis, with up to half of this being spent on biologics.(2) IBD Registry data shows that 14.4% of patients switched biologics at least once during a three-year study period from 2016-2019, which implies that their disease was not controlled. This is disruptive for patients and means the disease has been allowed to progress whilst optimal therapy is being sought. In the meantime, patients' symptoms and bowel damage remain unchecked, and finite resources are spent on ineffective medications. The effect on quality of life can be profound. A high proportion of patients suffers from depression and anxiety which, along with the physical symptoms of IBD, can have deleterious effects on academic and career progression, and relationships with family, friends and intimate partners.(3–5)

Treatment has been revolutionised by anti-immune biologic medications, including infliximab and adalimumab (both anti-tumour necrosis factor-alpha (TNFα)), ustekinumab (anti-interleukin (IL)12-/IL23-p40) and vedolizumab (anti-$\alpha_4\beta_7$ integrin, reduces lymphocyte trafficking), and small molecule drugs that inhibit intracellular signalling pathways, such as tofacitinib (pan-JAK inhibitor). Currently, when the step-up to biological therapy is deemed clinically appropriate, once conventional medications have failed, the specific drug is chosen based on mode of delivery, cost and comorbidities, with no reference to the underlying molecular disease process itself. Similarly, once there is inadequate response to one biologic, there is no choice but to move blindly to another until clinical benefit is hopefully achieved.

'Precision Medicine' focuses on identifying which treatment options for a given condition will be most effective in a specific patient based on the various factors that make them unique. This includes their genetics, lifestyle and environmental exposures. This approach is underway in other areas of medicine, such as oncology (e.g. anti-HER2 biologics are given to specific patients with breast cancer) and respiratory medicine (e.g. the number of eosinophil cells can predict effectiveness of anti-IL-5 biologics in asthma).(6) Despite the increasing number of biologic medications available to treat IBD, and the various immunological pathways they target, randomised control trial data has failed to demonstrate consistent steroid-free remission (i.e. being well without the need for steroids, which can have significant short-term and long-term side-effects) for any of these. Furthermore, 40% of patients do not respond at all to a given biologic, whilst 40% of the remaining patients will lose response after one year.(7–12) This suggests huge heterogeneity in the chemical drivers of patients' inflammation, even when they have the same clinical diagnosis.(13)

IBD is known to be one of the many complex immune-mediated inflammatory diseases, like psoriasis and rheumatoid arthritis, where the immune system reacts inappropriately to substances within the body, leading to inappropriate inflammation. In IBD, this trigger seems to be the trillions of bacteria that normally reside harmlessly in the gut (the 'microbiome') and actually play a major role in good health; for instance, they are known to heavily influence many chemical reactions that are crucial for glucose and cholesterol metabolism, fat storage, muscle mass and the efficacy of medications.(14) They are also pivotal in the brain-gut axis, where gut health is intrinsically linked with mental health, in part, because many of the neuro-chemicals that affect the brain also affect the gut.(15,16) The inflammation that ensues in IBD, therefore, is highly complex and dependent on many factors. These include the constituent microorganisms that make up the microbiome, the metabolome (the chemical reactions), and the specific immune molecules that drive the inflammation (the transcriptome), all of which will vary somewhat between individuals. Furthermore, given how closely the gut is linked with

the rest of the body, other factors, such a patient's nutritional status and psychological state, may affect this inflammation.

The factors determining response to biologic therapy are also, then, likely to be complicated. It is becoming increasingly crucial, however, to unpick this complexity so that effective treatment can be provided, with consequent effects on disease burden, quality of life and NHS resources. Moreover, biologic drugs that target novel parts of the immune system are currently being developed. If we can develop logistic and scientific processes to gather and store data that can predict response to current medication and better appreciate the molecular drivers of treatment response and resistance, this will be invaluable for delivering effective care in the future. Detailed disease knowledge may also permit the safe use of targeted combination biologic therapy. Further understanding and identification of predictors of response to specific biologics could mean precision medicine becomes a real possibility for IBD patients.

Tissue transcriptomics (quantification of gene expression at mRNA level) is a promising tool for precision medicine and biomarker discovery. This has been driven by the emergence of cost-effective, high-throughput next generation RNA-sequencing (RNA-Seq), growing informatics expertise and increased access to novel computational tools. Transcriptomics can be used to stratify patients according to the likelihood of responding to anti-integrin therapy. For example, four genes (*PIWIL1, MAATS1, RGS13* and *DCHS2*) predict response to vedolizumab when expressed in inflamed colonic tissue.(17) Promising data has also been reported using transcriptomics to differentiate responders and non-responders to anti-TNFα biologics. Gene expression profiling of colonic biopsies sampled immediately prior to the initiation of therapy demonstrated that five transcripts predict mucosal healing in UC patients treated with infliximab, whilst expression of oncostatin M (*OSM*), oncostatin receptor (*OSMR*) and a module of co-expressed transcripts in colonic biopsies predicts non-response.(18) Soon-to-be-published work from our laboratory at Imperial also demonstrates a role for the interleukin (IL)23/IL22 axis in predicting response to both ustekinumab and infliximab.

Higher levels of short chain fatty acid synthesis in the gut may predict response to anti-TNF therapy, suggesting metabolic considerations may also be pertinent.(19) Gut microbial composition may also be important, with greater alpha-diversity and higher abundance of *Roseburia inulinivorans* and a Burkholderiales species predictive of response to vedolizumab.(20)

1.2 RATIONALE FOR CURRENT STUDY

Within this study, we aim to analyse various features of a patient's pathobiology and demographics – including age, gender and ethnicity – to explore if there are predictors of response or resistance to specific biologic medications and to biologic medications overall. There is increasing evidence of a multifactorial aetiopathogeneis of IBD. This seems to involve changes within the microbiome and metabolic environment, which then influence the transcriptomic response that generates the various specific inflammatory cytokines. These factors are all inter-related and a multiomic approach is therefore likely needed to understand individuals' unique inflammatory environment.

We hypothesise that this will allow us to identify predictive factors that will then help us to make clinically translatable predictions about effective therapeutic options for patients requiring biologic (or small anti-inflammatory molecule) treatment for active IBD.

Many of the aforementioned studies were performed retrospectively. The promising data supports an urgent need for a prospective, multiomic approach to research predictors of treatment response and resistance that could directly benefit our patients.

2. STUDY OBJECTIVES

Primary objective: to generate multiomic tools to predict treatment response or resistance to biologic / small molecule intracellular signalling inhibitor medication in patients with active IBD.

Secondary objectives:

1. To develop a large prospective database of demographics, clinical information, multiomic biological and psychological data, and clinical progress of patients with active IBD who may start biologic medication or switch from one biologic to another.
2. To understand if an IL22-related transcriptome signature can predict response to treatment.
3. To understand if ethnicity plays a role in response to disease phenotype and treatment response in IBD.
4. To collect prospective information about psychological state and quality of life in patients with IBD, understand more about the biochemical mechanisms underpinning psychological morbidity in IBD, and explore the implications for choice of anti-immune drug therapy.
5. To investigate the role of patients' nutritional state and body composition in determining their response to biological therapy.
6. To deepen understanding about peripheral blood mononuclear cell function in patients with active IBD

3. STUDY DESIGN

We aim to perform a prospective observational cohort study to identify multiomic predictors of response to different biologic therapies in IBD.

Adult outpatients and inpatients who are due to start a new biologic or change biological therapy will be invited to participate. The choice of biologic and other clinical treatment will be determined by the treating clinical team. Patients will be identified in various ways including review of clinic lists (telephone and face-face), screening of endoscopy schedules, operating theatre lists and in-patient ward lists, via IBD multidisciplinary team meetings, and when attending for endoscopic procedures. Their medical records will be reviewed to determine whether or not they are eligible. If they meet the inclusion criteria, the study will be discussed by telephone or during a routine clinical encounter at the hospital. The rationale for the project will be explained along with the need for sample collection and any additional time commitment. A copy of the patient information sheet will be provided by post or in-person. Whilst it is envisaged that no invasive procedures or hospital visits will be required other than those normally required as part of standard medical care, this may sometimes be beneficial for the study, for instance, if a stool or urine sample needs to be brought to the hospital, or if a specific research-related blood test is needed. This will be discussed with the patient when relevant, in case this is not acceptable to them. Such tests will be limited to minimally invasive procedures such as blood tests.

Informed consent will be obtained in writing or electronically and will be documented in line with NHS Health Research Authority (HRA) guidance (https://www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf).

Participants will attend hospital for routine clinic appointments and diagnostic investigations, including blood tests, lower gastrointestinal endoscopy and to deliver stool samples. The opportunity will be taken to obtain extra biological samples for the purpose of the research project, such as extra stool for microbiological analysis, urine for metabolomic analyses, blood samples (up to 40mls, fewer than three tablespoons) and colonic biopsy samples. Questionnaires regarding quality of life, psychological health and diet will be provided, with paper and electronic options.

Samples will also be sought from healthy patients without IBD to act as controls. Healthy patients will be approached during routine clinical appointments, for example, when they attend for endoscopic procedures to investigate gastrointestinal symptoms. They may also be asked to contact the research team if they are interested in taking part in the study.

Whilst it would be ideal to obtain all the listed prospective samples and measurements from all participants to generate a rich source of data, this will sometimes not be possible for logistical or clinical reasons. However, prospective +/- longitudinal collection of any of the following samples or psychological assessments is still useful and should be sought.

Sample labelling

All patient samples will be labelled as per the standard operating procedure developed for the study with a pseudonymised alphanumeric code. This will identify the trust, the patient number (001, 002, 003 etc), a code for the type of sample obtained (F for faeces [microbiome], B for blood RNA [Tempus tube], R for tissue biopsies in RNALater solution, U for urine, S for serum [metabolome, red top], O for organoid samples, P for peripheral blood mononuclear cells), the date of collection, and the anatomic location for tissue biopsies. Only the local site team will be able to link this code back to an individual patient, which will be necessary for longitudinal data collection.

Endoscopy

If a clinician decides endoscopic examination is indicated for a patient with an IBD flare, the outcome will often be the main determinant of treatment escalation. It is also likely, therefore, to take place before final treatment decisions are made. Careful monitoring of endoscopy lists and tracking of patients referred for endoscopy from clinic or MDTs are therefore vital to optimise recruitment so endoscopic biopsies can be collected. Patients can ideally be contacted before the procedure to explain the study, or could be approached once they have attended for their appointment, as long as they are given sufficient information and time to provide informed consent (see below).

The patients' clinicians will determine if colonoscopy, flexible sigmoidoscopy or Lumeneye® video proctoscopy (SurgEase Innovations, UK) examination is required. During the procedure, extra colonic mucosal biopsy samples will be taken. During an endoscopy to assess active IBD, 2mm biopsies will normally be taken from areas of the mucosa that look most inflamed, and multiple biopsies are often obtained; for instance, during colonoscopy to assess IBD activity, 12 biopsies are often taken for clinical reasons. Biopsies impart negligible extra risk to the patient and rarely cause significant discomfort. If this is the case, the endoscopist will decide if it is appropriate to take research biopsies. Similarly, if a patient is taking blood-thinning medication, the endoscopist's discretion will be used to assess if the number of biopsies requested is appropriate or not.

In active ulcerative colitis, most patients will have rectosigmoid inflammation, so extra rectosigmoid biopsy/ies will be required to facilitate pan-cohort standardisation; rectal biopsies should be taken in those with sole proctitis. If these areas are macroscopically unrepresentative of more proximal inflammation (e.g. due to recent acute topical therapy), biopsies should be taken from the most macroscopically inflamed area. CMV staining should be specifically requested on the histology request forms for the clinical biopsies. In selected centres, patients who have not undergone recent flexible endoscopy examination may be asked to undergo Lumeneye® proctoscopy examination just prior to biologic infusion, where biopsies may be taken. This procedure would last 5-10 minutes and prior bowel preparation would not be required.

In Crohn's disease, the inflammation is likely to be patchy and it may be difficult to label a single area as being "the most inflamed". In cases where there are multiple similar areas of significant inflammation, representative biopsy/ies should be obtained for the study at the endoscopist's discretion, from a maximum of three anatomical sites.

RNase-free tubes containing 500 microlitres of *RNALater* RNA preservation solution will be provided to study sites; these can be stored at room temperature. Research biopsies should be taken using a fresh pass of the biopsy forceps down the endoscope channel. As soon as they are removed, the tissue sample should be transferred into a tube of *RNALater*; RNases are ubiquitous in the environment, so any environmental exposure should be limited. One 'bite' is needed from a specific anatomical area. The container should be inverted 2-3 times to ensure adequate *RNALater* penetration of the tissue. A different tube should be used for different sites of inflammation. It is likely that 1-2 tubes will be needed per patient, and possibly 3 if inflammation is heterogeneous in severity and distribution. Samples can be stored at room temperature for up to 7 days (though, ideally, less than 72 hours), or stored in a 4 degrees Celsius fridge for one month. Delivery to Hammersmith Hospital will be organised, where samples will be stored at -80 degrees Celsius.

At selected sites, an additional 'bite' should be placed into an unprepared Eppendorf tube. This should be stored at -80 degrees Celsius within 3 hours of collection; appropriate delivery to St Mary's or Hammersmith Hospitals will be organised.

On occasion, further biopsies will be required to culture organoids or analyse mucosal white cells. As per the standard operating procedure, up to 12 mucosal biopsies should be placed into a tube containing phosphate-buffered saline (freely, not on a strip of cardboard) and 2 samples into RNA Later. Urgent transfer can then be organised to the central research team.

Phlebotomy

Patients will normally attend the hospital for blood tests before starting a new biologic and during treatment to assess disease activity; this commonly includes full blood count, renal function, liver function and C-reactive protein. Many will also have a 'pre-biologic screen' set of bloods taken. Patients are also often cannulated before endoscopic procedures and biologic infusions. At these times, research-specific bloods (and clinical bloods if not recently taken) can be obtained without the need for an additional skin puncture.

This will include collecting blood in a *Tempus™ Blood RNA Vacutainer tube* to permit analysis of transcriptome expression. The tube should be filled to the black line (3mls blood, one teaspoon) and shaken vigorously straight after collection for 15 seconds. This can be stored at room temperature or in a 4 degrees Celsius fridge for 5 days. In some cases, where a research blood test is needed without other clinical indications, a separate skin puncture will be needed, which will be discussed with the patient first.

At some sites, blood should also be taken in three red-top Vacutainer tubes (6mls each) for serum metabolic analysis. This will be discussed with each site separately as samples will need to be processed in the laboratory shortly afterwards.

To be collected:

- Full blood count
- Renal function
- Liver function
- Bone profile
- Ferritin
- Vitamin D
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- *Tempus™* Blood RNA tube (fill to black line – 3mls – and shake vigorously for 15 seconds)

- 3 x 6ml red-top bottles for metabolomic studies (site-specific)
- 2 x 10ml lithium heparin (green-top) bottles for peripheral blood mononuclear cell analyses (*site-specific*)

Stool collection

Stool is routinely collected from IBD patients to assess:

- Faecal calprotectin and
- Microbiological testing.

Faecal calprotectin level should be checked within one month of the endoscopy (before or after), so the level should correlate with endoscopic appearances.

A further stool sample will be taken for microbiome and metabolic analysis *at selected sites*. Patients will be provided with a Fecotainer or 'blue-top' container before their clinical encounter. The stool container should be kept on ice and transported to an appropriate laboratory site. It needs to be aliquoted and frozen at -80 degrees Celsius within 6 hours of production, as per the standard operating procedure. If a patient is due to provide stool samples, transport arrangements to a laboratory will be organised. A faecal calprotectin sample should be sent simultaneously for local clinical analysis.

Urine

A urine sample would not normally be taken as part of an IBD assessment, but this is non-invasive and imparts no risk of harm to the patient. A mid-stream urine collection will be collected for metabolomic analysis *at selected sites*. The sample should be kept on ice and transported to the lab on the day of collection for processing and storage.

Standard operating procedures will be provided regarding collection of all these separate samples (SOP).

Questionnaires

Participants will be asked to complete questionnaires relating to diet, quality of life and psychological health.

The dietary questionnaire should correlate with the timing of their urine sample production, as outlined in the SOP.

The brain and gut are intrinsically linked neuro-biochemically, the 'brain-gut axis', and psychological health is likely to impact upon response to biological treatment, compliance with treatment, disease progress generally and concurrent irritable bowel-type symptoms. There is also evidence of a higher risk of developing IBD in patients with anxiety or depression, and vice versa, further highlighting these complex aetiopathogenic links. Psychological screening is recommended in clinical guidelines for IBD for these reasons (Lamb et *al.* Gut 2019).

An academic psychiatrist with an interest in IBD has advised that the following questionnaires, or a subset thereof, should be completed by participants to gain a global understanding of each individual's burden of psychological disease:

- Patient Health Questionnaire-8 (depression),
- Generalised Anxiety Disorder-7 (anxiety),

- Sub-sections of Fatigue in IBD (http://www.fatigueinibd.co.uk/questionnaire/) (fatigue),
- Standardised Assessment of Personality (personality),
- 3-item UCLA Loneliness Scale (loneliness),
- Birmingham Irritable Bowel Syndrome-Specific Questionnaire (IBS symptoms),
- Arizona Sexual Experience Scale (sexual experience),
- Pittsburgh Sleep Quality Index (sleep),
- IBD-Control (various aspects of living with IBD),
- Brief Resilience Scale (resilience),
- Altman Self-Rating Mania Scale (mania).

They would take approximately 35 minutes to complete in total, which can be done at any stage from consent to the end of their first medication dose. These might most conveniently be performed during their first infusions if they are receiving intravenous medication, though this is the last chance to complete them, so prior completion is preferable in case patients cannot do this during the infusion for any reason. Questionnaires will be available in paper or electronic format so participants can complete them in their own time.

If a specific psychological condition is flagged as being likely, the patient should be contacted by their clinical team and, with consent, their GP should be informed so review in Primary Care +/- onward referral can be organised. If other local processes exist for IBD patient referral for psychological support, these can also be followed. None of these questionnaires specifically identifies patients who are suicidal. Outcome scores from the PHQ-8 questionnaire relating to depression have been shown to correlate with more severe IBD disease course when adjusted for disease activity at baseline. (Kochar et al. 2018) The PHQ-8 does not include a specific question about suicidal ideation.

Nutritional assessment

Body composition and nutritional status seems important in determining response to treatment and overall outcomes in IBD. Sarcopaenia and malnutrition are particularly common in IBD, with an average of 60% reduction in muscle mass compared with healthy controls (21,22) and changes in lean body mass composition. (21,23) However, few studies have reported radiological or functional correlates of this which are highly relevant clinically. Sarcopaenia and malnutrition are common and, importantly, modifiable, so understanding their effect on treatment response is important for effective holistic patient care. Radiological correlates of sarcopaenia have been validated, e.g. skeletal muscle index at the level of the 3rd lumbar vertebra (24) and total psoas area/index (25,26).

We will aim to measure these from participants' scans using deidentified images sent electronically and securely to expert radiologists within the UK. Measurements will be compared before, during and after treatment using historic CT or MRI scans and future radiological investigations performed for clinical reasons. In sites where the equipment is available, other non-invasive measurements will also be taken at baseline and at week 10-14 to evaluate nutritional status, including bioimpedance assessment and handgrip strength.

Data collection

Members of the research team on the various sites will have access to all of the patients' previous and current health records. Data from here will be entered under the pseudonymised codes on a secure, password-protected Microsoft© Excel© or REDCap© platform, as described below. It will be collected by trained members of the clinical (e.g. consultants, clinical research fellows, specialist registrars, medical trainees or students under appropriate supervision) and research (e.g. clinical research nurses) teams. It will include:

- Demographic information, including ethnicity

- IBD diagnosis and relevant phenotypic details
- Past medical history
- Drug history
- Smoking history
- Details of recent flares (past 6 months)
- IBD drug history
- Details of current flare including:
    - clinical activity scores and their subsets (Mayo and SCCAI for UC and IBD-U; Harvey-Bradshaw Index and Crohn's Disease Activity Index (CDAI) for Crohn's) at the time of worst flare symptoms this episode (i.e pre-steroids), from which PRO-2 (UC) and PRO-2 (CD) can be calculated;
    - new acute medication started;
    - response to acute medication, including up-to-date clinical scores, as above, in the days leading up to endoscopy (i.e. pre-bowel preparation);
    - endoscopic severity scores (Mayo and UCEIS for UC, SES-CD and CDEIS for Crohn's)
- Treatment changes
- 10–14 week and 28–32 week follow-up for clinical scores, psychological questionnaire results, longitudinal microbiome collection (in some cases), and clinical decisions regarding new biologic treatment

It is hoped that most research-related activity can occur when the patient is already attending hospital for clinical reasons, and the study is designed as such. However, on some occasions, patients will need to be contacted out of these times and may need to provide further samples or answer further questions. Patients will be advised about this during the consent process.

Timeline:

Pre-biologic:
- Endoscopic biopsy/ies, as described
- Faecal calprotectin sample within one month of endoscopy
- Stool sample for multiomic analysis *(site-specific)*
- Urine sample for metabolomic analysis with dietary questionnaire *(site-specific)*
- Blood samples for clinical measurements, RNA expression, metabolomics analyses and PBMC collection
- Psychological / quality of life questionnaire completion
- Clinical summary completion by clinical / research team

Week 4-8 post-biologic (*site-specific)*:
- Blood samples for clinical measurements and metabolomic analyses
- Urine samples for metabolomic analyses with dietary questionnaire
- Stool sample for multiomic analyses

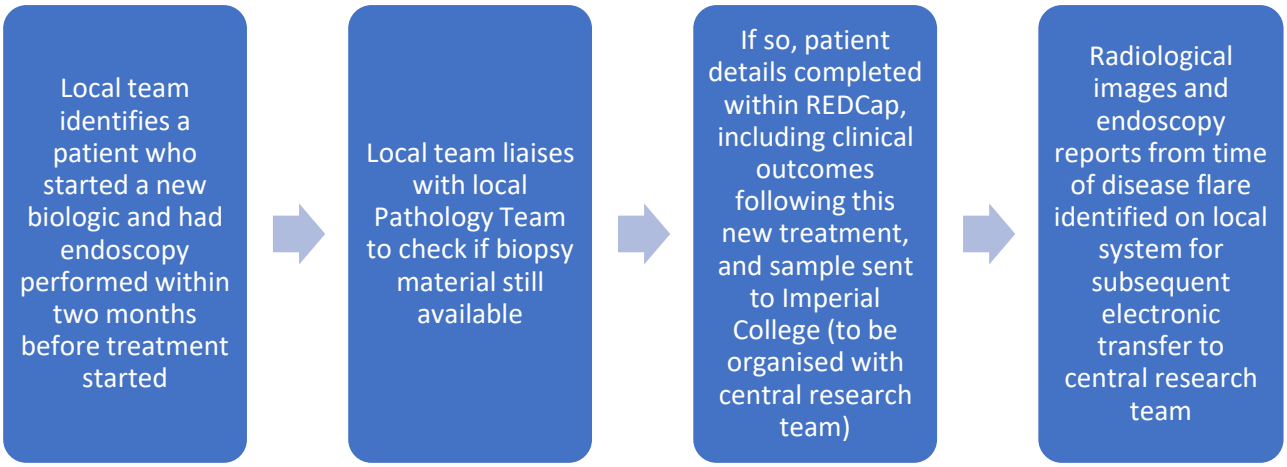
Week 10-14 post-biologic ("**post-induction**"):
- Update clinical summary data
- Psychological / quality of life questionnaire completion
- Faecal calprotectin
- Blood samples for clinical measurements and metabolomic analyses (*site-specific)*
- Urine samples for metabolomic analyses with dietary questionnaire (*site-specific)*
- Stool sample for multiomic analyses (*site-specific)*

Week 28-32 post-biologic start:

- Update clinical summary data
- Psychological / quality of life questionnaire completion
- Faecal calprotectin
- Blood samples for clinical measurements and metabolomic analyses (*site-specific)*
- Urine samples for metabolomic analyses with dietary questionnaire (*site-specific)*
- Stool sample for multiomic analyses (*site-specific)*

Retrospective review

New technology that allows transcriptomic characterisation of paraffin-embedded biopsies means that retrospective analysis of stored biopsy samples (that are no longer required for diagnostic purposes) could be highly fruitful. Patients who had active disease that necessitated a change in treatment *and* who underwent mucosal biopsies can be identified from clinical databases. These patients will be identified by local sites and their pseudonymised clinical details and outcomes can be sent electronically via REDCap to the central research team and the biopsy tissue can be sent via courier. Linked previous endoscopy reports and radiological scans will also be reviewed retrospectively. This will allow transcriptomic and radiological (including radiological surrogates of nutritional status) predictors of response to be explored retrospectively.



Schema for retrospective tissue analyses

Separate consent process if patient identified at endoscopy appointment

On occasion, despite the other possible methods of identification, potential participants will first be discovered when endoscopists are reviewing their lists on the day of a patient's procedure. Because of the nature of the main study, where further samples and questionnaires will need to be completed over the course of 6 months, a 48-hour period is provided to allow patients to consider the study before consenting. As patients will be ethically unable to undergo repeat endoscopy to provide intestinal samples after this period, and the relatively low time burden and medical risk involved in providing extra biopsy samples, patients can be consented for the colonic biopsy part of the study, and an extra RNA analysis blood test (Tempus tube, as above), at the time of endoscopy consent. From experience, patients keen to help are happy to consent to this within minutes.

A separate consent form ("Consent Form B") and a separate abridged information sheet ("Patient Information Sheet 2") will be provided. The patient should be asked if they would consider taking part

in the main study; if so, the main PIS can be provided and contact details should be taken for research team follow-up. The PIS also states that all patients, unless they decline, will be contacted about the full study regardless. Tissue and blood RNA data would still, in themselves, be valuable for the project. Clinical activity scores and future outcomes (including faecal calprotectin, which should be taken for clinical purposes anyway) should still be collected as stated above and entered on REDCap. The paper consent form can be uploaded to REDCap and stored in the site file.

Separate consent process for patients with inactive IBD or healthy controls

There is a separate written consent form ("Consent Form C") and patient information sheet ("Patient Information Sheet 3") for those with inactive (quiescent) IBD and healthy controls. This notes that there is no follow-up required. It also explains that some patients with seemingly quiescent IBD clinically can have active inflammation endoscopically which may necessitate a change in treatment. In these instances, biopsies of inflamed mucosa will be taken as above and there will be an opportunity to participate in the main study.

Patients undergoing surgery

Surgery is relatively common in IBD and implies that medical therapy has been ineffective. Analyses of surgical specimens from IBD patients and non-IBD controls would therefore be valuable for understanding why medications sometimes do not work. A separate consent form ("Consent Form D") and information sheet ("Patient Information Sheet 4") should be used. A mucosal sample from the excised specimen should be taken as per the standard operating procedure. This should then be stored or transported based on the standard operating procedure, depending on the types of analyses required. As surgery is planned in advance, the nature of the samples required can be discussed with the central research team pre-operatively.

For patients with Crohn's, entry to the full study could be offered post-operatively if they meet the inclusion criteria.

Procedure for patient identification and collection of colonic biopsies

Adult patient with active IBD who will potentially start a new biologic

Patient identification:

- IBD helpline calls – worsening symptoms, acute steroid courses etc
- Directly from consultants or registrars who have reviewed patients in clinic
- Endoscopy lists schedules
- Flare clinic
- IBD MDM
- Directly from endoscopy list

Phone call to patient to explain trial aims, investigations and follow-up
Post / email Patient Information Sheet + provide contact details

CONSENT FOR TRIAL on paper or electronically via REDCap

*If Pt identified by endoscopist on the day, can explain trial and **consent** there and then*

Ileo-colonoscopy / flexible sigmoidoscopy / Lumeneye examination

Organise faecal calprotectin test within one month of endoscopy

Mild macroscopic changes and biological therapy not immediately indicated
Take standard diagnostic biopsies
EXCLUDED FROM TRIAL(if patient eventually needs biologic, would require repeat biopsies)

Biologic therapy remains likely:
- Take standard diagnostic biopsies

PLUS

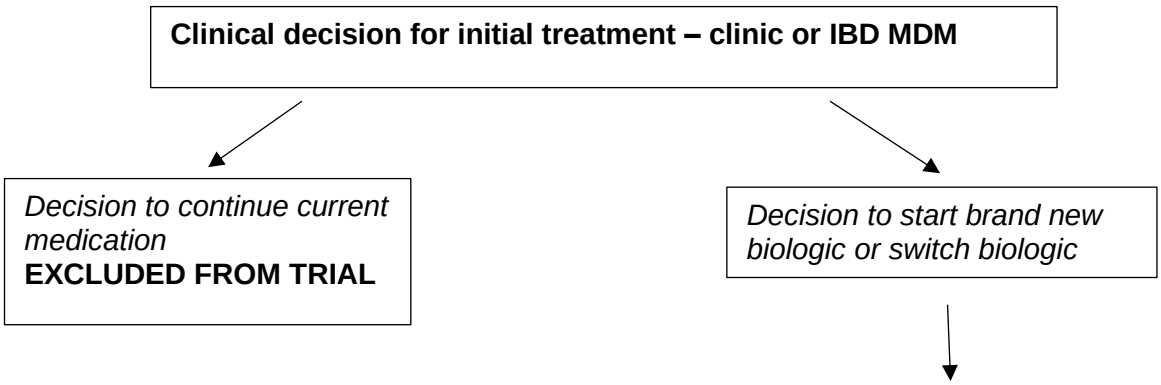
Crohn's
- Take one biopsy from most inflamed area(s) of the ileocolon, up to 3 sites

UC
- Take one biopsy from the rectosigmoid junction and/or areas representative of the most marked inflammation

Place research samples directly in to *RNALater* solution. This will be provided in Eppendorf tubes. Up to two biopsies from the same anatomical region can be placed in each tube, but one 'good' sample should suffice. Label the tubes with:

- Patient's pseudonymised ID code (see SOP) + R1 / R2… etc denoting *RNALater* sample 1, 2 etc
- Anatomical site of biopsy
- Date of collection and hospital site code

RNALater samples can be stored at room temperature for up to 7 days but, ideally, less than 72 hours, or in a 4 degrees Celsius fridge for one month, pending transport to Hammersmith Hospital lab (-80 degree freezer), which will be organised by the central research team.



BEFORE BIOLOGIC INDUCTION:

- Bloods:
  - Full blood count
  - Renal function
  - Liver function
  - Bone profile
  - Ferritin
  - Vitamin D
  - C-reactive protein
  - *Tempus*™ Blood RNA tube (fill to black line – 3mls – and shake vigorously for 15 seconds)
  - Three red-top bottles for metabolomic studies (site-specific)
  - 2 x 10ml lithium heparin (green-top) bottles for peripheral blood mononuclear cell analyses (site-specific)

- Stool:
  - Faecal calprotectin
  - Microbiome (equivalent of a three-quarter-full blue-top stool container)
  - Metabolomics

- Urine:
  - Metabolomics

- Patient to complete pro forma / REDCap form which will include:
  - Demographics (age, sex, ethnicity)
  - Diagnosis
  - Disease location, subtype (CD), year of diagnosis, previous treatments
  - Harvey-Bradshaw Index (CD) or partial Mayo score (UC) – can calculate PRO-2 from each
  - Smoking status
  - Height and weight
  - Comorbidities
  - Current drug history
  - More detailed dietary questionnaire for metabonomics / microbiome part of study
  - Psychological and quality of life questionnaire

Email m.saifuddin@nhs.net to notify about enrolment in the trial.

Timeline

Phone call to patient to explain study, or discuss **in clinic**

Send **Patient Information Sheet** (PIS)

Team will get contact you again after at least **48 hours** to answer any questions and see if you'd like to participate

Decision made re: starting biologic and which drug (**IBD doctor / IBD team meeting**) and scheduled locally

Site-specific – collection will be organised locally, aligned with a clinical visit, if possible:

- *Blood samples (clinical + metabolome)*
- *Urine sample and dietary questionnaire (metabolome)*
- *Stool samples (multiomic)*

Week 0 | **Wk 4-8** | **Wk 10-14** | **Wk 28-32**

- **Consent** for research can be completed on paper or electronically (REDCap)
- **ASSIGN STUDY ID** for all labelling from now
- Patient attends for **colonoscopy / flexible sigmoidoscopy** (if clinically required)
  - Intestinal **biopsies** – the number taken will be discussed beforehand
- Clinical team will ask questions to determine your **disease activity scores** (at this stage, or any stage before new medication starts)
- **Blood tests** (can often be done during cannulation for procedures, or when you are having clinical blood tests done)

Face-to-face/ telephone **Pre-Biologics Clinic**, **IBD Nurse appointment** or equivalent – a researcher may meet you here to collect samples and answer any questions you have, or your clinician can ask a researcher to call you

Patient attends for **biologics infusion /** starts at home

- **FINAL CHANCE FOR SAMPLES** – i.e. stool / bloods / urine / nutrition status assessment
- **Psychological / quality of life questionnaire** completion now, or any time before, on REDCap or on paper
- Disease activity scores

- Disease activity scoring by clinical research team, updated on REDCap
- Repeat psych. / QoL questionnaires
- Faecal calprotectin
- Therapeutic drug monitoring if applicable
- Nutrition assessment
- Further clinical input as required (bloods etc)

- Disease activity scoring, updated on REDCap
- Repeat psych. / QoL questionnaires
- Faecal calprotectin
- ?endoscopy, if clinically indicated to evaluate response to treatment
- **FINAL research follow-up**
- Clinical follow-up continues as normal

Bloods (pre-biologic screen + disease activity + research) / urine

FCP * +/- microbiome — **No sample**** — **Microbiome**

Psychological and quality of life questionnaires
Nutritional status assessment, if available (hand grip / bioimpedance)

*Check faecal calprotectin (FCP) within 1 month before / after endoscopy
**Do not check FCP from bowel prep to 2 weeks after endoscopy

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IRAS 290708

3.1 STUDY OUTCOME MEASURES

At the aforementioned pre-specified assessment time-points, the local research teams will evaluate the clinical effectiveness of each patient's treatment based on the following parameters (27):

Crohn's disease

Clinical *response*:

Unweighted PRO-2 (CD):
≥ 30% decrease in average daily stool frequency (SF)
and/or ≥ 30% decrease in average daily abdominal pain score (AP),
and neither worse than inclusion scores at baseline.
And

Faecal calprotectin < 250mcg/g or decrease from baseline of >50%

PRO2 (CD) is a patient-reported outcome measure for Crohn's disease clinical activity.(28,29) It is validated and is being used in IBD-RESPONSE and CD-metaRESPONSE, UK-wide multicentre studies investigating microbiome and metabolome predictors of response in IBD. It is simple to calculate:

PRO2 (CD) = mean stool frequency over the previous 7 days + mean abdominal pain score over the previous 7 days,

where abdominal pain is scored as: no pain = 0, mild = 1, moderate = 2, severe = 3.

Ulcerative colitis / IBD-U

Clinical *response*:

PRO-2 (UC) decrease ≥ 3 from baseline

And

Faecal calprotectin < 250mcg/g or decrease from baseline of >50%

PRO2 (UC) is also a validated measure of disease activity (30):

PRO2 (UC) = mean stool frequency score for the previous 3 days + mean rectal bleeding score for the past 3 days (both means rounded to nearest whole number before addition),

where stool frequency is scored as:
0 = normal
1 = 1-2 stool(s) per day more than normal
2 = 3-4 stools per day more than normal
3 = >4 stools per day more than normal

and rectal bleeding is scored as:
0 = none
1 = visible blood with stool less than half the time
2 = visible blood with stool half the time or more

3 = passing blood alone (and ≥ 50% of bowel movements contain visible blood AND there is ≥ one bowel movement with blood alone)

Clinical remission has not been defined as a separate end point.

Additional indications of non-response or lack of remission:

IBD-related surgery
Continuation of pre-biologic steroids, or commencement of a new course of oral steroids
Clinician decision to switch to a different biologic for reasons other than those listed beneath.

Treatment discontinuation unrelated to disease response:

Treatment discontinuation due to:
- adverse drug reaction (e.g. serious infection, malignancy, severe dermatological side-effects), or
- antibody-mediated loss of response, or
- patient choice

will need to be assessed within the clinical context, in case the patient's inflammation was being well-controlled on the medication before these other effects occurred. In this case, the patient would have responded in the context of multiomic prediction of response, despite a change of medication being required for another reason. The reason for switching medication should be documented within the case report file, along with the clinical status at the time.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Pre-registration study screening investigations will have been undertaken for clinical purposes before recruitment; for example, raised faecal calprotectin or inflammatory blood test parameters will have been noted by researchers screening patient lists before initially approaching potential study participants. No other screening tests will be required. If subsequent tests or clinical assessments deem that the patient does not have active disease or is not going to switch biologic, they will be removed from the study.

4.2 INCLUSION CRITERIA

- **IBD patients**: patients with a confirmed diagnosis of ulcerative colitis, Crohn's disease or IBD-unclassified

- **Active disease** as determined by standard clinical parameters, measured within the two months prior to recruitment:
  - **Crohn's** symptom flare as indicated by Harvey-Bradshaw score >5 or unweighted PRO-2 (CD) of average daily stool frequency (SF) score ≥4 and/or average daily abdominal pain (AP) score ≥2
  - faecal calprotectin ≥250micrograms/gram,

  OR

- **UC / IBD-U** symptom flare as indicated by PRO-2 (UC) of ≥3 including a rectal bleeding score of ≥1
- faecal calprotectin ≥250micrograms/gram

- **Inactive disease**: patients with a confirmed diagnosis of IBD and absence of active disease features

- **Healthy controls**: patients with no diagnosis of IBD and no clinical suspicion of undiagnosed IBD

- Age ≥ 18 years-old
- Able to consent to the study

4.3 EXCLUSION CRITERIA

- Unable to provide informed consent

4.4 WITHDRAWAL CRITERIA

Participants will be able to withdraw from the study at any point without giving specific reasons and with the reassurance that this will not affect their clinical care. This is an observational study so the main samples will have been taken early in the study, prior to biologic commencement. Patients may withdraw consent during the initial sample collection phase or withdraw consent from providing longitudinal samples or completing follow-up questionnaires. In each case, unless the patient specifically objects to it, the samples that have already been collected will remain within our analyses. If a patient withdraws consent for the study team accessing their records or contacting them to monitor clinical progress, this will cease without detriment to their clinical care.

Patients can inform the research coordinators of this via the telephone number or email address provided to them, or they can inform a member of the research or clinical team in-person, who will arrange for this to be updated within their case report file. This process will be detailed in the Patient Information Sheet and explained upon recruitment.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but

may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs
An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to IBD, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Yorkshire & The Humber - Sheffield Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email: nicholas.powell@imperial.ac.uk
Please send SAE forms to: nicholas.powell@imperial.ac.uk
Tel: 020 3313 4824 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Clinical follow-up will then occur as per standard practice. Participants will all have access to IBD Nurses via email and telephone helplines who are able to assist directly or escalate to the patient's IBD medical team.

They will normally be followed-up 'post-induction' by their usual clinical team (between weeks 10-14 post-commencement) to evaluate response to the new biologic treatment, in order to determine if this should be continued or modified in some way, or if another treatment should be considered because of lack of response or side-effects.

Clinical assessment will be both subjective (specialist clinician's global opinion about clinical progress) and objective (e.g. faecal calprotectin, blood tests, objective patient-reported outcomes, repeat endoscopic and/or radiological assessment). These parameters and expert local clinical management will allow researchers to determine the efficacy of treatment for each patient. If any relevant information is not detectable from clinical notes, researchers should contact the patient to ensure full outcome measures are documented, namely:

Crohn's disease

- Crohn's Disease Activity Index (CDAI)
- Harvey-Bradshaw Index (HBI)
- PRO2 (CD) – i.e. daily stool frequency and abdominal pain score for the past seven days (see above)

Ulcerative colitis / IBD-U

- Partial Mayo score
- PRO2 (UC) – i.e. stool frequency above normal for the past three days and rectal bleeding (see above)

Where possible, the psychological and quality of life questionnaires should be repeated; again, paper and electronic versions will be available.

Some sites will be asked to collect longitudinal stool samples from patients for microbiological analysis.

A further research review should occur between weeks 28-32 post-commencement, where clinical scores and psychological questionnaires should be repeated again, as above, where possible. This may align with routine clinical review.

Therapeutic drug monitoring should continue as is appropriate for standard clinical care (i.e. thiopurine dose optimisation, infliximab and adalimumab drug level monitoring, and vedolizumab drug level monitoring where local protocols exist).

Longitudinal follow-up of multiomic data may also be collected to observe the effect of treatment, and to compare changes between responders and non-responders.

Patient follow-up will cease after the 28-32 week review.

'Reviews' can take place face-to-face or remotely. Participants can be sent electronic links to complete the questionnaires or forms can be sent in the post with a stamped addressed envelope to the local study site, so the results can be transcribed to REDCap.

Control patients will not require follow-up.

If appropriate consent is provided on the informed consent form, any incidental findings will be reported to the patient's clinical IBD team or GP who will then determine the need for hospital or Primary Care follow-up.

Follow up of psychological / quality of life questionnaires

If a patient scores $\geq$10 points on either the GAD-7 or PHQ-8 questionnaires, this is suggestive of moderate-to-severe anxiety or depression, respectively. In these instances, a letter should be sent to the patient's GP from the clinical team stating this score so further evaluation +/- onward referral can be made from Primary Care. If the patient has not consented to their GP being told about involvement in the study or incidental findings, the local IBD team should contact the patient to discuss the findings so appropriate support can be provided.

Patients may also contact the IBD team or their GP to discuss other quality of life issues resulting from the questionnaires, e.g. loneliness, for which support and advice can be provided locally.

7. STATISTICS AND DATA ANALYSIS

Bioinformatic and pseudonymised clinical data will be preserved for at least 10 years, as per Imperial College London policy, under the stewardship of Dr Powell on the Imperial College server. Upload to reposited databases, such as GEO, will ensure appropriate archives exist.

Dr Cozzetto, the senior bioinformatician in the research team, has performed a power calculation based on preliminary data, using the Mann Whitney U test. To demonstrate a difference in clinical remission of 19% between patients given ustekinumab with low IL22 signature enrichment and high enrichment, as observed in our previous analyses, 45 patients will be needed (α<0.05, β=0.80, pooled standard deviation = 0.300). Assuming a similar effect for anti-TNFα medication and tofacitinib for transcriptomic prediction, and a similar effect for other -omic predictors of response, we aim to recruit at least 45 patients starting each of these drug groups (135 in total), with similar numbers of healthy patients and patients with inactive IBD, to act as controls (= 90 controls).

Regarding microbiome and metabolome patients, the investigators are aiming for 50 Caucasians with active IBD and 50 healthy controls, 50 patients of Middle-Eastern descent with IBD and 50 healthy controls, and 50 patients of South Asian descent and 50 healthy controls. This is based on previous wide experience in this field, as it is difficult to calculate power calculations given that this type of study involving predictors of response using the microbiome / metabolome of patients with different ethnicities has not been performed in the past.

Assuming that 50% of patients each provide all samples (i.e. colonic tissue, blood, stool, urine, psychological questionnaires), whilst the others provide only a subset of these (e.g. only colonic biopsies and blood, or only stool and urine (e.g. if they are not undergoing clinical endoscopy)), approximately 458 patients will need to be recruited in total.

(45 x 4 biologic groups = 180 + 45 healthy controls = 225.
50% will give all samples → 113
+ 100 x 3 = 300 = 413.
413 + 45 patients with inactive IBD (no stool or urine from these patients) = **458**)

Bioinformatics, statistics and data analyses will be performed by members of the research team with appropriate expertise, or external support will be sought if required.

Samples from surgical specimens are not part of the prospective cohort *per se* but will still be valuable for achieving the study objectives. We aim to collect samples from 10 such patients during the study period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Yorkshire & The Humber - Sheffield Research Ethics Committee (REC) and Health Regulator Authority (HRA) (Ref: 22/YH/0043). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be

conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

The option to consent electronically (e-consent) will be available via REDCap. Patients will be able to initial the boxes for each section of consent, in the same way as the paper consent form, and sign it. This will be emailed to them and stored within REDCap.

Study-related data will be held under Task in the public interest, meaning that, if a patient withdraws from the study, further samples cannot be collected, but pre-existing data can be kept and used for analyses.

Consent will not be specifically sought to use patients' samples stored in hospitals that are no longer needed for diagnostic purposes. Once identified as meeting inclusion criteria by the direct clinical team, they will be assigned a study code and details will be logged on REDCap, as above, with scans and biological samples labelled with this pseudonymised code subsequently. Researchers outside the clinical care team will not have access to information that links this code to personal information. This is in line with section 1 (9) of the Human Tissue Act 2004.

8.3 PATIENT AND PUBLIC ENGAGEMENT

James Lind Alliance (JLA) is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre. It facilitates patients, carers and clinicians to consider the major outstanding research priorities in a disease area. Professor Hart led the UK's JLA exercise for IBD in 2014 (Hart et al. 2017). Overall, 531 people submitted perceived IBD treatment uncertainties (78% patients or carers, 22% clinicians). The top 25 were discussed by a steering group comprising patients and clinicians. They generated the "Top 10 research questions in IBD". The top priority was "What is the optimal treatment strategy considering efficacy, safety and cost-effectiveness in IBD management: selecting the right patient group and right stage of disease [...]?" Key stakeholders, therefore, agree precise treatment approaches remain an unmet need and that such research should be actively, and urgently, prioritised.

Local patient and public engagement involved 21 patients with moderately active IBD. Twenty responded that precision medicine would be beneficial for patients and 20 said dedicated research would be valuable. Sixteen would consent to extra endoscopic biopsy sampling. Some explained biopsies can be uncomfortable/painful, which will now be explicitly mentioned during consent. Eleven would attend hospital specifically for the study and only 8 would undergo endoscopy solely for research. Hospital visits will therefore be minimised and biopsies will only be taken opportunistically, rather than proposing flexible endoscopies when not clinically indicated. Patients have also helped to develop the Patient Information Sheet.

8.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act (2018).

Data will be pseudonymised.

Study data will be transferred to Imperial College London, King's College London (to facilitate colonic organoid culture), Barts and The London School of Medicine (PBMC and radiological analyses), University of Westminster (radiological analyses). Sample processing and data analyses will also be facilitated by industry partners, including Janssen, Abbvie, Bristol Myers Squibb, Astra Zenea and Pfizer, with whom the central research team already collaborates academically.

8.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.6 SPONSOR

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.7 FUNDING

Unrestricted funds from St Mark's Hospital Foundation, a project grant from Crohn's and Colitis UK and a grant from NIHR Imperial Biomedical Research Centre (BRC), Imperial College London are funding this study, including costs relating to staff salaries, sample processing and storage, and laboratory analyses. This is an observational study where participants will be undergoing many of the costly investigations, such as endoscopy, as part of standard clinical care, with extra sampling required for the study. A Schedule of Events Cost Attribution Template (SoECAT) has been completed by AcoRD specialists at NIHR North West London Clinical Research Network which demonstrates that no excess NHS costs will be accrued. There are no per-participant payments to collaborators.

8.8 AUDITS AND INSPECTIONS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Powell Lab, Department of Metabolism, Digestion and Reproduction, Imperial College, London.

10. PUBLICATION POLICY

Publication of the research findings will be sought in high impact, peer-reviewed journals, and in abstract form following presentation at international and national conferences. Author contribution statements will be sought and authorship will be determined after consideration of this contribution to the work, including manuscript preparation and critique, sample collection and processing, analyses, interpretation and study design. Authors will agree to be accountable for all aspects of the work. All authors will be able to review and sign-off academic output before submission to journals or conference selection committees.

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