Trial Procedures Manual

Trial Title:	PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr (PROFILE) trial
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1 Abbreviations

AE	Adverse Event
CCTU	Cambridge Clinical Trials Unit
CRF	Case Report Form
CV	Curriculum Vitae
DMC	Data Monitoring Committee
FBC	Full blood count
GP	General Practitioner
GCP	Good Clinical Practice
ICF	Informed Consent Form
LFT	Liver Function Tests
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SmPC	Summary of Medical Product Characteristics
TC	Trial Coordinator

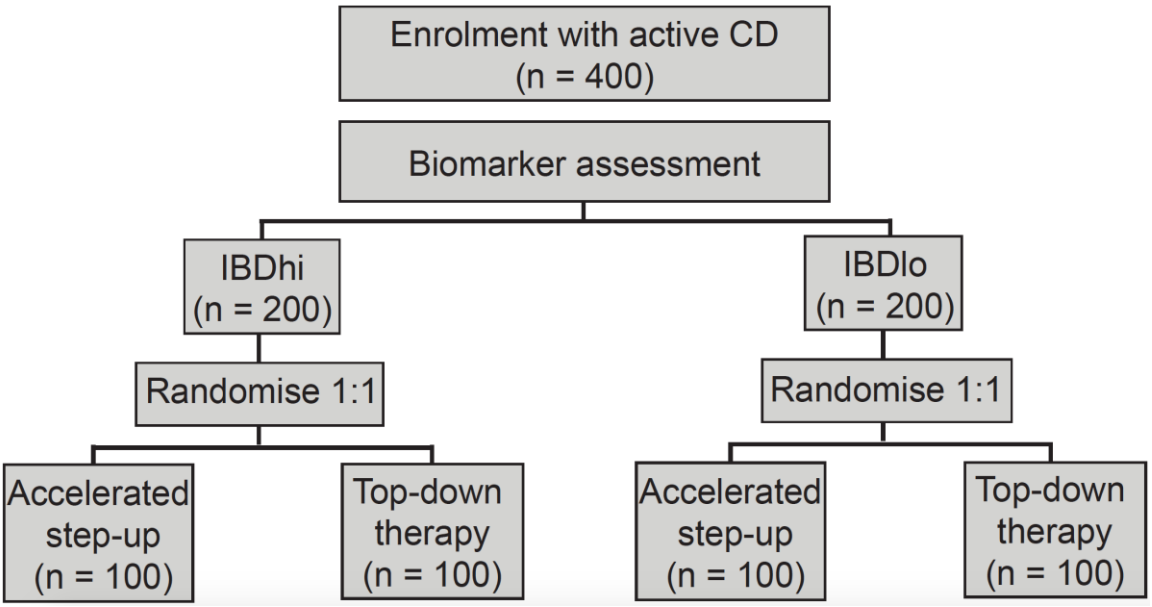
2 Trial Procedures Manual guideline

This trial procedures manual is a supplement to the PROFILE protocol. It is not a replacement for the protocol but provides detailed instructions on how to carry out key aspects of the trial. Please read it carefully in conjunction with the protocol and the regulatory guidelines that govern Good Clinical Practice.

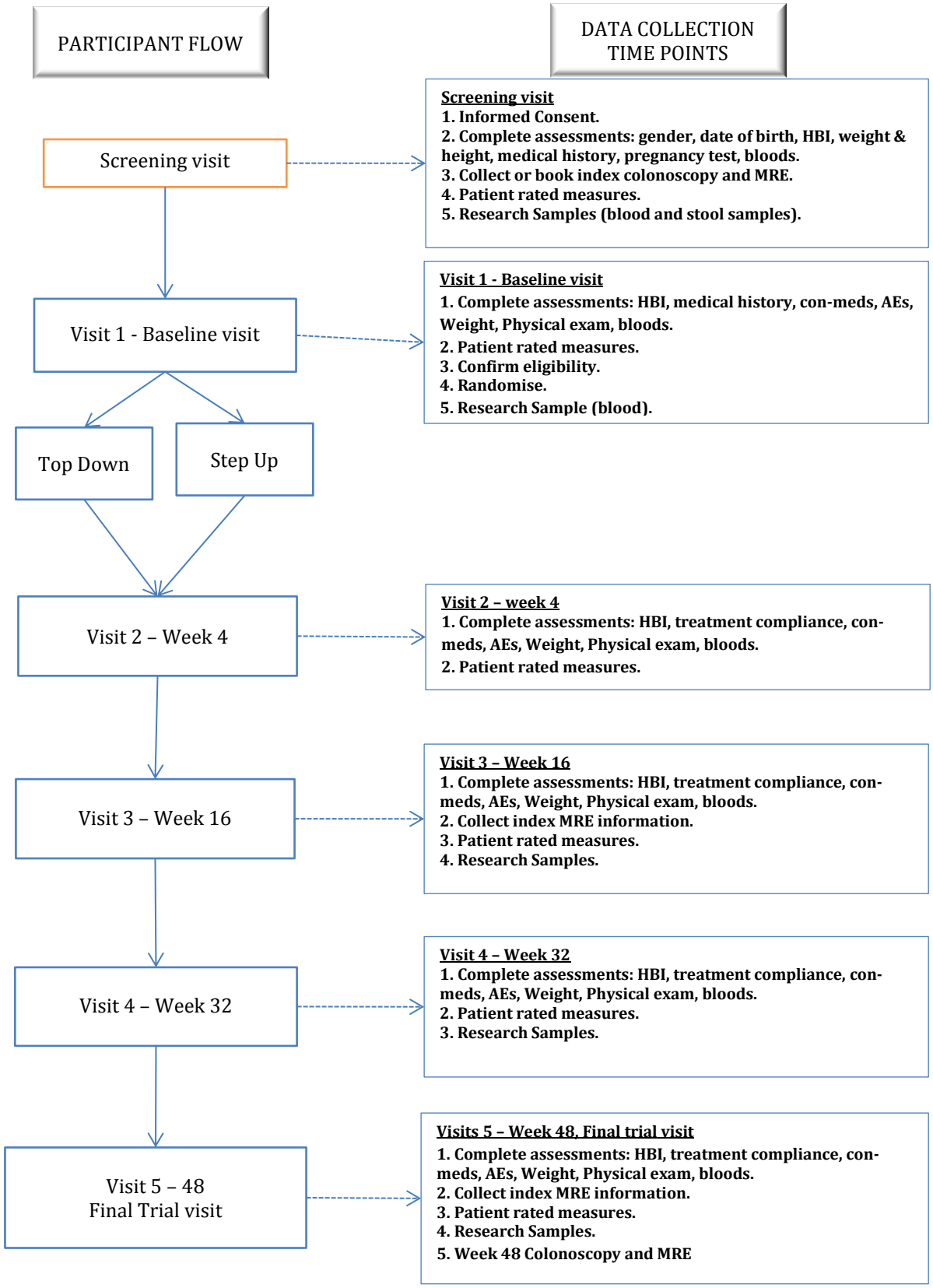
2.1 Patient Recruitment

400 patients with newly diagnosed Crohn's disease will be enrolled into the study and randomised to either "Accelerated Step-Up" or "Top-Down" treatments. Target recruitment rate for all sites is 5 patients to be randomised per year but sites are welcome to recruit more (competitive recruitment). Recruitment is expected to last for approximately two years. Subjects require evidence of active inflammation including colonoscopic evidence of activity (NB the colonoscopy is not repeated for study inclusion: we use the index / diagnostic colonoscopy)

3 Study Design Flowchart



3.1 Participant Flow and Data Collection Time points Flow chart



4 Potential Participant Referral/Identification

Potential participants will usually be identified in Gastroenterology/Surgery clinics by the local investigator or an appropriately delegated member of staff. This is not the exclusive route for patient identification (endoscopy, ward etc.). Potential candidates may also be identified by staff who are triaging out-patient referral letters or colonoscopy requests, where the history is indicative of a diagnosis of Crohn's disease. N.B. such index / diagnostic colonoscopies should be videoed where possible (see below).

It may be worth mentioning the study to people who are being investigated for possible Crohn's disease; and it may be worth trying to stream such referrals to the local PI's endoscopy list and clinic to aid videoing / SES-CD scoring of the index colonoscopy and subsequent patient recruitment.

Once the diagnosis of Crohn's disease has been confirmed the local investigator or an appropriately delegated member of staff will introduce and discuss the study with potential participants. The potential participant will be given the Participant Information Sheet and asked to consider the study, and will be given as much time as they require to make an informed decision.

Potential participants who would like more time to think about the study should be booked for early review, even within a few days. Please note that as study inclusion requires the biomarker blood test to be done off-steroid medication, it may be worth deferring the start of steroid medication by a few days if patients require this time to consider the study.

Please note patients can be recruited any time within 6 months of diagnosis. This can include them having had a course of steroids provided they have been off these for at least a week and provided their disease is active at the time of screening. The preference, however, is for patients who are steroid-naïve.

5 Screening Procedure

Potential participants will attend a clinic for the screening visit.

Potential participants confirm that they wish to participate by signing the Informed Consent Form (ICF).

Once participants have signed the consent form and had their study bloods taken (including the biomarker) they will all be started on a course of corticosteroids.

5.1 Consent Process

An appropriately delegated member of staff will explain the study, answer any questions and then obtain informed, written consent from each patient before the performance of any protocol-specific procedures. The voluntary nature of participation and the ability for an individual to withdraw consent at any time will be emphasised.

The Informed Consent 'script' should contain (at minimum) the following points:

- Background/Purpose
- Why the patient has been invited
- Brief overview of the study
- Brief descriptions of the procedures
- Benefits and disadvantages
- What happens to the results
- What if there is a problem – contact details/out of hours
- GP to be informed of participation on the trial
- State the patient can withdraw at any time for any reason which they do not need to give
- Any questions the patient may have
- Carefully read the consent form and initial in each box
- Travel expenses, how and when these will be paid

An ICF must be signed *before* any research procedures are performed.

The original signed ICF together with the relevant version of PIS must be filed in the Investigator Site File. A copy must be given to the patient and a copy filed in the medical notes.

5.2 Patient Screening ID and Trial ID Numbers

Patient Screening ID numbers for each site will be allocated sequentially. The participant screening log will be pre-populated with the Screening ID numbers and will start with the site identifier (one letter and three numbers that identify a site) followed by a three digit sequential numbering system. These must be allocated to each subject upon identification and invitation to participate in the trial.

For participants who, upon completion of screening procedures, are enrolled into the trial, their Screening ID number will become their Trial ID number (i.e. Trial number). This will be entered into the "Sealed Envelope" randomisation service and will be the same throughout the duration of the trial for each participant, and must be entered on all completed CRF pages for the participant.

5.3 Participant Logs

5.3.1 Participant pre-screening log

The participant pre-screening log must be updated whenever a new patient is pre-screened for the trial. The reason for being excluded from screening should

be recorded. The pre-screening log should be submitted to the data manager add-tr.profile@ns.net at the end of each month.

5.3.2 Participant screening log

The participant screening log must be updated whenever a new patient is screened for the trial. The screening log will have a unique pre-populated screening number for all participants. For patients that are screened and not recruited into the trial, the reason should be recorded. The screening log should be submitted to the TC on a monthly basis and should be completed in full.

5.3.3 Participant randomisation log

The participant randomisation log must be updated whenever a new patient is randomised for the trial. The randomisation log contains patient identifiable data and should remain at each site and not sent to the trial coordinating centre.

5.4 Confirmation of Eligibility

Before randomisation, patient eligibility must be confirmed by completing the Inclusion/Exclusion CRFs. **The site principal investigator or appropriately delegated member of staff must confirm the patient's eligibility.** The name of the investigator who confirms eligibility must be written clearly on the form. Please refer to the current version of the Protocol for patient eligibility criteria.

Principal Investigator (PI) Responsibilities

> **The PI has overall responsibility for the conduct of the trial at his/her site and for ensuring compliance with GCP guidelines.**

This includes:

- Ensuring the trial is conducted in accordance with the current trial protocol.
- Ensuring that trial participants meet inclusion criteria and are negative for exclusion criteria.
- Having overall responsibility for the safety of all trial participants at the site; recording and reporting safety events and taking appropriate action.
- Ensuring that written informed consent is signed by a patient before any trial-specific procedures begin on the patient.
- Ensuring the collection and recording of all trial data is performed accurately and in a timely manner in source notes (medical records) and CRF's.
- Ensuring that all members of his/her team undertaking trial-related procedures are appropriately and adequately trained for their duties

including GCP training as appropriate. Trial team members must be on the Delegation of Responsibilities and Signature Log clearly stating their duties in the trial.

- Ensuring that CVs of all members of the team outlining qualifications, training and experience are available. CVs must be filed in the Investigator Site File and a copy sent to the trial coordinator (TC) to be filed in the Trial Master File.
- GCP training should be updated in accordance to local Trust policy. GCP certificates must be filed in the Investigator Site File and a copy sent to the TC to be filed in the Trial Master File.

5.5 Delegation of Responsibilities and Signature Log

Any member of staff performing trial-specific procedures must sign the delegation log and the PI must also sign to confirm that the member of staff is suitably qualified to carry out their tasks. This must occur *prior* to the member of staff performing any trial-specific procedures.

New members of staff should be added to the log and an end-date should be entered on the log if members of staff leave. The delegation log will be kept in the ISF and a copy should be sent to the TC at CCTU whenever it is updated.

5.6 Trial Specific Training Record

All trial team members of staff must be trained on the protocol and trial procedures prior to performing any trial-specific procedures. The Trial Specific Training Record must be completed when the member of staff is trained.

6 Randomisation

Please see the 'Randomisation User Manual' for information on the process of randomising a participant using the internet based randomisation system. Upon randomising a patient, the randomisation log should be completed.

Training will be provided at the site initiation visit.

The names of study personnel who need to access the randomisation system need to be recorded on the delegation log and notified to the TC. Once these details have been received, the individual will receive an email with a link to "Sealed Envelope" randomisation website and log in details (email address and temporary password). Staff will be prompted to change their passwords on first login. Once randomised, participants are eligible for help with travel funds (£40 per visit to a max of £240 per participant, via invoice). Travel costs should be invoiced quarterly in-arrears based on the actual costs incurred. Invoices should be sent to the R&D Finance Department, Flat 42 - Barton House, Box 114, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's, Hills Road, Cambridge, CB2 0QQ.

7 GP Letter

A GP letter must be sent to inform the patient's GP that the patient is enrolled into the trial. The GP letter must be sent within 10 days after a patient has been randomised.

8 Study measurements

Each contact with the participant should be documented in either the patient medical records or trial specific workbook (which should be stored with the medical records).

This manual provides a detailed description of procedures for PROFILE trial assessments. However, there may be instances where local practices and guidelines should be followed, as detailed below.

The schedule of assessments table provides an overview of the study measurements / information that need to be completed / collected for this trial.

- Physical examination.
- Height & weight.
- Physician review.
- Tests performed at screening visit: (PAXgene RNA tube for biomarker assessment, FBC, Urea & electrolytes, creatinine, LFT and CRP, Hepatitis B serology, Hepatitis C serology, TPMT and varicella serology, Tuberculosis screening).
- Research samples: (PAXgene RNA tube, serum tube, EDTA tube).
- Stool samples: (Stool sample in sample pot with buffered solution, stool sample in sample pot with no additive buffer solution).
- Monitoring tests: (FBC, Urea & electrolytes, creatinine, LFT and CRP, Thiopurine metabolites, Infliximab drug level).
- Clinical assessments.
- Patient booklets.
- Concomitant medication.
- Colonoscopy.
- Magnetic Resonance Enterography (MRE).
- Concomitant Medications.

Schedule of Assessments

Procedure	Screening Wk -2	Baseline Wk 0	Wk 4	Wk 16	Wk 32	Wk 48	Ad hoc
Consent	✓						
Disease assessment - Harvey Bradshaw Index (HBI)	✓	✓	✓	✓	✓	✓	✓
Concomitant medication	✓	✓	✓	✓	✓	✓	✓
Weight in Kg	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓	✓	✓
Eligibility confirmed		✓					
Randomisation		✓					
PAXgene RNA tube for biomarker assessment	✓						
PAXgene RNA tube for research sample	✓	✓		✓	✓	✓	✓β
Serum tube	✓			✓	✓	✓	
EDTA tube	✓						
Bloods (FBC, CRP, U&E, Creatinine, LFT)	✓†	✓	✓	✓	✓	✓	✓
Bloods (Hepatitis B & C, VZV, TPMT and Tuberculosis testing)	✓						
Bloods (6-TGN and 6-MMP = thiopurine metabolites)			✓α	✓α	✓α	✓α	✓α
Stool sample for faecal Calprotectin	✓	†		✓	✓	✓	✓β
Buffered stool sample	✓					✓	
Stool sample for m&s							✓
Patient rated Questionnaires	✓	✓		✓	✓	✓	✓
Colonoscopy	✓*					✓	
Magnetic Resonance enterography or enteroclysis (MRE)	✓¥					✓	
Adverse event reporting		✓	✓	✓	✓	✓	✓

* Screening colonoscopy results can be taken from the participants index colonoscopy performed as part of their standard care within 6 months of the screening visit. Ideally a video of the colonoscopy should be recorded for central reading.

[α]6-TGN and 6-MMP (thiopurine metabolite)s only to be measured if participants are taking either Azathioprine or 6-Mercaptopurine.

[β] stool for faecal calprotectin and PAXgene tube (if treatment escalation for active disease, otherwise no PAXgene tube or faecal calprotectin samples required).

†Results of blood tests and faecal Calprotectin performed as part of standard care can be used for eligibility provided performed up to 2 months prior to the baseline visit – however a repeat stool sample should still be sent for central processing

(as Central lab results will be used in subsequent analyses). Sample pot for faecal Calprotectin will be provided at screening visit and patients advised to provide sample promptly (posted from home) so that central Calprotectin result is available at the baseline visit.

¥ It is anticipated that all patients newly diagnosed with Crohn's disease will undergo MRE. An MRE performed as part of standard of care can be used; and if not already performed should be undertaken within 3 months of the screening visit. The results of this index MRE will be collected at the week 16 visit. It will be used for central reading and allow comparison with MRE at week 48.

8.1 Physical Examination

The relevant page of the CRF will ask you to confirm whether the physical examination has been completed, the date, and record any abnormalities. The findings of specific assessment for peri-anal Crohn's disease and extra-intestinal manifestations should be recorded. Please ensure this information is documented in the participants' medical records or trial specific workbook.

Procedures for height and weight measurements are outlined below.

8.1.1 Height

Equipment required:

- Wall height chart / stadiometer.

Procedure:

- The subject is asked to remove their shoes.
- Subject stands against height wall chart / stadiometer, with their feet shoulder width apart.
- Subject's heels, bottom, shoulder blades and head should be in contact with the wall chart / stadiometer.
- Ask subject to look straight forward.

Wall chart/ stadiometer should be held level against top of subject's head.

Height is recorded in centimetres.

8.1.2 Weight

Equipment required:

- Weighing scales.

Procedure:

- The subject is asked to remove shoes and socks and any heavy items of clothing / objects inside of clothing.
- Scales are 'zeroed'. Subject stands on scales and weight is recorded in kilos.

8.2 Screening Tests

Blood samples for screening blood tests will be processed through local laboratories. The screening tests include:

FBC, Urea & electrolytes, creatinine, LFT and CRP, Hepatitis B, Hepatitis C, varicella serology, TPMT, and Tuberculosis testing (TB testing as per local preference and Chest X-ray).

Patients who still have a TB result awaited or the result is indeterminate, when they attend their baseline visit, they can still be randomised if their chest x-ray shows no evidence of TB and they are considered low risk for development of TB, and at clinician discretion. If testing for TB subsequently returns as positive, then the participant should be withdrawn from the trial.

8.3 Research blood samples

Please note these will be taken at the same time as 'Monitoring bloods' (see section below)

Research blood samples (screening, baseline, Week 16, Week 32 & Week 48 visits) are pseudonymised and will be linked only by their trial ID number and DOB.

Research samples should be sent to the central coordinating study site. A request card for Cambridge University Hospitals NHS Foundation Trust will be found in each "Safebox" (provided by the central trial team). The date and time of sampling should be entered onto this form prior to posting samples.

Full instructions for the collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

8.3.1 PAXgene RNA tube samples

PAXgene RNA tubes should be collected at the following visits:

- Screening visit (2 samples to be collected at this visit).
- Baseline visit (1 sample to be collected at this visit).
- Weeks 16, 32, and 48 (1 sample to be collected at each visit).

8.3.2 Serum tube samples

Serum tubes should be collected at the following visits:

- Screening visit.
- Weeks 16, 32, and 48.

8.3.3 EDTA tube samples

EDTA tubes should be collected at the following visit:

- Screening visit.

8.4 Monitoring Blood Tests

Monitoring blood tests will be collected at each participating centre and processed through your local laboratories.

The results of the screening and monitoring tests should be printed out and attached to the patients' medical records, to allow subsequent completion of Case Report Forms. A clinician must review the results and record that they have done so.

The monitoring blood tests include:

- FBC, Urea & electrolytes, Creatinine, LFT and CRP:
    - These should be performed at Baseline visit (week 0), and weeks 4, 16, 32, 48, and ad-hoc visits.
- Thiopurine metabolites (6TG and 6MMP).
    - Thiopurine metabolites are only to be measured if participants are taking either Azathioprine or 6-Mercaptopurine. These should be performed at weeks 4, 16, 32, 48, and ad-hoc visits.
- Infliximab drug level.
    - Infliximab drug level is only to be measured if participants are taking Infliximab and meet indication i.e. if concern of non-response when participants arrive for their third dose of Infliximab, as defined by fall in HBI of <3 points AND/OR HBI score $\geq$ 7.

8.5 Stool samples

Stool sample in sample pot with no additive solution, should be collected following these visits:

- Screening visit (Sample pot for faecal Calprotectin will be provided at screening visit and patients advised to produce study sample and post promptly so that central Calprotectin result is available at the baseline visit).
- Weeks 16, 32, and 48.

Stool sample in pot with buffered solution, should be collected following these visits:

- Screening visit.
- Week 48.

Stool samples will be produced by participants at home using kits provided and then posted to the central study site (refer to Laboratory manual)). The postal address will be pre-completed on all Royal Mail "Safeboxes". A request card for Cambridge University Hospitals NHS Foundation Trust will be completed and accompany the sample.

Full instructions for the collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

Participants will be asked to get in touch with trial sites to inform of date that stool sample was posted. This will allow local trial teams to complete the shipping log.

If no participant expected contact has been received by the local research team within 7 days of the respective trial visit, a member of the local trial team (e.g. local investigators/research nurse etc.) should get in touch with the with participant to encourage the sample to be sent.

These samples are pseudonymised and will be linked only by their trial ID number and DOB (unbuffered stools are also linked by gender). Please ensure the details e.g. Trial ID etc, have been completed on all documents/pots prior to providing the equipment to the participant.

The participant will need to complete the date and time of sampling on the request card prior to posting samples. Local trials sites should ensure the participant is aware of this

8.6 Pregnancy Test

A urine pregnancy test must be conducted at screening as per standard practice in women of child-bearing potential.

Equipment required:

- Urine sample collection, as per standard practice.
- Urine pregnancy test kit.
- Gloves.

Procedure:

- Check expiration date on test kit.
- Remove the testing strip from the package.
- Wearing gloves, dip the testing strip into the urine sample.
- Check for result after appropriate timepoint and record in participants' medical records.

8.7 HBI

The Harvey-Bradshaw Index is a medical scale used for the assessment of symptom severity in participants with Crohn's disease. It usually takes less than 5 minutes to complete. There are 5 individual questions to ask and then a total score to be calculated based upon responses to these five questions:

1) How many liquid stools has the patient had in the past 24 hours?
2) What level of abdominal pain does the patient have? (none, mild, moderate, severe).

3) Does the patient have an abdominal mass? (none, possible, definitely, definitely and tender).
4) How is the patient's general well-being? (very well, slightly below par, poor, very poor, terrible).
5) Does the patient have any extraintestinal manifestations? (none, arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissure, new fistula, abscess).

Results of these assessments should be recorded in the participants' medical records.

8.8 Participant Booklets

Electronic versions of the participant questionnaires and cover sheets will be provided by the coordinating centre.

Site staff should provide each participant the questionnaires and cover sheet stapled together. Please ensure the cover sheet is completed by local trial staff prior to giving it to the participant.

Site staff should provide the questionnaire booklet to the participant and allow them enough time to complete every question.

Some people may have difficulties with questionnaires. Research staff can aid them in the completion of the questionnaires but responses must be the opinion of the participant.

The EQ-5D is a quality of life index used for the assessment of disease impact upon quality of life for participants, usually takes 5 minutes to complete. Please ensure every question is answered.

The IBDQ is a quality of life measure using 32 questions and takes approximately 10 minutes to complete. Please ensure every question is answered.

The resource usage questionnaire will be used as part of the comprehensive health economic analysis. It should take approximately 10 minutes to complete. Please ensure every question is answered.

8.9 Concomitant Medication

All concomitant medication will be assessed/reviewed and recorded at each time point. Keep a copy of all concomitant medications CRFs at site and update the CRF (following CRF completion guidelines) if there are any changes. Treatments used as part of the trial protocol or to manage infusion reactions e.g. chlorphenamine, do not need to be recorded on the concomitant medications form.

8.10 Colonoscopy

To be conducted after week 48 visit as per local guidelines and in accordance with the Colonoscopy manual for the PROFILE trial.

Screening colonoscopy results can be taken from the participants index colonoscopy performed as part of their standard care within 6 months of the screening visit.

Week 48 colonoscopy needs to occur within +4 weeks of the week 48 visit. Given waiting times for departments please book this in plenty of time.

8.11 MRE

To be as per local guidelines and in accordance with the MRE manual for the PROFILE trial.

Initial MRE needs to occur within +/-3 months of Screening visit.

Week 48 MRE, needs to occur within +6 weeks of the week 48 visit. Given waiting times for MRI departments please book this in plenty of time (ideally all trial procedures included MRE should be booked after randomisation).

8.12 Medications

Corticosteroids

8 week course prescribed at screening: Examples of a typical 8 week regime include either Prednisolone 40mg to be taken daily, reducing by 5mg every week to 0mg (i.e. 40mg per day for one week, then 35mg per day for one week etc.), or Budesonide 9mg to be taken daily.

For those in the "Top-Down" group, the rate of weaning should be accelerated once Infliximab is commenced from a reduction of 5mg/week to 10mg/week.

The 8 week steroid courses can be shortened when participants commence anti-TNF (to avoid triple immunosuppression).

Oral vitamin D and calcium replacement to be prescribed as per local hospital guidelines, whilst on regimen of corticosteroids.

If during the steroid course, participants experience a sustained deterioration of symptoms attributed by the local PI to a flare of Crohn's disease (HBI $\geq$ 7) the participant will move to the next "Step" if on "Accelerated Step-Up" treatment (i.e. 12 week reducing course of Prednisolone starting at 40mg/day and reducing by 5mg/week to 20mg/day then 5mg every 2 weeks to 0 **plus** starting an immunomodulator).

If symptoms remain refractory to the 12 week course of corticosteroids and immunomodulator (fall of HBI of <3 AND/OR HBI $\geq$ 7) or if the disease re-flares, the participant can "Step-Up" to Infliximab, at treating clinicians' discretion.

Azathioprine

For participants with normal TPMT activity who are aged less than 65 years old, Azathioprine 2.5mg/kg oral tablet(s) to be taken daily. For participants with intermediate TPMT activity this dose should be halved. Participants with

complete TPMT deficiency or aged >65 years old, should not receive Azathioprine, and should receive Methotrexate instead. Specific dosing may vary from the exact calculated dosing due to tablet configurations (dose rounding/tablet splitting/alternate day dosing to be guided as per local practice).

Azathioprine intolerance

Participants who are intolerant of Azathioprine should be started on either Methotrexate or low dose 6-Mercaptopurine and Allopurinol (details below) as per the preference of the local Investigator, unless Azathioprine-induced pancreatitis occurred in which case Methotrexate must be used.

Low Dose 6-Mercaptopurine (6-MP) & Allopurinol combination

For participants who are intolerant of Azathioprine (for reasons other than pancreatitis) or who preferentially metabolise Azathioprine to 6-MMP: start Allopurinol 100mg oral tablet(s) and 6-Mercaptopurine 0.3-0.4mg/kg oral tablet(s) to be taken daily (dose rounding/tablet splitting/alternate day dosing to be guided as per local practice). Specific dosing may vary from the exact calculated dosing due to tablet configurations. The combination of Allopurinol and low dose Mercaptopurine is safe provided appropriate monitoring, including therapeutic drug monitoring (included within the study design). Dosing may be adjusted for weight, TPMT levels, white blood count or following measurement of 6-TGN and 6-MMP levels with targets as per normal reference ranges of local laboratory.

Women of child-bearing age or men who are sexually active receiving Allopurinol must use contraception.

Methotrexate & Folic acid combination

For participants who are TPMT null, or older than 65 years, or who develop Azathioprine-induced pancreatitis, Methotrexate 15-25mg is to be taken weekly (no titration), either as oral tablet(s) or subcutaneous injection. Lower doses may be required if any evidence of impaired renal or liver function.

Women of child-bearing age or men who are sexually active receiving Methotrexate must use contraception. Folic acid, 5mg, to be taken as an oral tablet the day after Methotrexate, or as per local practice for prescription of folic acid.

Anti-TNFα Infliximab

Infliximab 5mg/kg to be infused intravenously, over a period of up to 2 hours. Following first infusion, subsequent infusions will be 2 weeks after (+/- 7 days), then 6 weeks after the first infusion (+/- 7 days), and then infused 8 weekly thereafter (+/- 7 days), i.e. standard induction and treatment regimen for Infliximab.

Exact dosing may vary slightly from the calculated dose e.g. dose may be rounded up or down in line with local practice.

Infliximab costs will only be covered for up to 9 separate infusions per patient over the course of the trial. For the first order of Infliximab for the first participant recruited by each trial site, the trial co-ordinator will be required to approve the order. This stock will be stored in pharmacies as per the SmPC.

For those with clinical non-response to Infliximab (fall in HBI of <3 points AND/OR HBI $\geq$ 7 at the 3rd dose of Infliximab) a blood sample for Infliximab drug levels should be taken and an additional dose of Infliximab will be provisionally scheduled to take place 4 weeks after the 3rd dose.

This additional Infliximab infusion should only be given if pre-dose Infliximab levels, taken at the 3rd Infliximab infusion date, are confirmed to be less than 20µg/ml (or upper limit of local assay where upper limit is less than 20µg/ml) and the disease remains active at one week prior to this additional infusion (checked via telephone consultation). Participants with persistent non-response at their following trial visit after this additional dose, should have treatment terminated.

Anti-TNFα Adalimumab

If participants are either severely intolerant of Infliximab, experience persistent, mild intolerance despite a slower infusion rate and pre-treatment as per local practice, or develop anti-infliximab antibodies then they can be switched onto Adalimumab **only after discussion with the Chief Investigator**.

This is delivered subcutaneously every two weeks. First dose is 160mg, second dose is 80mg and all further doses are 40mg.

Non-severe infusion reactions

If participants develop a non-severe infusion reaction following administration of Infliximab, or experience other mild allergic symptoms, then all subsequent infusions should be delivered at a slower rate and pre-treatment as per local policies and practice.

8.13 Impact of Coronavirus Pandemic

Due to dynamic PHE guidance and legislation around the coronavirus, it is anticipated that social distancing/shielding, lockdowns, non-essential travel and outpatient local hospital policies may lead to missing or delayed data.

In instances where the patient cannot attend face to face visits, telephone calls may be used to capture as much self-reported data as possible. 'Visit by telephone' will need to be captured on a Non-Compliance form.

Please contact the trial coordinators if needing to complete visits by telephone for the first time, as they will be able to provide support and guidance. They will

also have a template non-compliance forms available, that can be used as a guide.

The Non-Compliance form should capture:

Trial activities that were not performed/data not collected:

- physical examination and consequentially unable to fully score the HBI
- examination of extra intestinal manifestations and perianal disease
- research bloods
- stool sample

Trial activities/data with caveats:

- Weight: the participant was able to provide a weight from their scales at home and this has been recorded in the source data and CRF.
- Routine safety bloods: these may be missed entirely or depending on local shared care arrangements and laboratory accreditation, may have been taken elsewhere e.g. GP surgery
- End of trial colonoscopies and MREs may be significantly delayed by the coronavirus and can be collected up to 4 months after their Week 48 visit.

'Trial Information Sheets' and guidance for using these are also available to trial teams. These were designed during the initial outbreak and were intended to be used in instances where the trial team were unable to contact the participant on their scheduled visits date due to e.g. redeployment. Please consult your Site File for further details.

Please contact the trial coordinators if needing to complete phone visits for the first time, as they will be able to provide support and guidance.

9 Adverse Events

Is any untoward medical occurrence in a clinical trial subject administered a treatment and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a treatment, whether or not considered related to the treatment.

For the purpose of the study, only AEs that are related to Crohn's disease (disease flares or surgery) or drug therapy for Crohn's disease (**sufficiently severe to require a switch to an alternative treatment**), or the associated biomarker sample collection will be recorded and assessed.

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a participant has yet received treatment.

9.1 Recording Adverse Events

Individual adverse events should be recorded in the trial-specific AE log and evaluated by the Principal Investigator or a delegated member of the site team. This includes the evaluation of its seriousness, causality and any relationship between the Biomarker and/or concomitant therapy and the adverse event. When recording the final outcome of the adverse event, option "on-going" can only be used at the end of the trial.

The AE log is a live document and should be kept updated at each trial visit.

9.2 Serious Adverse Events (SAE) Reporting

Each Principal Investigator needs to report serious adverse events to the Chief Investigator using the trial-specific SAE form within 24 hours of becoming aware of the event. The Chief Investigator is responsible for ensuring the assessment of SAEs for expectedness and relatedness has been completed by the PI and for the onward notification of all SAEs to the Sponsor within 24 hours after first notification. The Sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The reporting process begins by emailing completed SAE forms to the PROFILE TC, using the following contact details:

Cambridge Clinical Trials Unit (CCTU), Clinical Trial Coordinator Email: add-tr.profile@nhs.net

The TC will then forward the forms to the Chief Investigator and Sponsor.

(See Sections 11 of the protocol for full safety details)

You should complete all information available at the time of reporting on the SAE CRF. Please indicate if this is an initial or follow up report, and complete the remaining details.

9.3 Pregnancy Reporting

All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification. Pregnancy reporting should stop 3 months after the patient's last dose of study medications.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE**.**

All pregnancies should be followed up until resolution. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE. Trial-specific pregnancy form completion guidelines and reporting instructions will be provided in the PROFILE pregnancy form.

10 Unblinding

The investigator and participants are unblinded to all trial treatments. The biomarker status will remain blinded for the duration of the trial.

11 CRF Completion Guidelines

Full CRF completion guidelines can be found in the CRF completion guidelines manual.