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PROFILE:

PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr trial

Participant Information Sheet & Consent Form

Contact numbers

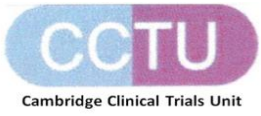
Local PI:

Local Nurse:

Local PALS or equivalent service:

CCTU: Francis Dowling (01223) 254666

The trial is being funded by the Wellcome Trust



PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

PRedicting **O**utcomes **F**or Crohn's d**I**sease using a mo**L**ecular biomark**E**r (PROFILE) trial

You are being invited to take part in a research study into the outcomes of different treatment options for patients with newly diagnosed Crohn's disease. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully. Please ask us if anything is not clear or if you would like more information.

Introduction

Crohn's disease is a type of inflammatory bowel disease (IBD) that can affect any part of the intestine. The severity of Crohn's disease varies a lot between different people, and this means that what might be the best treatment for one person may not be appropriate for someone else.

This study will see whether a simple blood test ('biomarker') can improve Crohn's disease outcomes and reduce the number of flares experienced by enabling delivery of 'personalised therapy' (that is, treatment tailored to the individual person based on their predicted disease course and severity).

All patients enrolled will receive established treatments (there are no new drug therapies being trialled – rather, it is the new blood 'biomarker' that is being tested). The goal is to see if the biomarker allows us to choose the right strategy for the right patient at diagnosis, and so improve short-term and long-term outcomes.

It is a randomised study. Half the people enrolled will be treated with a course of 8 infusions (up to a max of 9) of Infliximab ("Top-Down") over the first year together with an additional tablet-based treatment (immunomodulator). This is currently the most effective treatment in Crohn's disease and is usually reserved for patients who have developed severe disease. The other half will follow the usual standard of care ("Step-Up"), which may include infliximab if the disease flares recurrently. The study will include 400 patients from hospitals across the UK.

Section 1: Purpose and outline of the trial

1. What is the purpose of the trial?

The trial is testing a new 'biomarker' blood test which has been shown to predict disease severity in the years following diagnosis. Following the biomarker result, trial participants who have been recently diagnosed with Crohn's disease will be randomised to one of two treatment strategies, both of which use standard Crohn's therapies but differing in the order they are used. The aim is to see if use of the biomarker allows treatment strategies to be personalised (i.e. tailored to predicted disease course) in a way that leads to a reduced number of Crohn's flares and hence improved outcomes.

2 What are the drugs being used?

The medications being used in the PROFILE trial are all currently in regular use in patients with Crohn's disease. The standard care strategy is often called "Step-Up" and this will be compared with a "Top-Down" strategy, which is thought to be more effective in patients destined to run a more severe disease course.

Step-Up strategy – is in line with the usual standard of care and NICE guidelines for Crohn's disease. It is based on the treatment that you would receive from your gastroenterologist if you did not take part in the trial.

At the outset of the trial, you will receive an 8 week reducing course of steroid tablets. A reducing course is when a patient is given a drug regimen that starts at a particular dose that is then slowly reduced over a period of weeks to zero.

If you were to experience a relapse during the trial period (known as a "flare"), you would then receive a 12 week reducing course of steroid, and would also be started on a medication called Azathioprine (immunomodulator tablet). If you were not able to tolerate Azathioprine we would use an alternative, such as low dose Mercaptopurine with Allopurinol or Methotrexate with Folic acid

If your Crohn's were to flare again despite the above medications you would then receive Infliximab (also known as anti-TNF therapy) in combination with one of the above immunomodulator medications.

At each stage, you will only move on to the next step of the treatment strategy if your Crohn's disease is flaring up and is not satisfactorily controlled with your current medication.

Top-Down strategy – involves using more potent medications from the time of diagnosis This is not routinely used in patients with newly diagnosed Crohn's disease in the UK, although it is sometimes used like this in other parts of the world. The study aims to show that using this approach improves clinical outcomes and is cost effective in individuals predicted by the biomarker to run a more severe disease course.

At the beginning of the trial you will receive a reducing course of Prednisolone.

You will also receive Infliximab in combination with Azathioprine. If you were not able to tolerate Azathioprine we would use an alternative such as low dose Mercaptopurine with Allopurinol or Methotrexate with Folic acid.

For any additional flare in your Crohn's disease you will receive a reducing course of steroid.

Prednisolone, Azathioprine, Mercaptopurine, Allopurinol, Methotrexate and Folic acid usually come in the form of small tablets. The exact form of these tablets may vary and will depend on local availability or preference. You will not be liable for prescription charges for these or any trial-related drugs.

In some cases it may be necessary to give prednisolone or an equivalent corticosteroid as an injection. Methotrexate is also available in injection form. Infliximab is given as an intra-venous infusion at the hospital.

3 Why have I been invited?

You have been invited to participate in this trial because you have recently been diagnosed with Crohn's disease (within the last three months).

We plan to include 400 participants with Crohn's disease from approximately 50 hospitals across the UK.

4 Do I have to take part?

Participating in this trial is completely voluntary. If you decide to participate you will be asked to sign a Consent Form. If you chose not to participate or to leave the trial, your future medical treatment and normal standard of care will not be affected in any way.

5. What will happen to me if I take part?

Consent

You will be given time to decide whether you would like to take part in the study and have the opportunity to ask any questions and to discuss these with your doctor. If you agree to participate, you will be asked to sign the consent form at the end of this information sheet.

Even if you sign this consent form, you can still withdraw your consent at any time without having to give an explanation.

Randomisation
As we do not know which way of treating patients is best, we need to compare the different treatment strategies, each of which has potential advantages and potential disadvantages. You will be allocated one of the treatment strategies for this trial in a random way (by chance). You will have a 50% chance of receiving either the "Step-Up" or the "Top-Down" treatment strategies described above.

You will be told which group you have been assigned during the baseline study visit.

<u>Study visits</u> – each visit will take approximately one hour.

Screening (Visit 1)
After you have given consent, the study doctor or nurse will record some basic information. Blood samples totalling approximately 35mls (equivalent to 2 tablespoons) will be drawn for the study at the same time as routine clinic bloods. Depending on local practice, you may be required to have a chest X-ray. We will also ask you to provide two stool samples for analysis and a member of your local hospital team may call to confirm you have posted these samples using the provided stool pots and safe box.

Baseline (Visit 2)
The study doctor or nurse will record some basic information, including details of your current symptoms relating to Crohn's disease. Blood sample totalling approximately 2.5mls (equivalent to ½ teaspoon) will be drawn for the study at the same time as routine clinic bloods.You will need to complete a short quality of life questionnaire (entitled "IBD quality of life"), and provide a stool sample and a member of your local hospital team may call to confirm you have posted these samples. Results of your colonoscopy will be reviewed.

Weeks 4, 16 and 32 (Visit 3, 4 & 5)
As above, you will visit your hospital where a study doctor or nurse will record information regarding your health status. We will also draw blood samples of totalling approximately 25mls (equivalent to 4 teaspoons).

At week 16 and 32 visits, in addition to the above, we will ask you to complete the IBD quality of life questionnaire, and to provide a stool sample and a member of your local hospital team may call to confirm you have posted these samples.

Week 48 (Visit 6 - final study visit)
You will visit your hospital for interview as above, and have a colonoscopy (which will be recorded in anonymised form) and MRI scan of your abdomen within 4 weeks of this visit. Colonoscopy involves taking a bowel preparation and attending the hospital for examination of your colon after you have been sedated. Diagnostic colonoscopy such as this carries a very low risk of complications (approximately 1 in 2000 for significant bleeding or perforation) The MRI scan involves drinking a special solution and lying down while the scan is performed. If you suffer from claustrophobia please tell your medical team. Both of these tests allow the doctors to assess the activity of your Crohn's disease.

This will be the final participant visit for the trial and all treatment decisions after this point will be at the discretion of your treating doctor.

The colonoscopy videos and MRIs will be used for analysis and be anonymised for central readers.

Step-Up treatment
If randomised to "Step-Up" therapy, you will only be required to have study visits as described above.

Top-Down treatment
If you are randomised to "Top-Down" therapy, you will receive 8 infusions (up to a max of 9) of Infliximab over a 48 week period as is standard for all patients receiving this therapy. Infusions will start at week 2 with following infusions required at weeks 4, 8, 16, 24, 32, 40 and 48. Each infusion requires a visit to hospital. Each infusion will take approximately 2 hours.

The study visits have been timed to minimise the impact on you, with trial visits being aligned to infusion dates and expected out-patient review dates.

Schedule of events

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Consent	✓					
Symptom assessment	✓	✓	✓	✓	✓	✓
Record of all medications	✓	✓	✓	✓	✓	✓
Weight in Kg	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓	✓
Eligibility confirmed		✓				
Randomisation		✓				
Blood tests for clinical and research samples	✓	✓		✓	✓	✓
Stool sample	✓	✓		✓	✓	✓
Quality of Life measures	✓	✓		✓	✓	✓
Colonoscopy						✓
MRI of the bowel	✓					✓

6. What will I have to do?

If you join the trial you will be required to have a total of 6 study visits which should coincide with your out-patient clinic appointments.

It is important that you take any trial medication regularly as directed by your trial doctor. You will need to keep an accurate record of the trial medication.
There are no dietary restrictions in the trial.

Please share the following information with your partner or family members as appropriate.

If Methotrexate or Allopurinol are required (which will be the case for approximately 20% of study participants), women of childbearing potential will be required to use adequate contraception for the 48 week duration of the trial and for 3 months after the last treatment. Contraception may include:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection or implant etc)
- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)

Men on Methotrexate will be required to use adequate contraception for the 48 week duration of the trial and for 3 months after. This includes:

- Barrier contraception (condom and spermicide) even if their partner(s) are using another method of contraception or are already pregnant.

Men on Methotrexate treatment should also refrain from donating sperm for the duration of the trial and for 3 months after.

If you or your partner becomes pregnant during the trial or within 3 months of stopping treatment, you should inform your trial doctor. Of note Azathioprine and Infliximab are safe in pregnancy. The outcome and progress of any pregnancy would be followed and you would be asked questions about the pregnancy and baby, if appropriate.

If you have any major concerns or are feeling unwell during the course of the study please contact your local hospital doctor using the contact numbers at the end of this information sheet. You should discuss your participation in this trial with any insurance provider you have.

7. What are the side effects of the drug being used?

Although the lists of side effects can look intimidating the majority of people tolerate these medications without significant problems. It is also important to consider that these are the same drugs that will be used in the treatment of your Crohn's disease whether or not you participate in the study. Tell your doctor right away if any of the above side effects occur. The team looking after your Crohn's disease will carefully monitor all of your medicines and check for any possible interactions.

Infliximab

Common side effects include:

- Skin rashes.
- Muscle or joints aches.
- Increased risk of infection.

Significant but rare side effects include:

- Swelling of the face or hands.
- Difficulty swallowing or breathing.

Azathioprine and Mercaptopurine

The following side effects can occur with Azathioprine:

- Feeling generally unwell, aches or flu-like symptoms.
- Dizziness, headaches.
- Nausea, vomiting or abdominal pain.
- Fever.
- Abnormal liver function.
- Skin rashes.
- Hair loss.

Significant but rare side effects include:

- Pancreatitis (which can present with abdominal pain).
- Reduced bone marrow activity which can lead to an increased risk of infections and anaemia.
- Increased risk of lymphoma and skin cancer.

Methotrexate

Diarrhoea and mild aches and pains may occur initially but should settle within two weeks. Other side-effects include:

- Nausea.
- Increased risk of infection.
- Skin rashes.

- Hair thinning.
- Abnormal liver function.

Allopurinol
Side-effects of allopurinol are generally rare, particularly when taken in low doses, as in this trial. Side effects can include:

- Skin rashes.
- Nausea and vomiting.

Significant but rare side effects include:

- Abnormal liver function.
- Reduced bone marrow activity which can lead to an increased risk of infections and anaemia.

MRI of the bowel
Side effects can be mild skin reactions, nausea or abdominal cramps from the contrast material used.

8. What are the possible disadvantages and risks of taking part?
There will be some discomfort and inconvenience associated with the study-related assessments including the additional blood samples, stool samples and pregnancy test (if applicable to you), and the extra MRI and colonoscopy. Chest x ray where required exposes you to a very small radiation dose equivalent to 3 days natural background radiation Additional hospital visits will also be required. We do not foresee significant excess risk from the medications used in this study, as all regularly used in Crohn's disease.

9. What are the possible benefits of taking part?
We would expect you to experience relief in your symptoms or an improvement in your disease, **as all participants will be receiving active treatment** (there are no placebos / dummy drugs being used). We anticipate that information collected as part of your participation in this trial may benefit patients with Crohn's disease in the future.

10. What are the alternatives for treatment?
If you do not wish to participate in the trial you will receive standard care from your doctor. This will be very similar to the "Step-Up" arm of the trial protocol.

11. What happens when the trial stops?
After your week 48 trial visit, your treatment for Crohn's disease will be at the discretion of your local doctor. The treatments received as part of the trial may continue. Doctors and hospitals are under no obligation to continue the trial related medications.

12. Expenses & Payment?
You will not receive any payment for participating in this trial, however we can reimburse any reasonable travel and parking costs incurred up to the value of £40 per trial visit (6 total). You will not benefit financially if this research leads to the development of a new test.

Section 2: Trial Conduct

13. What if new information becomes available?

Sometimes during the course of a trial, new information becomes available which might affect your decision to continue participating. Your trial doctor will contact you to discuss any such new information. If you still wish to continue on the trial, you may be asked to sign a new Consent Form.

The trial sponsor, the regulatory authority or the trial doctor may decide to stop the trial at any time. If that happens we will tell you why the trial has been stopped and arrange for appropriate care and treatment for you.

14. What if I decide I no longer wish to participate in the trial?

You are free to come out of this trial at any time without giving a reason and without affecting your future medical treatment. If you decide not to participate any further, you will no longer receive the trial treatment. No further tests will be performed on you and no further research samples will be collected. Any data already collected or results from tests already performed on you or your samples will continue to be used in the trial analysis.

The trial doctor may also choose to withdraw you from the trial if they feel it is in your best interests or if you have been unable to comply with the requirements of the trial. Reasons for trial withdrawal could include:

- You have experienced a serious side effect
- You are unable to complete the visits, medication or trial documentation as required
- The trial doctor feels you no longer appear to benefit from the treatment.

15. What if there is a problem?

Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Addenbrooke's Hospital, Cambridge or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). The University has insurance which provides no-fault compensation (i.e. for non-negligent harm) and you may be entitled to make a claim for this in certain circumstances where you have experienced harm.

The NHS does not provide no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. They are able to consider an ex-gratia payment in the case of a claim.

If you have a concern about any aspect of this study, you should ask to speak to the researcher *[Sites to enter name]* who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can contact your local Patient Advice and Liaison Services (PALS) group or local equivalent group.

16. Will my taking part in this trial be kept confidential?

All information collected about you as a result of your participation in the trial will be kept strictly confidential. Your personal and medical information will be kept in a secure file and be treated in the strictest confidence. You may ask to see your personal information at any time and correct any errors if necessary.

Patient data confidentiality will be strictly maintained in accordance with each hospital trust's data management policy.

The result of the biomarker blood test will not be known to you or to your doctor and will only be incorporated in our analysis at the end of the trial, to prevent affecting the results of the study.

If you agree to participate in this trial you will be allocated a unique trial number which will be used on all your trial documentation along with your initials and date of birth. Your date of birth and initials are considered to be personal information. We collect this personal information on trial documentation to help ensure that the data we receive as part of your trial participation is correctly allocated to you. By cross checking these three unique references we can ensure the integrity of the data. This number will be linked to your personal information; however you will only be identified by this unique number. Your consent to the use of study data or your personal data does not have a specific expiry date, but you may withdraw your consent at any time by notifying your study doctor.

Cambridge University Hospitals NHS Foundation Trust (CUH) and The University of Cambridge are the Sponsor(s) for this clinical trial based in the United Kingdom. They will be using information from you and your medical records in order to undertake this trial and will act as the data controller for this trial. This means that they are responsible for looking after your information and using it properly. The Sponsor organisation(s) will keep identifiable information about you for 5 years after the trial has finished to ensure your safety and allow the trial to be reviewed by the authorities after it has finished.

Your rights to access, change or move your information within the trial are limited, as the Sponsor organisation(s) need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how the Sponsor (s) use(s) your information using the information below:

- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information, or email the Data Protection Officer at: gdpr.enquiries@addenbrookes.nhs.uk

- For University of Cambridge, please visit:
https://www.medschl.cam.ac.uk/research/information-governance/, or email
the Information Governance team at: researchgovernance@medschl.cam.ac.uk

(Add site name) will keep your name, NHS number, date of birth and contact details to contact you about this trial, and make sure that relevant information about the trial is recorded for your care, and to oversee the quality of the trial. Certain individuals from the Sponsor(s) and regulatory organisations may look at your medical and research records to check the accuracy of this trial data.

(Add site name) will keep identifiable information about you from this study for <##> years after the study has finished. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. Only anonymous trial data, without any personal information will be published at the end of the trial.

If you agree to take part in this trial, anonymised information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. This information will not identify you and will not be combined with other information in a way that could identify you. The information

will only be used for health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

By signing the informed consent form, you consent to the study doctor and their staff collecting and using medical and personal data about you for the purposes of the study (study data). Authorised study staff may require access to your records to verify the data for this study and ensure that it is being conducted in accordance with UK law. All information will be treated in the strictest confidence.

Any personal identifiers attached to your MRI scans to allow their transfer within the secure NHS PACS network will be removed prior to central reading / analysis. Images will be stored in an anonymised format.

During and following the end of the study, collection of additional health data will be performed. It will enable the study to look at both health economic performance of the biomarker and the long term changes in your health. This information will be collected during and for up to 5 years after completion of the study. You will not be contacted for the collection of this information and all it will be treated in the strictest confidence. Any results of the research will always be published anonymously.

We will need to inform your GP of your participation in this trial so that any medical decisions made by your GP account for any treatment you are receiving as part of this trial.

17. What will happen to my samples?

Your blood and stool samples will be sent to a central storage facility. All samples will be stored securely prior to being sent for biomarker analysis by an accredited central laboratory. The samples will not have any of your personal identifiable information on them, but can be linked back to clinical outcome data via your unique study number.

Stool samples you provided will be used to identify what microorganisms ('bugs' that live in the gut of everyone) are present and what chemicals they are making. Materials derived from these bugs will be stored for future exploratory scientific research; the remaining stool sample will be disposed of.

Genetic material such as DNA and RNA, as well as proteins, metabolites and other chemicals will be extracted from the blood samples you provide. These samples will be stored for future analysis and research. The analysis may include determining the sequence of part or all of your DNA code to understand how this influences the development of your Crohn's disease. The results will only be used for research: the PROFILE study will not feedback any genetic results obtained from samples taken for research purposes.

An important part of this trial is to make sure that discoveries get turned into tests for people with Crohn's disease as quickly as possible. This new test will be developed by a commercial company in collaboration with the NHS. Your blood and stool samples, data derived from the samples and the results from your participation in this clinical trial may be used for commercial as well as academic purposes, and will initially explore whether a newly developed test known to predict the course of Crohn's disease can be used to guide treatment. You will not benefit financially from involvement in this trial.

18. What will happen to the results of the trial?

Results may be published in peer reviewed medical journals and used for medical presentations and conferences. They will also be published on the EU Clinical Trials Register website, a central registry for all clinical trials conducted in the EU. You will not be able to be identified from any of the material produced.

Anonymous datasets from the trial may also be made available to other researchers in line with national and international data transparency initiatives.

If you would like to obtain a copy of the published results please contact your trial doctor who will be able to arrange this for you. Results of your biomarker status will be made available on request following final publication of the trial results.

19. Who is organising (sponsoring) and funding the trial?

This trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

The trial is being funded by Predictimmune, a company whose purpose is to develop and bring a test to the market using a Wellcome Trust Translational Award. The Wellcome Trust is a UK based biomedical research charity.

20. Who has reviewed this trial?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given favourable opinion by Cambridge South Research Ethics Committee.

21. Further information and contact details

For further information about the study, please contact: *[Sites to enter name, address, email address, telephone numbers including the 24 hour emergency contact number, can be 999].*

To contact your local Patient Advice and Liaison Services (PALS) group or local equivalent group: *[Sites to enter name, address, email address, telephone numbers].*

In the event of an emergency please contact:

[Sites to enter 24 hour emergency contact detail here – this must match the information provided on the patient ID card and will be used to test the out of hours procedure for the trial.]

TO BE PRINTED ON HEADED PAPER

INFORMED CONSENT FORM

Trial Title: PROFILE

Principal Investigator: **Participant Number:** _____

If you agree with each sentence below, please initial the box **INITIALS**

1	I have read and understood the Participant Information Sheet version 4.0, dated 29.11.2018 for the PROFILE trial. I have had the opportunity to ask questions and am satisfied with the answers and explanations provided.	
2	I understand that my participation in this trial is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3	I understand that I am providing my information to [Trial Site] for the purposes of this clinical trial, and that [Trial Site] will only share my information with the other organisations involved in the trial who also need access to that information. I understand that my personal data will be retained by [Trial Site] and the other organisations working with [Trial Site] for as long as required to complete the trial and any subsequent scientific analysis.	
4	I understand that I have various rights under data protection laws, including the right to withdraw my consent to share my personal data at any time. Patient data confidentiality will be maintained in accordance with the hospital trust's data management policy.	
5	I understand that my GP will be informed of my participation in this trial.	
6	I have read and understood the compensation arrangements for this trial and understand that I will not benefit financially if this research leads to the development of a new test.	
7	I understand that the doctors in charge of this trial may close the trial, or stop my participation in it at any time without my consent.	
8	I have read and understood my responsibilities for the trial including using appropriate contraception as listed in section 6.	
9	I agree to the storage and (anonymised) analysis of my radiology scans and endoscopy photographs and videos, including those taken prior to study enrolment, as part of the PROFILE trial. I understand that if I withdraw or am withdrawn from the study, the images and videos that have already been provided will be retained for analysis.	

10	I agree to give blood and stool samples. I understand that giving these samples is voluntary and that they will be anonymised and sent to a central laboratory for storage and future scientific analysis.	
11	I understand that samples I donate will be used for the genetic analysis of DNA and RNA and that these research results will not be fed back to me.	
12	I agree to the academic and commercial use of the blood and stool samples, data derived therefrom, and the results of the trial overall.	
13	I understand that if I withdraw or am withdrawn from the study, the samples that I have already provided will be retained for analysis.	
14	I understand that my clinical team may be contacted in the future by the trial team for information regarding my health status.	

I agree to participate in this trial:

_____	_____	_____
Name of participant (capitals)	Signature	Date

_____	_____	_____
Name of person taking consent (capitals)	Signature	Date

1 copy for the patient, 1 copy for the study site file, 1 copy for the CCTU, 1 copy to be retained in the hospital notes.