TO BE PRINTED ON HEADED PAPER

PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

Randomised Double Blind Clinical Trial in Acute Severe Colitis: The IASO Trial

You are being invited to take part in a clinical trial. 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 and talk to others about the trial if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this trial and what will happen to you if you take part. Section 2 gives you more detailed information about the conduct of the trial.

Section 1: Purpose of the trial and what will happen

1. What is the purpose of the trial?

Ulcerative colitis is a condition in which the large intestine, also known as the colon, becomes inflamed. In most patients, ulcerative colitis involves some periods without many symptoms but also periods where the symptoms become more severe (called flares).

Sometimes, the intensity of your symptoms means that you need to be admitted to hospital. If this happens, you will be given drugs called corticosteroids (commonly known as steroids) to reduce the inflammation. If these make you better you can then leave hospital, usually after a few days.

If the corticosteroids aren't making the condition better, other medicines can be given to try to help. This would normally be either a drug called infliximab or ciclosporin. Either drug can be used and both are equally effective.

If these treatments still don't work, then the next course of treatment would be surgery to remove the colon. This is called a colectomy.

Currently, we know that around half of patients given the corticosteroids will get better, whilst the other half will go on to need one of the other medications, and some patients will still need to go on to surgery.

This trial will test whether giving patients another medicine, called anakinra, in addition to the initial treatment with corticosteroids will reduce the number of patients who go on to receive additional medical treatments or surgery.

2 What is the drug being tested?

Anakinra is a drug that is used to treat inflammation in patients with rheumatoid arthritis. Anakinra has not been tested in ulcerative colitis yet and does not have a license for use in this disease.

Anakinra works by reducing the effects of an inflammatory messenger called interleukin-1 in the body. Patients with severe ulcerative colitis have large amounts of interleukin-1 in their colon. Therefore, the team conducting this trial think that the way anakinra reduces interleukin-1 could also make it effective at treating inflammation in patients with severe ulcerative colitis.

3 Why have I been invited?

You have been invited to participate in this trial because you have been admitted to hospital with symptoms that the doctors treating you think are due to a severe flare of ulcerative colitis.

We plan to include 214 participants with severe ulcerative colitis flares from 20 hospitals across the UK.

4 Do I have to take part?

Participating in this trial is completely voluntary. You will have the opportunity to speak to the trial team and ask any questions you have about the trial. If you decide to participate you will be asked to sign the Informed Consent Form at the end of this document and be given a copy to keep. However you are still free to change your mind and leave the trial at any time without giving a reason. If you chose not to participate or to leave the trial, your future medical treatment and care will not be affected in any way.

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

Once you have signed your informed consent form you will be asked some basic medical information about yourself (such as what medicines you are currently taking), to confirm that you are definitely suitable for the trial. For women who are able to become pregnant this would also include performing a urine pregnancy test, since we will not be including pregnant women in this trial.

Following this, if you are suitable for the trial, you will be asked some more medical questions and to complete 2 short questionnaires about your current symptoms (called EQ-5D and CUCQ-32). You will then have a blood sample taken (about 3 teaspoons or ~15 mL). You will also be provided with a collection kit and be asked to collect a stool sample next time you open your bowels.

At this point, you will be randomly allocated, by computer, to one of two, equal sized groups (randomised). Both groups will receive the standard treatment with corticosteroid injections. In addition to this standard treatment, one group will receive the trial drug (anakinra), and the other group will receive a dummy drug (called placebo). Placebo looks exactly the same as the anakinra, but it contains no active ingredients.

The reason we have to do this is because we don't know whether anakinra will help patients or not, so we need a group of patients who are not receiving the drug to compare all the results to. Neither you, nor the trial team or your doctors will know which treatment you are receiving. This is called a double-blind trial. However in an emergency, your doctors can find out which treatment you are receiving.

The first dose of trial drug will usually be given on the same day as all the steps above, or sometimes as soon as possible the next day, if it is already late in the day. The first dose is given as an injection into your vein (also called an IV injection). Almost immediately after this, you will receive your second dose as an injection given using a very fine needle just under the skin (also called an SC injection).

You will continue to receive the injections into the skin twice a day (morning and afternoon) approximately 12 hours apart. Each day whilst you are in hospital, your medical condition will be reviewed with you and recorded in your medical notes. In addition to the normal blood tests that you will be having as part of your standard care, you will also have an additional research blood sample taken (about 2 teaspoons, ~10 mL) at least once every 72 hours and to a maximum of once a day. Wherever possible we will try to take this sample at the same time as your normal blood samples.

On Day 5, you will be provided with another sample collection kit and asked for a second stool specimen.

You will continue to receive the injections for up to 11 total doses (1 IV and 10 SC) over 5 days. If you become much better, or you wish to stop receiving the injections, or if your doctors feel that you should no longer receive the trial drug, then we will stop the

trial treatment, but still visit you to monitor and record your condition until Day 5, or the point you leave hospital (whichever comes first).

If you want to stop all participation in the trial at any stage, you will be free to do so and your future medical treatment and normal standard of care will not be affected in any way.

In the event that you undergo a camera examination of the bowel (endoscopy) as part of your standard treatment, then we will ask the clinical team to record some additional photographs of the inside of your bowel for research purposes. No extra endoscopy examinations are part of the main trial, so this would only happen if your clinical team wanted to perform an endoscopy as part of your normal standard care treatment.

Trial Follow-Up

It is important to keep record of what happens to you after you leave the hospital. Sometimes we will be able to find out enough information from reviewing your medical notes, but in most cases, you will be contacted by a member of the trial team at the following times:

- 10 days after you received your first injection with the trial drug
  - To confirm whether you needed any additional treatment and to see if you had any side effects up to this point

- 3 months after you were randomised
  - To see if you needed any surgery up to this point
  - To ask you to complete the 2 short symptom questionnaires (by post, with telephone reminder if needed)

- 6 months after you were randomised
  - To ask you to complete the 2 short symptom questionnaires again (by post, with telephone reminder if needed)

The questionnaires will be sent to you by post from the central trial coordination centre. When you receive the questionnaires, you will also receive a pre-paid return envelope to send the completed questionnaires back to the central trial coordination centre in Cambridge.

Depending on the results of the trial, we may want to understand the long-term impact on the health of trial participants. In this instance, we would track your hospital admissions and health data (e.g. if you needed a colectomy at a later time) for up to 5 years after time of randomisation. This can be done using existing national NHS data resources (NHS Digital) and without further contact with you, but we require your permission to access your records in this way.

NHS Digital is the national provider of information on healthcare in the United Kingdom. NHS Digital collects, stores and analyses information from a variety of sources. If you participate in the trial, we will send identifiable data (NHS number, Date of Birth and your initials) to NHS Digital. NHS Digital link this information to HES (Hospital Episode Statistics) data. This data includes when, why and for how long each patient is hospitalised. In England, this is known as **Hospital Episode Statistics (HES)**. By collecting information from HES, we can tell what happens to the health of participants in the trial. For example, if someone has a colectomy, this should result in admission to hospital and would show up in the information we collect. By doing things in this way, it means that we can use the information the NHS already holds rather than asking patients to complete ongoing questionnaires for a number of years.

Equivalent systems to HES exist in Wales (**Patient Episode Database for Wales, PEDW**), Scotland (**Information Services Division Scotland**, **ISD**) and Northern

Ireland (**Health and Social care services Northern Ireland, HSNI**). If you live in these areas, the trial team will similarly obtain information on hospital admissions from these sources.

6. What will I have to do?

You should tell the trial team if you feel unwell or different in any way. If you have any major concerns or are feeling very unwell please tell the ward staff and they will contact the trial team immediately. If you have left hospital and have any concerns or are feeling very unwell, then you can contact the trial team using the contact numbers at the end of this information sheet.

There are no additional hospital or GP visits required as part of this trial.

Participation in this study should not affect any existing life insurance, critical illness or income protection insurance which you have but you should discuss your participation in this trial with any travel insurance provider as failure to notify them could affect or invalidate your cover. Private medical insurance does not usually cover the cost or consequences of taking part in any clinical research so you may also wish to discuss your participation in this study with any private medical insurance provider you have.

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

Very Common (more than 10% of patients)

- Local skin irritation at the site of injections
- Headache
- Increase in blood cholesterol

Common (less than 10% of patients)

- Low blood cell counts (may affect white blood cells or cells called platelets)
- Serious infections, most commonly bacterial infections (such as lower respiratory tract or urinary tract infections).

Uncommon (less than 1% of patients)

- Rash
- Allergic reactions including itch, skin swelling/redness, and anaphylaxis (severe allergic reaction to drug).

8. What are the possible disadvantages and risks of taking part?

You may develop bruising or localised skin irritation at the site of the skin injections. This can occur with either the drug or the placebo, but does not require any special treatment. You will also be required to give some additional blood (up to 15 mL, about 3 teaspoons each day) for research purposes. Donating this additional blood should not cause you any problems and wherever possible we will try to coordinate the research blood collection with your standard routine care blood tests. However, there may be some occasions when this is not possible and you have two blood samples taken on the same day.

Other than the potential side effects of anakinra listed in section 7, there are no additional risks of disadvantages from taking part in the trial. It is important to know that no treatment is being withheld as part of this trial – all participants will receive the usual standard medications for the full duration of the trial, with half of the group also receiving anakinra on top of this standard care.

9. What are the possible benefits of taking part?

There is no guarantee that you will benefit from taking part in this trial. You may experience relief in your symptoms or an improvement in your disease. However, information collected as part of your participation in this trial may benefit patients with severe ulcerative colitis flares in the future.

10. What are the alternatives for treatment?

If you do not wish to participate in the trial you will continue to receive the standard care treatment for your ulcerative colitis flare from your doctor as normal.

11. What happens when the trial stops?

Once you have completed your participation in the trial, you will return to your normal treatment for the management of your ulcerative colitis. Should you have a further flare you will receive the standard care treatment offered by your hospital.

12. Expenses & Payment?

You will not receive any payment for participating in this trial and we do not expect that you will incur any expenses by taking part in this trial.

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 in this trial. If this happens, your trial doctor will contact you to discuss the new information and whether you wish to continue participating in the trial. If you still wish to continue on the trial, you may be asked to sign a new Informed 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 off this trial at any time without giving a reason and without affecting your future care or medical treatment. You can decide whether you wish to stop receiving the trial treatment and continue with the rest of the assessments and follow-up or whether you wish to come off the trial entirely, in which case no further tests will be performed on you and no further research samples or information will be collected. However, any data already collected or results from tests already performed on you or your samples will continue to be used in the trial analysis.

Your 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 assessments, 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. If you have any concerns about any aspect of this trial you should speak to your trial doctor who will do their best to answer your questions.

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 Cambridge University Hospitals NHS Foundation

Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for harm that occurs but no one has acted negligently, you may be entitled to make a claim for this.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this trial, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the *(to be completed locally as appropriate – in England this will refer to the Patient Advice and Liaison Service (PALS))* at your hospital.

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 secured 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.

Once you have agreed to participate in this trial you will be allocated a unique trial number which will be used on your trial documentation and samples along with your date of birth and initials. This number along with your date of birth and initials will be linked to your personal information and in most cases you will only be identified to the wider trial team by this unique number to ensure you remain anonymous to them.

Your anonymised data will then be analysed by members of the trial team to determine if the trial drug had any impact on the patients in the trial. Anonymised data will also be shared with other scientific collaborators within the UK. Any serious side effects that occur during the trial will also be reported to anakinra's manufacturer using anonymised data. We will not share any of your personal data with any research collaborators.

However, in order to send you the 3- and 6-month questionnaires and to monitor your long-term health via the NHS national registries (NHS Digital – Hospital Episode Statistics), the central trial team based in Cambridge, will keep your name, address and NHS number in a secure database with restricted access. This will be separate to the database which holds your trial data to ensure it remains anonymous. Your personal data will be shared with the national registries to enable linkage of your data. Only a very small number of people will have strictly controlled access to your personal data and your personal data will not be shared with any other researchers or collaborators and you will not be identified in any publications or reports.

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 have received as part of this trial.

Authorised staff, who work for or with the sponsor of the trial, the hospital R&D Department or the Regulatory Agency responsible for drug research may require access to your personal information and/or medical records to verify the data for this trial and ensure that it is being conducted in accordance with UK law. All information will be treated in the strictest confidence during the review process. The central trial team will, in accordance with UK law, retain your personal information, including initials date of birth and unique trial number for at least 5 years after the end of the trial to ensure your safety and allow the trial to be reviewed by the authorities after it is finished.

17. What will happen to my samples?

Your blood and stool samples will be sent for analysis by scientists based at the University of Cambridge, as well as collaborators based in other institutions, including the Wellcome Trust Sanger Institute (Hinxton), the University of Newcastle, the

University of Manchester and the University of Swansea. It is possible that other UK collaborators may be given access to these trial materials as part of the analysis work. The main aim of this analysis will be to try to identify markers that can help us understand how the treatment has affected your body and to help us understand who may benefit the most from the treatment. Anonymous data and materials derived from your samples may be stored indefinitely. However, these data and materials will be stored in such a way to have no connection to your name or other personal identifiers.

Any unused samples at the end of the planned trial analysis will be stored in an approved facility to allow for use in future approved research, which may also include further genetic testing. This may include future research undertaken in partnership with academic or commercial collaborators within the UK. Where relevant, these samples will be stored after the trial in accordance with the Human Tissue Act 2004.

Genetic Testing
Genetic material such as DNA and RNA will be extracted for research purposes from the samples you provide and will be analysed within this trial. We will not be identifying any genes with sufficient accuracy to be of individual clinical relevance to you and therefore results of the analysis will not be shared with you or your doctor.

Anonymous genetic information produced by studying your DNA may be placed in an electronic data archive. This information may be kept there indefinitely but it will have no connection to your name or other personal identifiers. In addition, this archive will only be accessible to *bona fide* researchers worldwide who will use the anonymous results to advance scientific and medical understanding.

18. What will happen to the results of the trial?
The results of the trial will be anonymous and you will not be able to be identified from any of these results. When the results of this trial are available they 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.

Anonymous datasets from the trial may also be made available to other researchers in line with national and international data transparency initiatives. The drug manufacturer will be given a report of the trial which will contain anonymous data.

All trial publications will be made available at the trial's website (https://www.journalslibrary.nihr.ac.uk/programmes/eme/1420102/#/) along with a lay summary of the findings.

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 the Efficacy and Mechanism Evaluation program, which is a partnership between the National Institute for Health Research and the Medical Research Council. The Wellcome Trust Sanger Institute will also be providing financial support.

The pharmaceutical company Swedish Orphan Biovitrum (Sobi) will be providing the anakinra and placebo for the trial.

20. Who has reviewed this trial?
All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, in order to protect your interests. This trial has been reviewed and given favourable opinion by (name of REC here). The Medicines and

Healthcare Products Regulatory Agency (MHRA) who are responsible for regulating medicines in the UK have also reviewed this trial.

21. Further information and contact details

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

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 will be used to test the out of hours procedure for the trial.]

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INFORMED CONSENT FORM

Trial Title: IASO

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 1.1, dated 22 September 2017 for the above trial and I confirm that the trial procedures and information have been explained to me. I have had the opportunity to ask questions and I 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 sections of my medical notes or information related directly to my participation in this trial may be looked at by responsible individuals from the sponsor, regulatory authorities and research personnel where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4	I understand that my GP will be informed of my participation in this trial and sent details of the IASO trial.	
5	I understand that the trial team will send my name, NHS number, date of birth and gender to NHS Digital for linkage with HES data. I understand that, if I live in Scotland, Wales or Northern Ireland, this information will be obtained from the equivalent sources described in section 5	
6	I understand that members of the central trial team will have access to my personal information as detailed in section 16 in order to send me the trial questionnaires by post.	
7	I have read and understood the compensation arrangements for this trial as specified in the Participant Information Sheet.	
8	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.	
9	I agree to give blood and stool samples for research in this project. I understand how these samples will be collected and that giving these samples is voluntary. I understand that my anonymised blood and stool samples will be sent to central trial laboratories for storage and analysis. I understand that materials and data obtained from these anonymised samples may be stored indefinitely with no connection to my name or other personal identifiers.	
10	I understand that samples I donate will undergo analysis that will include genetic analysis, the results of which will not be shared with me or my doctors.	
11	I understand that my samples may be used for future research within the UK and that this future research may include further genetic analysis and that that the anonymised genetic information produced by studying my DNA may be placed in an electronic data archive indefinitely with no connection to my name or other personal identifier.	

I agree to participate in this trial:

_____	_____	_____
Name of patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date

Time of Consent (24hr clock) _____:_____

1 copy for the patient, 1 copy for the trial team, 1 copy to be retained in the hospital notes.