PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

A phase 1 clinical trial evaluating the safety and efficacy of up to two administrations of the adrenal PET tracer [^{18}F]CETO in healthy volunteers and patients with primary aldosteronism

Information Sheet for Healthy Volunteers

You are being invited to take part in a research 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?

Primary aldosteronism (PA, often referred to as Conn syndrome) is a condition caused by over production of a hormone called aldosterone. Aldosterone is released from the adrenal glands, which sit on top of the kidneys.

After confirming a diagnosis of PA, it is important to identify whether only one or both adrenal glands are responsible for the high aldosterone levels. Deciding whether one or both adrenal glands are responsible is currently dependent on a procedure called adrenal vein sampling (AVS). However, AVS is an invasive procedure, which requires small catheters to be inserted through the groin and success rates vary significantly between centres but may be as low as 50%.

To address this, we have previously developed an alternative technique, which uses a radioactive tracer [^{11}C] Metomidate ([^{11}C]MTO, which we will refer to as MTO) to visualise the adrenal glands using a technique called Positron Emission Tomography – Computed Tomography (PET-CT). A radiotracer is a compound that, when administered by injection, travels throughout the body, before accumulating in a tissue/organ of interest which can then be visualised as a bright spot using a specialised type of scan (PET-CT). However, the existing tracer is only active for a very short amount of time once it is produced. This means the scan can only be performed in centres with special facilities to produce it (only one centre in the UK is currently making MTO). To see if we can address this, we have created a new tracer called [^{18}F]CETO (which we will simply refer to as CETO). This radiotracer is more stable than MTO and can therefore can be distributed to centres without special facilities, making it more widely available for PA patients. This clinical trial will investigate whether CETO can be used safely to investigate PA.

2 What is being tested?

We will use a newly developed short-lived radioactive tracer (CETO) that, following injection into a vein, is rapidly concentrated in the adrenal glands. This produces a ‘bright’ signal when visualised using a PET-CT scan.

CETO is later removed from the body's circulation through the kidneys' normal filtering system and it is estimated that there will be no tracer left in the body 2 hours after the injection.

3 Why have I been invited?

You have been invited to participate in this trial because you have expressed an interest in being a healthy volunteer for this clinical trial.

As this is the first time CETO will be studied in humans, it is important for us to investigate that it can be administered safely without any side effects.

The trial will also seek to understand the pattern of tracer uptake in healthy individuals, as it is helpful to know what things look like in people with normal adrenal glands.

As this is an early phase clinical trial, there are strict rules about who can participate as a healthy volunteer in the UK. Therefore please be aware that you will <u>not</u> be able to participate in this trial if any of the following apply to you:

- You are under the age of 50.
- You are taking medication at the time of the PET-CT scan
- You are a woman who has not yet undergone menopause.
- You are routinely exposed to radiation during your work.
- You have received more than 10 mSv of radioactivity in the past 12 months (e.g. from routine procedures and/or scans).
- You take recreational drugs, or have an alcohol or drug dependency.
- You have a known history of allergy to contrast agents, which may have been given during previous scans, or a medication known as synacthen.
- You have previously been involved in a medical trial which has involved the use of a new medication or tracer.
- If you are claustrophobic or are unable to lie still for approximately 2 hours

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 an Informed Consent Form; however, you are still free to change your mind and leave the trial at any time without giving a reason. If you choose 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?

If you agree to participate in the trial, you will sign the Informed Consent Form at the end of this document and be given a copy of this to take away and refer to later. You will be compensated for your time (as detailed in Section 12).

Details of what will happen at each of the individual visits are set out below:

<u>Screening Assessment (Visit 1)</u>
On arrival at the Endocrine Investigation unit (EIU), a member of the research team will confirm your identity (via passport or photographic driving licence) and discuss the trial with you in detail. They will then confirm that you are willing to participate in the trial and you will both sign the Informed Consent Form. They will ask you some questions about:

- Your general health
- Any medical conditions/allergies you have
- Any medications/drugs you are taking.

They will then perform a physical examination and take a urine sample to confirm there aren't any recreational drugs in your system. Anything that is discovered following this test will not be shared with anyone outside of the trial (e.g. your GP) but you will not be eligible to participate further if the test indicates you have any recreational drugs in your system.

The trial is not suitable for female healthy volunteers who are capable of having a child. If you are a woman, we will therefore ask for some information regarding menopause and as a precaution, you will have a blood test (5 mLs, equivalent to approximately one teaspoon) performed to ensure you are not pregnant before we proceed with any of the following investigations. In the instance of a positive pregnancy test, you will be withdrawn from the trial.

A member of the research team will perform the following:

- An ECG (a tracing of your heart to check the heart's electrical activity)
- Collect a further blood sample. The blood sample amount is 15-20 mLs, which is equivalent to approximately one tablespoon. The blood samples are required to check that there are no abnormalities with how your various body systems are working, and will include assessment of infection markers, kidney and liver function.
- A special investigation called a synacthen test. This is used to assess the function of your adrenal glands, and involves injecting a medication (called synacthen), which stimulates the adrenal glands to produce cortisol. A further blood sample (5 mLs = 1 teaspoon) will be collected 30 minutes after the injection to check the rise in your cortisol levels. In the unlikely event that the test comes back abnormal, we would not proceed with the trial and would instead refer you for further clinical tests.

The visit duration will be a maximum of 2 hours.

Following this visit, the research team will contact your GP to confirm your medical history and medication use. We will also review The Over-Volunteering Prevention System (TOPS) database to check if you have recently volunteered for another trial. If there isn't an entry for you already, we will register you on the system. More details about TOPS are provided in Section 16 of this document. Following these reviews, the research team will contact you to confirm your eligibility to continue in the study, and will arrange a suitable date for your next visit (called baseline). In the unlikely event that an abnormal test result is detected, we will refer you for further clinical assessment, and you will be withdrawn from the trial.

<u>Baseline Visit & PET-CT Scan (Visit 2 – within 28 days of Visit 1)</u>

You will be asked to come fasting (no food for 4 hours before the appointment, water is permitted) to the EIU at Addenbrooke's Hospital, where you will meet a member of the research team. At the visit we will reconfirm your identity (via passport or photographic driving licence).

An ECG will be performed and a blood sample will be taken – the amount is 15-20 mLs, which is equivalent to one tablespoon. You will then be taken to the PET-CT unit where the CETO injection and the PET-CT scan will be performed. On arrival at the PET-CT unit you will be asked to change into a patient gown and to remove all of your jewellery and metallic objects. The trial staff performing the procedure will fully explain the procedure to you when you arrive for your appointment. You will be asked to empty your bladder prior to the scan.

Before the start of the PET-CT scan you will have a "cannula" inserted. A cannula is a very small flexible plastic tube (about the thickness of a piece of string), which is inserted into a blood vessel under the skin to make it easier to inject the CETO tracer

(approximately 30 seconds). The scan will then take place over approximately 90 minutes and will require you to lie flat and still for its duration.

Once the PET-CT scan has been completed, an ECG and vital signs (pulse and blood pressure) will be recorded and repeated approximately every 30 minutes. You will be able to eat and drink as normal, with no restrictions. You will remain in the PET-CT unit for 4 hours, where you will be monitored by a member of the research team. You will then be taken to our Clinical Research Facility (CLRF) where you will have one more vital sign check upon arrival. After this you will stay overnight with further vital sign checks only performed if clinically necessary. During your time on the CLRF, you will stay in a small ward/room and will be able to eat and drink freely (you are also welcome to bring your own food and drink to the unit). You will be allowed to have visitors. However, you will not be able to leave the CLRF between arrival at the unit following the scan, up until the point of discharge the following day. You will have access to WIFI/media during your CLRF stay. The CLRF is fully equipped to deal with any issues that may arise and has direct access to the Addenbrooke's emergency department in the case of an emergency.

Blood sampling including a repeat synacthen test will be performed on the morning after the scan in order to check for any effect on your adrenal glands. The total amount of blood taken will be 10 mLs, which is equivalent to half a tablespoon. The results from these samples will be reviewed before you go home from the CLRF. The time from CETO injection to leaving the CLRF will be approximately 24 hours.

<u>Follow-up visit (Visit 3 – within 7 days after Visit 2) – Only if required</u>

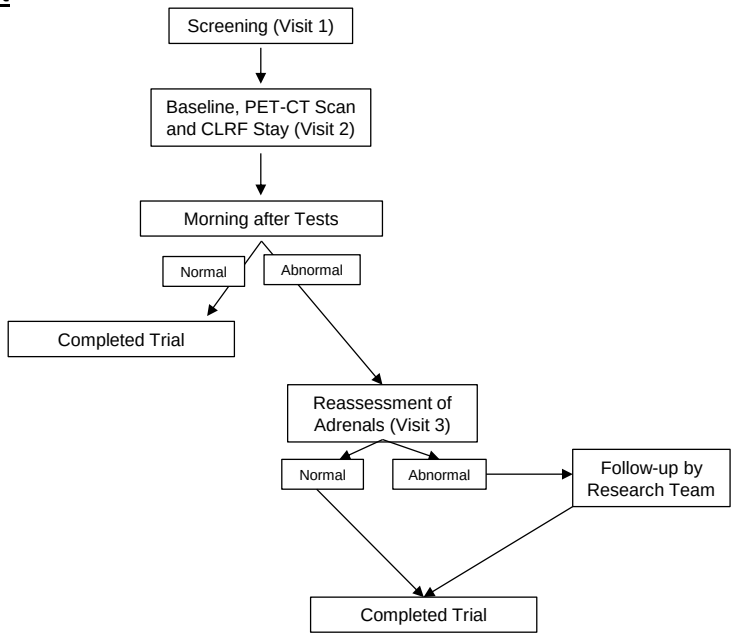
As there is a small possibility of a temporary lowering of blood cortisol levels after the scan, we will check your cortisol levels by performing a short synacthen test as described above on the morning after your scan. If any abnormalities are identified, we will bring you back for a review at Addenbrooke's Hospital approximately 7 days after the scan. During this interval, you may be required to take a small dose of hydrocortisone each day, administered as a tablet taken two or three times daily to ensure that the adrenal function remains at normal levels. During the visit, you will be reviewed by a clinical member of the research team and have further blood samples taken for repeat testing as needed. In the highly unlikely event that you still have any abnormalities on the blood tests at this point, we will withdraw you from the trial but continue to track your condition on an ongoing basis until we are satisfied that it has resolved. We will inform your GP about this to ensure your medical records are up to date, and the research team will periodically access your medical records, and/or contact you, to check on your clinical progress.

Visits Summary

A summary of the visits is shown below in the table and flow chart:

Assessment / intervention	Screening (Visit 1)	Baseline, CETO PET-CT Scan and CLRF Stay (Visit 2)	Follow-up Visit (Visit 3)-if necessary
Informed consent	X		
Clinical assessments including physical examination	X	X	X
Vital signs	X	X	X
Blood samples and Tests	X	X	X
Urine sample	X		
ECG	X	X	
Collection of basic information (e.g. age, gender, medical history)	X	X	
Confirmation of identity	X	X	
CETO administration		X	
Overnight observation		X	

Trial Flow Chart



6. What will I have to do?

As described above, you will be required to attend two or three visits as part of the trial. Photo identification (e.g. passport or photographic driving licence) will be required for each visit.

You will be required to fast for 4 hours before your baseline visit (Visit 2), although water will be permitted during the fasting period. You will not require any additional medications before the PET-CT scan. For your baseline visit (Visit 2), in preparation for your CLRF overnight stay, we would advise that you bring a suitable set of clothes for sleeping in overnight. You will be provided with food and drink whilst on the CLRF, but please let us know in advance if you have any specific dietary requirements.

Trial medicines (in this case the radioactive tracer CETO) could harm an unborn baby or nursing infant. You will not be able to take part in this trial if you are pregnant or breastfeeding. You should not participate in this trial if you are planning to father a child during the trial.

Because of the risk mentioned above, you will be required to use effective contraception for the duration of the trial and for 7 days after completion of the last scan. Men must use a condom and spermicide (chemical that kills sperm) for any sexual activity occurring during the trial period.

If you are male and your partner becomes pregnant in the interval between the CETO injection and 7 days later, you should also notify the trial team. You should check with the trial team before taking any newly prescribed medicines while participating in the trial.

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 contact your trial doctor immediately 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 (e.g. travel insurance, protection insurance, life insurance, income protection, critical illness cover and private medical insurance) and seek advice if necessary, as failure to notify them may affect or invalidate your cover.

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

We do not anticipate any side effects in this study. Because CETO works by binding to key proteins in the adrenal glands which are responsible for the production of hormones such as cortisol, we have included an assessment of this in the trial – all participants will be admitted to the CLRF until approximately 24 hours after CETO injection and will have a repeat synacthen test on the morning after the PET-CT scan (please see question 5 above). This will be important for providing reassurance that the use of CETO in routine clinical practice will be safe.

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

Involvement in this trial will require two visits to hospital, including a one-night stay. At each visit blood samples will be taken. Some patients may find this uncomfortable and bruising may occur at the site of the blood sample. Before the PET-CT scan a cannula will be placed in a vein, and this will be used for injecting the tracer into the blood. There may be local bruising following insertion of the cannula.

Immediately following injection of synacthen (performed at Visits 1 and 2), some patients may report a warm sensation with flushing, and occasional nausea and light-headedness, which resolves within 1-2 minutes without the need for any treatment.

During the scan, you will be required to lie in the scanner for approximately 90 minutes and you may feel ‘closed in’ while lying in the scanner. However, every effort will be made to ensure you remain comfortable during this time. A member of the research team will be present during this time should you need to speak to them.

If you take part in this trial, you will have a single PET-CT scan. This will therefore be an extra scan compared to if you did not take part in the trial. PET-CT scans use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in

their life. Taking part in this trial will increase the chances of this happening to you by 0.02%.

In the highly unlikely event that any medical findings are discovered during the trial, we will want to discuss this with you and with your permission inform your GP, as you might need further tests or monitoring according to what has been discovered.

9. What are the possible benefits of taking part?

There is no anticipated benefit for healthy volunteers participating in this trial. However, information collected as part of your participation in this trial may benefit patients with PA in the future.

10. What happens when the trial stops?

Once you have completed your stay at the CLRF, we anticipate you will not require any further follow up.

However, in the event that there are any concerns about your blood cortisol levels on the morning after the CETO injection and PET-CT scan, we will arrange to see you again one week later to ensure everything has returned to normal. In the highly unlikely event that you still have any abnormalities after this point, we will continue to track your condition on an ongoing basis until we are satisfied this has resolved. We will also inform your GP about this to ensure your medical records are up to date.

At the completion of the trial, if you would like to hear more about our findings, then we will send you a brief summary.

12. Expenses & Payment?

You will be paid £250 once both visits have been successfully completed in recognition of the time and effort associated with participation. In the event that you are not eligible to continue in the study following the screening visit you will be paid £50 in recognition of your time and effort. Separate reimbursement to cover reasonable parking and transportation costs will be provided.

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. 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 will 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. Any data already collected or results from tests already performed on you or your samples will continue to be used in the trial analysis.

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 non-negligent harm, 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 Patient Advice and Liaison Service (PALS; contact details are included with question 21).

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

You must not take part in too many studies because it's not good for you. So to help research units, the Health Research Authority keep a database of healthy volunteers and when they take part in studies, this is called TOPS (The Over-volunteering Preventions System). We will enter into the database: your National Insurance number (if you're a UK citizen), or your passport number and country of origin (if you're not a UK citizen) and the date of your last dose of study medicine. If you withdraw from the study before you receive the radiotracer, the database will show that you never received a dose. Only staff at Cambridge University Hospitals and other medicines research units can use the database. We may call other units, or they may call us, to check your details. Data entered in TOPS is retained for the minimum period required and this is determined based on whether you receive a dose of the study medicine or not. If you receive a dose of the study medicine, this data will be retained in TOPS. If you do not receive a dose, your data will be retained in TOPS for two years. If we need to contact you about the study after you've finished it, but we can't because you've moved or lost contact with your GP, we might be able to trace you through the information in the database.

Cambridge University Hospitals NHS Foundation Trust (CUH) and The University of Cambridge are the Sponsor(s) for this clinical trial. 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 15 years after the trial has finished to ensure your safety and allow the trial to be reviewed by the authorities after it is finished.

Your rights to access, change or move your information 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 Sponsors use 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

Cambridge University Hospitals will collect your name, NHS number, hospital number and contact details to contact you about this trial, and to make sure that relevant information about the trial is recorded for your care, and to oversee the quality of the trial. Individuals from the Sponsor(s) and regulatory organisations may look at your medical and research records to check the accuracy of this trial. Cambridge University Hospitals will pass these details to the Sponsor(s) along with the information collected from you and/or your medical records. The only people in the Sponsor organisation(s) who will have access to information that identifies you will be people who need to contact you in relation to this trial and to audit the data collection process. Cambridge University Hospitals will keep identifiable information about you from this trial for at least 15 years after the trial has finished.

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 Trial ID Number. This is a unique trial number which will be used on all your trial documentation along with your date of birth. Your date of birth is 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 two unique references we can ensure the integrity of the data.

Your personal information will form part of the trial data held by the research team and will be used for monitoring, quality checking and analysis purposes. However, this personal information will not be shared with any other third parties and will not be published in any way. Only anonymous trial data, without any personal information will be published at the end of the trial.

We will need to inform your GP of your participation in this trial so that any medical decisions made by your GP take into account any treatment you are receiving as part of this trial. We will also need to confirm with your GP that there is nothing in your health records which would prevent you from taking part in the trial.

17. What will happen to my samples?

The samples that you provide will be used to check your overall health and will also help to analyse the results of the scan. All blood samples will be labelled with your name, date of birth and hospital number and sent to the hospital clinical laboratories for immediate analysis. Your samples will be destroyed once laboratory analysis is complete.

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 the data produced. This study will form part of a student's PhD qualification. When the results of this trial are available, they may be published in peer reviewed medical journals and used for medical presentations and conferences. Anonymous datasets from the trial may also be made available to other researchers in line with national and international data transparency initiatives.

At the conclusion of the study, if you wish to find out more about our findings, please let us know and we will provide you with a summary of the study 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 has been funded by a grant from the Medical Research Council (MRC). The research doctors are not being paid for including you in this 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, to protect your interests. This trial has been reviewed and given favourable opinion by the London – West London & GTAC Research Ethics Committee. The Medicines and Healthcare Products Regulatory Agency (MHRA), who are responsible for regulating medicines in the UK, and the Administration of Radioactive Substances Advisory Committee, who provide advice on the use radioactive substances in people, have also reviewed this trial.

21. Further information and contact details

If you have a question at any time about this trial, or need to report a trial-related illness or injury please call 01223 245151 and ask to speak to Prof Mark Gurnell, Dr Russell Senanayake, Dr Waiel Bashari or Dr James MacFarlane about the CETO trial.

If you require further advice about whether you should participate in this trial, please feel free to discuss it with members of the trial team or with your family, friends, GP or other health professionals.

If you have any concerns you can also contact:
Addenbrooke's Hospital PALS Details
Phone: 01223 216756,
Email: pals@addenbrookes.nhs.uk
Letter: Complaints Department, Box 53, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ.

In the event of an emergency please call 07538 321567 and your call will be answered by one of the trial team members directly Dr Russell Senanayake, Dr Waiel Bashari or Dr James MacFarlane.

INFORMED CONSENT FORM

Trial Title: A phase 1 clinical trial evaluating the safety and efficacy of up to two administrations of the adrenal PET tracer [^{18}F]CETO in healthy volunteers and patients with primary aldosteronism

Principal Investigator: Prof Mark Gurnell **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 19 December 2019 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 personal information about me (such as my date of birth) will be collected and used in accordance with this information sheet. This information will be kept in the strictest confidence and none of my personal data will be published.	
4	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 and that they will keep my personal information confidential. I give permission for these individuals to have access to my records.	
5	I understand that my GP will be informed of my participation in this trial and sent details of the CETO trial. My GP will be asked to confirm that there is nothing in my medical records which would prevent me from taking part in the trial.	
6	I understand that my GP will be informed in the unlikely event of any medical findings occurring during the trial.	
7	I understand that my personal details and participation in this trial will be registered on the TOPS (The Over-volunteering Prevention System) database	
8	I have read and understood the compensation arrangements for this trial as specified in the Participant Information Sheet.	
9	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.	
10	I have read and understood my responsibilities for the trial including using appropriate contraception as listed in section 6.	

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.