Participant Information Sheet for the PROUD Study:

PRe-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men.

Version: 1.1

Date: 10 September 2012

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CONTENTS

PARTICIPANT-RELATED INFORMATION

PARTICIPANT INFORMATION SHEET (PIS)

PIS COVER SHEET

ACRONYM (or Short Title of Trial)	PROUD
Protocol Version	1.1
Protocol Date	10 September 2012
PIS Version	1.1
PIS Date	10 September 2012

We are inviting you to take part in a research study called PROUD.

The PROUD study looks at whether using a daily tablet can reduce the risk of HIV transmission for gay men. It also looks at how taking a daily tablet may affect other risks and behaviour. Everyone in the study will be supported to reduce their risk of HIV in other ways. Some people will take a tablet from the start, and others after 12 months.

Before you decide whether to take part, it is important that you:
- understand what is involved, including any potential risks or benefits,
- understand why the study is being run,
- have time to read this leaflet carefully and have any questions answered clearly.

Please also discuss the study with your friends and/or family, with a health advisor, or your doctor or GP, if you want to.

Please ask us if anything is not clear or if you would like someone to read through it with you. Take time to decide whether you would like to take part.

This information sheet is in three parts:
- Part 1 describes the aim of the PROUD study and what is involved.
- Part 2 includes details about why the research is being done.
- Part 3 includes general information about taking part in this study.

This study is sponsored by the UK Medical Research Council (MRC). The MRC website includes more information about research and trials, including other HIV studies. www.ctu.mrc.ac.uk

Thank you for reading this information and for considering this study.

Part 1: The aim of the study and what it involves

1. What is the aim of this study?

This study is looking at a new way to reduce the risk of catching HIV.

This involves HIV negative men taking a daily tablet that includes two drugs commonly used to treat HIV. Taking a tablet to reduce risk of infection is called Pre-Exposure Prophylaxis, or PrEP. Prophylaxis refers to doing something to prevent an illness or infection.

Studies in other countries have already shown that PrEP significantly reduces the risk of catching HIV, but only if someone is careful in taking the medications. This is the first study of PrEP for gay men in the UK.

Although PrEP helps to reduce the risk of HIV, this study also looks at other factors that could be important. This includes:

- Whether people using PrEP change the number of partners they have sex with
- Whether people using PrEP change how often they use condoms
- Whether PrEP leads to higher rates of other sexually transmitted infections (STIs).

This information on changes in sexual activity is one of the most important aspects of the study, because we do not know what happens to people's sexual activity when they know they are taking PrEP. It's possible that the changes may increase the overall risk of catching HIV, so that PrEP is less effective. A very large study of about 5,000 men would be needed to find out if this is the case. The main aim of this study is to find out if we could do this much larger study in the UK.

2. What happens if I take part?

To answer this question, we are recruiting 500 volunteers from the UK and they will be placed at random into one of two groups. The first group will be given PrEP from the start of the study and the second will be given PrEP after 12 months. This will allow us to compare the difference that PrEP makes to sexual activity and the risk of sexually transmitted infections. The study will last a total of 24 months. People who are in the study will not be able to chose which group they join. However, everyone in the study will know which group they are in, and everyone will receive at least 12 months of PrEP.

As with earlier PrEP studies, both groups will be given advice on other ways to reduce the risk of HIV transmission in addition to the PrEP medication.

If you decide to take part we will introduce you to a researcher, who will answer any questions that you have. They will check the results of previous HIV and STI tests in your records to see that you are able to take part in the study.

If you are still interested you will be given an appointment to join the study. You will be asked to provide written consent. We will check your HIV and STI screen are up to date, and ask you some general questions about you, your health, and your sexual activity during an interview. You will be asked for a sample of your urine to test to test for infection and to see how your kidneys are functioning. We will also ask you to fill in a questionnaire about your sexual activity and your health and wellbeing in private, and place this in a sealed envelope.

Then you will be selected at random to join one of the two groups. Randomised selection is like tossing a coin. Neither you nor the doctor or researcher can chose which group you will join. The study is carried out this way as it makes the results between the two groups more comparable.

You will also be asked to take a blood test. This is to check that you are not already HIV positive. If you are to start PrEP straightaway, your blood will also be used to test how your kidneys are functioning.

Over the course of the study, you will be asked to come to the clinic for study visits at regular intervals (at least 10 visits over two years). The visits are every three months, except for one a month after you start the tablets.

3. What other tests are involved?

Every three months during the study, you will need to visit the clinic to give a blood sample for HIV (approximately 5 ml and/or collected after your finger is pricked). Every six months, you will have a STI screen, similar to that done in a routine sexual health screen. This will involve one blood test (approximately 5 ml) to test for HIV and syphilis, as well as swab tests for other STIs, such as chlamydia and gonorrhoea. Whilst on Truvada a urine test and maybe a blood sample will be taken to check kidney function.

We will collect an additional blood sample (approximately 5-10ml) from some participants to measure levels of the PrEP drugs. We plan to give you these results within a couple of weeks to give you an idea of the level of active drug in your blood. We may also store these samples for testing later.

You will be asked to fill in a brief diary every day about any anal sex that you have had, and whether you took any tablets for PrEP when this is available to you. Every month, you will be asked to fill out a short questionnaire about your sexual activity and the tablets you have been taking for PrEP over the last 30 days if relevant.

The study procedures are summarised in more detail in the Flow Chart on the next page, as well as the blood tests that will be taken.

4. What are the drugs being used as PrEP in this study?

The medicine we are going to use for PrEP in this study is called Truvada. Truvada is a single tablet combining two drugs, Tenofovir and Emtricitabine. Both these drugs have been widely used for many years to treat HIV.

Truvada has been used by several thousands of HIV negative people in other PrEP studies. It is the only drug that has been looked at as PrEP for gay men, so this is the only drug that we can offer you.

It is also commonly used by HIV negative people as part of PEP (post-exposure prophylaxis). The dose of Truvada used in PEP is the same as in PrEP, and it is also a daily tablet.

Side effects in the other PrEP studies were generally mild (e.g. mild nausea) and seen in the first few weeks. Serious side effects such as changes in bone mineral density (how much calcium and other minerals are in your bone) were rare, especially in HIV negative people, and usually reversed when the drug was stopped.

Part two of this leaflet includes more information about safety of Truvada including results in HIV negative people.

You will also be asked if you would like us to contact your GP to let them know that you are in the trial.

5. What other ways to support reducing HV risk are available in the study?

PrEP is only one of the ways we will encourage you to use to reduce HIV risk.

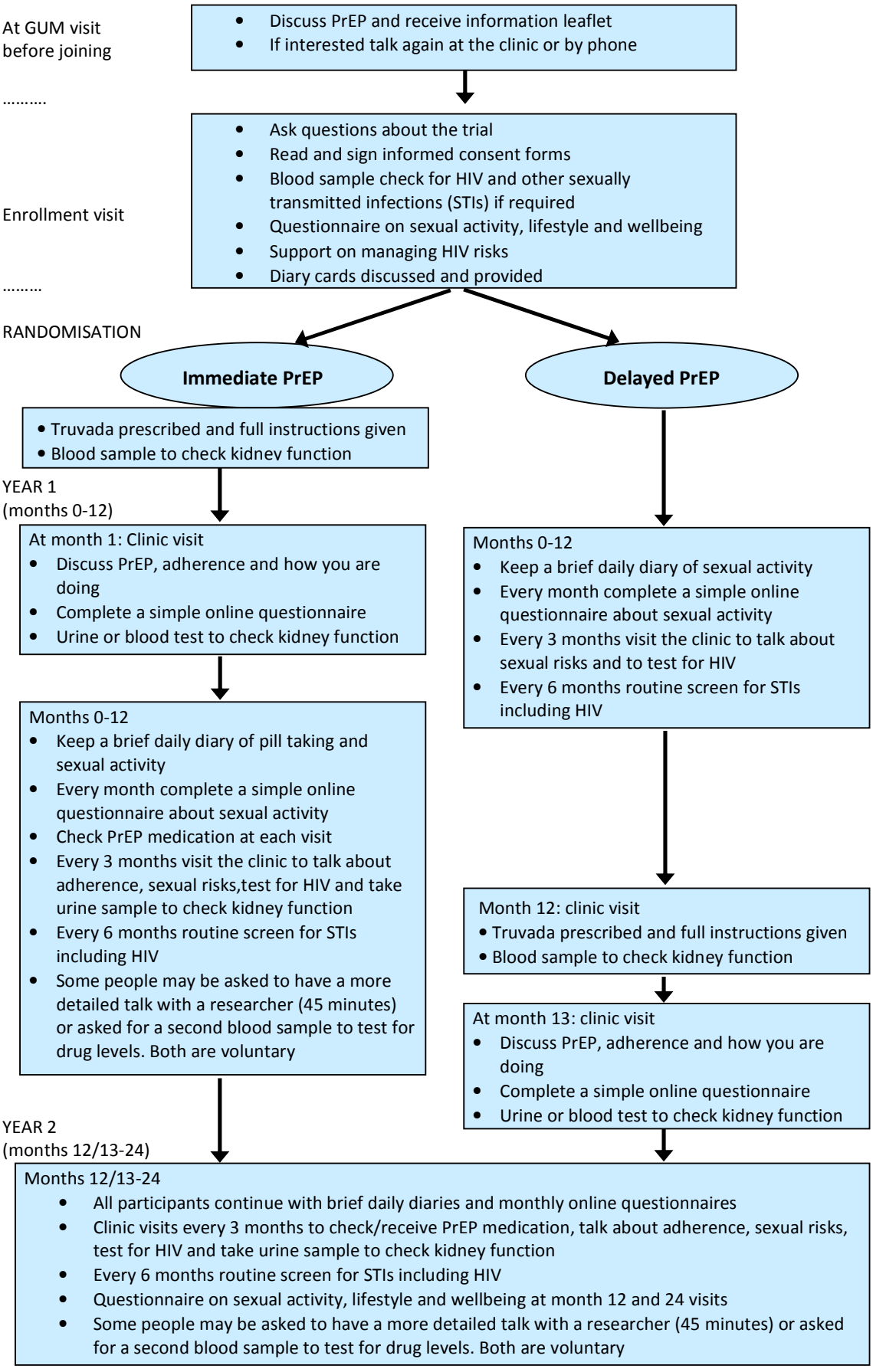
At each visit the research nurse will talk about HIV risk in general and your individual plan to reduce these risks.

This will focus on the things you would like to change to protect your health.

This plan could include a combination of:

* Individual, couple or group counselling at a local clinic or community organisation. This is where you can talk to a trained health worker about things in your life that are related to the decisions you take about your health.
* Motivational interviews or psychotherapy, in person, or possibly online. This is where you can talk about ways to help stick to goals and why this is often difficult.
* Other actions including post-exposure prophylaxis (PEP) as deemed appropriate by your doctor. PEP is where a month of HIV drugs can be given to reduce the chance of infection, after a risk. This is for people who are not taking PrEP. It would be indicated if you had stopped or interrupted your daily PrEP for a week before the risk.

6. Flow Chart for study and clinic visits



Blood tests taken during the study

Month	Test taken		Blood volume
	Immediate PrEP	**Deferred PrEP**	
Enrollment visit (after randomisation)	HIV Kidney function	HIV	5ml 5ml
1	Kidney function*		5ml*
12		Kidney function	5ml
13		Kidney function*	5ml*
Every 3 months	HIV Kidney function*		5ml** 5ml*
Every 6 months	Syphilis		5ml
Some participants 1-24 months	Active drug levels		5-10ml
Some participants 12-24 months		Active drug levels	5-10ml

* A urine sample will be collected in the first instance. A blood sample will only be collected if the urine sample indicates a need for further tests

** In some clinics this test may be done after pricking your finger

7. Who can take part?

All studies have factors that describe who can join a study.

For the PROUD study these are listed below.

You CAN take part if you	You CANNOT take part if
• Are aged 18 or older. • Were assigned to the male gender at birth. • Previously attended the clinic where you join the study at least once and completed a screen for HIV/STIs. • Are HIV negative. • Have had anal sex with a man without a condom in the previous 90 days. • Are likely to have anal sex with a man without a condom in the next 90 days. • Are willing and able to come to the visits and follow the study requirements. • Are willing and able to give informed consent.	• You have an acute viral illness that could be due to HIV until this possibility has been excluded. • There are reasons why you medically should not take the medicines in Truvada. • You are being treated/need treatment for hepatitis B.

8. Do I have to take part?

Whether you decide to join the study is entirely your choice.

You do not have to join if you do not want to. If you change your mind during the study you can stop at any time.

Whether or not you join or continue the study will not affect your medical care, although PrEP may not be available outside the study because it is not yet available in the NHS. If you do not join the study or if you leave it, we hope you will still continue with the HIV testing and screening for STIs.

You can also change your mind about taking PrEP. This would be something to consider if your circumstances change and you stop being at risk for catching HIV. In this case, you would still remain in the study and continue to fill in the questionnaires on sexual activity and have HIV

testing and screening for STIs. At each clinic visit, your clinician will rediscuss your circumstances with you in case you would like to recommence taking PrEP.

9. What are the possible advantages of taking part?

The potential benefits of taking part include:

- Reducing your risk of catching HIV. This could come from the use of PrEP or other health interventions.
- Taking PrEP will reduce your risk of catching HIV. In a large study called iPrEX (in almost 2500 gay men) the reduction in risk was modest for the study as a whole, but it was large in people who actually were taking PrEP every day.
- You will have access to PrEP for at least 12 months, and possibly 24 months.
- You will be connected to a team who will focus on your individual health and risks.
- The routine monitoring for HIV and other STIs should be better for your health as any infection will be diagnosed early.
- Taking a daily tablet may help you focus on other aspects of your health and life. You may decide that you can protect yourself from HIV without needing PrEP.

10. What are the possible disadvantages of taking part?

The potential disadvantages include:

- Mistakenly believing that PrEP **prevents** HIV. It does not, but it does reduce the risk. We are not sure by how much, but it works best if it is taken every day. It takes 2 weeks to reach a constant level in the tissues, so may not reduce risk much in this period. Missing 3 or more tablets in a week could also reduce effectiveness.
- If you become infected with HIV while taking PreP, there is a risk of developing drug resistance to one or both drugs. This would mean these drugs could not be used in the future as treatment. Other PrEP studies have reported this risk to be very low. If you restart PrEP after a break in which you unknowingly caught HIV, the risk of resistance will be higher.
- You will be at risk from other sexually transmitted infections when not using condoms. This risk will increase if you change your behaviour just because you are taking PrEP.
- The drugs in PrEP, like all other medicines, have potential side effects. In HIV negative people, nausea and diarrhoea were more common in the PrEP group compared to placebo (an inactive tablet), and this was mainly in the first month. A small proportion of HIV negative people taking the drugs in PrEP developed impairment in their kidney function in other trials, but these changes reversed on stopping the drug.
- It's possible that taking PrEP, or taking part in this study, will attract negative comments from your friends and/or family, or even the media. The research team is working closely with the community organisations to manage communications responsibly and to ensure balanced reporting.

11. What is expected of me?

We would like you to record your sexual behaviour and drug taking regularly through a daily diary and monthly questionnaire. This information is anonymised so that the clinic that provides your care does not connect this to you personally.

This information is important because it will help us understand the safest and most effective ways for people to use PrEP.

The more accurate the information, the more useful it will be for the research and future use of PrEP in the NHS. This includes information on when you take or miss doses of PrEP and when you do and do not use condoms. Regularly completing your daily diary and monthly questionnaires is important so the study can collect the information needed to answer the research questions.

Regularly attending the clinic every three months is also important so HIV infections can be diagnosed early. Truvada has been shown to be unsafe to take by itself if you have become HIV-positive and attending the clinic is required to reduce this possibility.

12. Will I be paid to take part?

There is no financial payment for joining the study.

We also cannot pay for travel costs or other expenses related to visits to the clinic.

13. Will I still get PrEP after the study ends?

At the moment PrEP is not available on the NHS outside this study.

At the end of your follow-up (two years at the most) the clinic team will let you know whether it is possible to continue PrEP, and how.

PrEP may be available in the public health programme, but this has to still be decided.

If this information has interested you, and you think you might like to take part in this study, please read the extra information in Parts 2 and 3.

Part 2: Why the trial is being run and what we know about PrEP

14. Why are we running this study in the UK?

In 2011 in the UK, there were more than 3000 new diagnoses of HIV among men who have sex with men (MSM). Many of these diagnoses were recent infections (caught within the previous 5 months). This was higher in younger age groups, especially 18-25 year olds.

Most people who are diagnosed with HIV find this stressful and difficult and find that it changes their lives in ways that they had not realised. Approximately two-thirds of people start treatment within the first year of being diagnosed. While treatment is effective for most people, it has to be taken daily, and until a cure is found, is likely to be life-long.

It is not fully understood why HIV infections are increasing, and the reasons are likely to be complicated. It is clear that we need new options for reducing the risk of HIV infection. PrEP could be one of these options.

Studies in other countries have shown that Truvada used as PrEP can reduce your chance of becoming infected with HIV. On the basis of their study, the US government is recommending daily Truvada for high risk HIV negative gay men. People have different risk factors and behave differently with respect to pill taking in different parts of the world. How good PrEP is at reducing the risk of becoming infected with HIV for gay men in the UK is related to these differences. We need to better understand these behaviours in the UK to avoid giving PrEP to people that don't need it, and to find out who wants to take it.

15. What is known about using Truvada for reducing risk of HIV infection?

There have been four main studies using daily Truvada as PrEP that reported results by the end of 2011. Three of these, including the iPrEx study in gay men, showed that Truvada reduces the risk of catching HIV. In all four studies, men and/or women were asked to take a tablet every day. These were randomised where participants either took Truvada or a placebo (an inactive tablet). In one of the four trials, there was an additional group taking only tenofovir (one of the drugs in Truvada).

Several important points came out of these and other studies to reduce risk of HIV infection:

- The risk of HIV was reduced most in those who said they took PrEP every day
- The greatest reduction in risk of HIV was seen in the people who not only said they took Truvada but who had active blood? levels of their drug (ie who were **actually** taking PrEP).
- That condoms still provide a very safe and effective way to prevent HIV and some other STIs

The iPrEx study is important because it included gay men **at high risk of HIV**.

- About half were under 25 years old
- They were sexually active (an average of 18 partners in the previous 3 months),
- 8 out of 10 gay men had had unprotected anal sex in the previous six months
- Very few people discussed HIV with their partners
- Condom use was low
- Alcohol use was common (more than 4 drinks on a drinking day in half of participants)

Truvada was used in the iPrEx study and it is the only drug that has been tested in gay men. That is why it is the drug we are using in our PROUD study.

The iPrEx study included gay men who had unprotected anal sex. Truvada only reduced the risk of HIV in men that reported unprotected receptive (bottom/passive) in the six months before they joined the study. There was no reduction in men that did not report this behaviour, which included men who only reported unprotected insertive (top/active) anal sex. However, in the PROUD study, we are including gay men who only report insertive (top/active) sex without a condom in the previous three months. This is because we know that there is a risk of catching HIV from both types of sex, even though the risk is highest with receptive anal sex. Studies in other countries using PrEP in gay men are also including gay men who have both insertive and receptive anal sex.

Safety and risks in the iPrEX study

The iPrEx study is the closest study to PROUD for information about safety and risks.

One outcome was that partipants in both the active and placebo group reported that during the study they reduced their risk factors for catching HIV. This may have been because of the individual support that the study provided. This could also occur in the PROUD study.

The study, in almost 2500 gay men, also showed that PrEP was generally safe with low risks.

Mild side effects were commonly reported, but the rates were similar in people using the placebo (ie the inactive drug) as those using the active PrEP.

One exception was that during the first four weeks 9% of people in the active drug group reported nausea compared to 5% in the placebo group. For the rest of the 96 weeks of the study there was no difference in rates of nausea between the two groups.

Body weight also increased slightly more in the placebo group compared to the active group but again only in the early months. In the first three months, weight increased by 0% in the active drug group vs 1% in the placebo group. It then increased by 1.5% per year in both groups.

One of the drugs in Truvada (tenofovir) is processed by your kidneys and your kidney function will be monitored during the study. In the iPrEx study, mild changes in kidney function occurred in only 2% of the active group compared to 1% of the placebo group and the difference in the two rates was not significant. These changes reversed when people stoped taking Truvada.

The development of drug resistance in the iPrEx study was also very low. This only occurred in two people in the active drug group and one person in the placebo group. Both cases were detected in the first four weeks of the study, indicating that the person was likely to have been infected with HIV before thay started taking PrEP.

In HIV positive people, tenofovir causes a small decrease in bone mineral density (how much calcium and other minerals are in your bone) during the first six months of use but after this there are no differences compared to other types of HIV drugs. This small reducton is not thought to be clinically important for most people and was not related to increased bone fractures.

The results of the iPrEX study were published in the New England Journal of Medicine in December 2010 and the paper is available free online:
http://www.nejm.org/doi/full/10.1056/NEJMoa1011205

Reports of the iPrEX study by community organisation like i-Base and NAM are at these links:
http://i-base.info/htb/14191

http://i-base.info/htb/14833
http://www.aidsmap.com/The-iPrEx-study/page/1746640/

Adherence

Adherence is a medical word for taking medication as it is prescribed.

Although taking PrEP daily is recommended, we understand that you may be late or miss an occassional dose. In lots of other health areas 100% adherence is rare – but the better you are at taking the tablets the more you reduce your risk. Taking PrEP just before you have sex may not reduce your risk. This is because it takes 14 days for Truvada to reach a constant high level in rectal tissue. It is really important that we know if you are having difficulty taking the tablets every day.

This means it is important that you attend your appointments and that you give as accurate answers as you can to the questionnaires. We need to know how easy PrEP is for people to take, or why it is difficult if this is the case. If you've missed several doses in the previous week and feel like you may have been exposed to HIV then please contact the clinic at the earliest opportunity.

Part 3: General information about taking part in this study

16. Will my joining the study be confidential?

Nobody outside of the research group and your clinical team will know you are part of the study. The information you provide will also be separated from your personal details like your name, so the researchers will not link you to the specific results.

We will follow guidelines developed by the NHS and legal requirements to make sure that all information about you is treated in confidence.

The Medical Research Council Clinical Unit (MRC CTU) is co-ordinating this study and will be collecting information about you if you decide to take part. The MRC CTU and Medicines and Healthcare products Regulatory Agency (MHRA), the organisation that monitors medical research in the UK, may need to check that the information is correct - but your confidentiality will be protected at all times.

Information held, for example by the NHS, may be used to provide information about your health status after your participation in the trial. The MRC CTU is registered under the UK Data Protection Act (DPA) to store this information. There is a question about this on the consent form that we will ask you to sign before you begin the study.

17. Who is organising this study?

This study is being organised by the MRC CTU, based in London. The MRC CTU is a not-for-profit organisation, which is funded by the UK government to run medical research in the public interest. You can find out more about us at www.ctu.mrc.ac.uk

The MRC is responsible for ensuring that this study is done properly.

18. Who has reviewed this study?

To protect your safety, rights, well-being and dignity, this study has been reviewed by the NRES committee London – London Bridge Research Ethics Committee. This committee has given this research the go-ahead. An independent patient representative, and the UK Community Advisory Board for HIV trials have also reviewed the trial protocol and have helped write this information leaflet.

19. Who is funding the study?

This study is being paid for by the UK Health Protection Agency and the MRC CTU. Gilead Sciences (who manufacture Truvada) are providing free drugs and are funding some of the costs such as blood and urine tests.

20. What will happen to any samples I give?

Most samples will be destroyed after they have been processed, but we may store some for future drug testing to better understand the result of the study.

21. What happens if I test HIV positive during the study?

Some people in the study are likely to still become HIV positive. Even with the best care and interventions, this will sometimes happen, just like it happens outside of studies.

If your results are positive, you will be contacted directly and the results will need to be confirmed. If the confirmed tests are positive you will be transferred to an HIV specialist for future care.

Because of the more frequent monitoring in the study, you are likely to find out about an HIV infection earlier than outside the study. This is likely to be better for your health.

If you become HIV positive, you would stop using PrEP.

22. Will any genetic tests be done?

We do not need to check your genetics for this study.

23. What will happen to the results of the research study? How can I obtain them?

The results of this study will be made public at medical meetings and hopefully published in a medical journal. These results are likely to be widely reported by community groups including i-Base, the National AIDS Manual, AIDSMap and the gay media.

We will send a copy of the aggregated results to your clinic, and you will be able to collect a summary or access it online if you wish. You will not be sent your individual results. You will not be identified in any report or publication. We will also publish a summary of the results of this study, in plain English, on the MRC CTU website. The address is www.ctu.mrc.ac.uk

We usually produce the summary at the end of the study which we anticipate will be 2015, but there may be interim reports, in which case the clinic team will tell you.

Further information about this research study

Your contact at your hospital for further information about this study is:

_____ **[Insert Info: Contact Name]**

You could also look at the information about this study that is on the MRC CTU website: www.ctu.mrc.ac.uk

Advice and information about PrEP to help you decide whether to take part in this study

These include:

- THT direct: 0808 802 1221
- i-Base treatment information phoneline: 0808 800 6013

You could talk to your GP if you would like another opinion about whether or not you should take part in this study. You could also talk about it with your partner, family and friends.

24. If something goes wrong, who should I contact?

We will try to answer any question or complaint about the way you are dealt with during this study, or any possible harm you may experience as a result of taking part in this research. If you have a concern about any aspect of this study, you should first ask to speak with the research nurse. She or he will do their best to answer your questions.

Contact:

[*Insert Info*: Name], [*Insert Info*: Job title], [*Insert Info*: Postal address], [*Insert Info*: Office telephone number]

[*Insert Info*: Name], [*Insert Info*: Job title], [*Insert Info*: Postal address], [*Insert Info*: Office telephone number]

If you are still unhappy, and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from:

_____ **[*Insert Info*]**.

In the event that something does go wrong, and you are harmed during this research, there are no special compensation arrangements. If you are harmed, and this is because of someone's negligence, then you may have grounds for a legal action for compensation, but you may have to

pay your legal costs. If you do this, the normal NHS complaints mechanisms will still be available to you.

25. What if new information becomes available during the study?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether or not you should continue in the study.

If you decide not to carry on, your research doctor will make arrangements for your care to continue.

If you decide to continue in the study, she or he may ask you to sign an updated consent form.

Occasionally, studies are stopped due to new information being discovered. If the study is stopped for this or any other reason, we will tell you.

26. Who should I talk to if I have more questions?

Your doctor or the researcher at the clinic should be able to answer most questions.

Some community organisations provide confidential infromation services to talk about whether a study is right for you.

These include:

- THT direct: 0808 802 1221
- i-Base treatment information phoneline: 0808 800 6013

The MRC website includes other information about health research and clinical trials: www.ctu.mrc.ac.uk.

This includes links to other websites with information about health research and clinical trials.

Thank you for taking the time to read this information sheet and considering this study.