PROUD

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: 1.2.1

Date: 14 October 2013

ISRCTN #: ISRCTN94465371

EUDRACT #: 2012-002373-56

CTA #: 00316/0244/001-0001

REC #: 12/LO/1289

Authorised by:

Name: Dr Sheena McCormack

Role: MRC CTU Project Lead/Chief Investigator

Signature:

Date:

Name: Dr David Dunn

Role: MRC/CTU Senior Statistician

Signature:

Date

GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. It describes the PROUD pilot, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU), and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the management of others. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the pilot but sites entering participants for the first time are advised to contact PROUD@ctu.mrc.ac.uk to confirm they have the most up-to-date version.

COMPLIANCE

The pilot will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

SPONSOR

The MRC is the sponsor and has delegated responsibility for the overall management of the PROUD pilot to the MRC CTU. Queries relating to MRC sponsorship of this pilot should be addressed to the Director, Regional Centre London, Aviation House, 125 Kingsway, London WC2B 6NH, UK or via the trial team.

FUNDING

The pilot will enrol up to 500 participants, funded through a variety of sources including MRC CTU and Public Health England (formerly the Health Protection Agency). An application to the Clinical Research Network for adoption of this phase of the trial into the portfolio will be made. Drug and support for protocol specific procedures and laboratory tests has been provided by Gilead for the pilot.

AUTHORISATIONS AND APPROVALS

This pilot protocol will not be implemented until approvals have been received from all the necessary regulatory and ethical bodies.

TRIAL REGISTRATION

The pilot has been registered with the ISRCTN Clinical Trials Register ISRCTN94465371

RANDOMISATIONS
Follow the working instructions to access the website
or
call or fax MRC CTU, Monday to Friday 08:30 to 17:00
Tel: 020 7670 4783 or Fax 020 7670 4659

SAE REPORTING
Within 24 hours of becoming aware of an SAE, please report to the MRC CTU using the template provided by either:
Fax: 020 7670 4659 or email information to PROUD@ctu.mrc.ac.uk

TRIAL ADMINISTRATION

Please direct all queries to Liz Brodnicki, the Trial Manager at MRC CTU in the first instance; clinical queries will be passed to the Chief Investigator and Medical Expert Deputies via the Trial Manager.

COORDINATING SITE

MRC Clinical Trials Unit	Switchboard:	020 7670 4700
Infections Theme	Fax:	020 7670 4659
Aviation House, 125 Kingsway	Email:	PROUD@ctu.mrc.ac.uk
London		
WC2B 6NH		
UK		

MRC CTU STAFF

Trial Manager:	Liz Brodnicki	Tel:	0207 670 4783
Statistician:	David Dunn	Tel:	0207 670 4739
Project Leader:	Sheena McCormack	Tel:	0207 670 4708
Social Science Lead:	Mitzy Gafos	Tel:	0207 670 4687

CHIEF INVESTIGATOR

Dr Sheena McCormack	Tel:	0207 670 4708
MRC Clinical Trials Unit	Fax:	020 7670 4659
Aviation House	Email:	smc@ctu.mrc.ac.uk
125 Kingsway		
London WC2B 6NH		
United Kingdom		

LEAD INVESTIGATOR FOR CHELSEA & WESTMINSTER NHS FOUNDATION TRUST

Dr Ann Sullivan	Tel:	020 8846 6199
Consultant Physician in GUM	Fax:	020 8846 6198
Chelsea & Westminster Hospital NHS Foundation Trust	Email:	ann.sullivan@chelwest.nhs.uk
369 Fulham Road		
London SW10 9NH		
United Kingdom		

CO-INVESTIGATORS

Professor Noel Gill	Noel.Gill@phe.gov.uk
Dr Anthony Nardone	Anthony.Nardone@ phe.gov.uk
Dr Monica Desai	Monica.Desai@ phe.gov.uk
Professor Brian Gazzard	Brian.Gazzard@chelwest.nhs.uk
Professor Anne Johnson	anne.johnson@ucl.ac.uk
Professor Rob Horne	Rob.Horne@pharmacy.ac.uk
Professor Andrew Phillips	andrew.phillips@ucl.ac.uk
Dr Jim Rooney	Jim.Rooney@Gilead.com

LABORATORY INVESTIGATOR

Professor Saye Khoo	Tel:	0151 794 5560
Bioanalytical Facility	Fax:	0151 794 5656
University of Liverpool	Email:	S.H.Khoo@liverpool.ac.uk
70 Pembroke Place		
Liverpool L25 6DU		
United Kingdom		

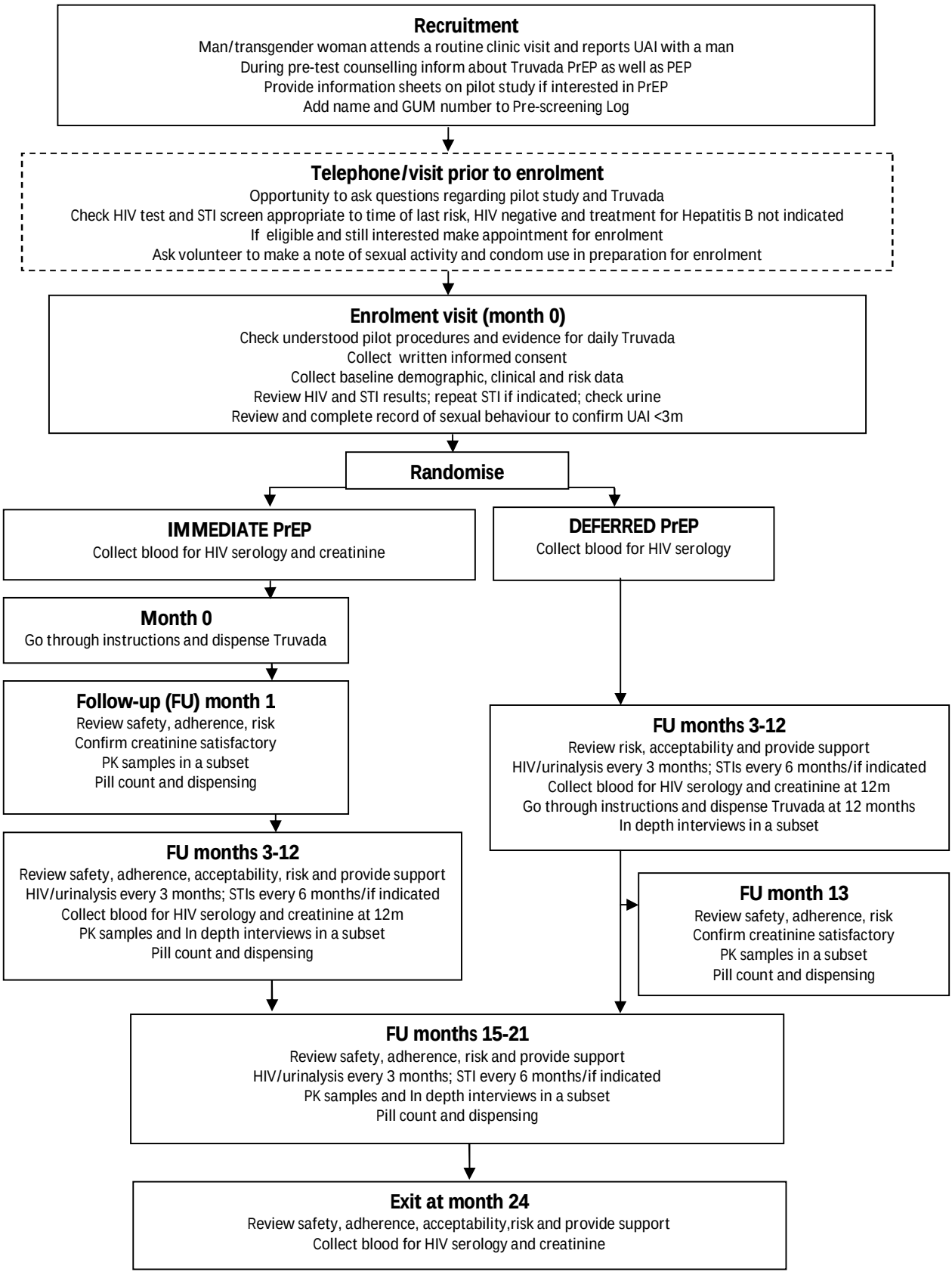
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM	PROUD
Long Title of Trial	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	1.2.1
Date	14 October 2013
ISRCTN #	ISRCTN94465371
EudraCT #	**2012-002373-56**
Study Design	A multi-centre, open label randomised design to immediate or deferred inclusion of pre-exposure prophylaxis as part of the package of HIV risk reduction interventions.
Type of Participants to be Studied	HIV negative men who have unprotected anal intercourse (UAI) with men
Setting	Genito-urinary medicine (GUM) clinics in the UK
Interventions to be Compared	All participants will be offered a risk reduction package that includes regular HIV testing, diagnosis and treatment of sexually transmitted infections (STI), support to reduce and eliminate high risk behaviour including free condoms, and other biomedical intereventions such as post-exposure prophylaxis where relevant. With or Without the inclusion of daily oral Truvada.
Study Question	In order to determine whether the immediate inclusion of anti-retroviral pre-exposure prophylaxis (PrEP) as part of the HIV risk reduction package for men who have sex with men who are at risk of acquiring HIV is clinically effective and cost-effective, a large trial would need to be conducted. The purpose of the pilot is to determine the feasibility of conducting such a trial in the UK.
Main Outcome Measures	Time to accrual of 500 participants Retention at month 12 and 24
Other Outcome Measures	HIV infection between randomisation and month 12 . Safety: • Serious Adverse Reactions attributable to Truvada • Adverse events that lead to interruption or cessation of Truvada • Renal function estimated using serum creatinine at 12m • Frequency of viral resistance in men who acquire HIV Adherence:

	• Proportion of doses taken according to self-report • Proportion of days covered according to dispensing records • Presence of active drug in blood in a subset Risk compensation: • Number of sexual partners with whom unprotected (insertive/receptive) anal intercourse takes place • Number of acts of anal intercourse, protected and unprotected • Proportion of acts of anal intercourse protected by either condom, PrEP or both • New STIs (urethral and rectal gonorrhoea or chlamydia, syphilis) Other: • Facilitators and barriers to adherence to a personal risk reduction plan in a subset
Randomisation	Participants will be randomised 1:1 to immediate inclusion of daily oral Truvada in the risk reduction package or deferred until 12m by phone, fax or via the internet.
Number of Participants to be Studied	Up to 500
Duration	Approximately fourteen months for recruitment, and a further two years follow-up.
Ancillary Studies/Substudies	No anciliary studies/substudies are planned.
Sponsor	MRC
Funder	MRC/PHE/Gilead
Trial Manager	Liz Brodnicki
Chief Investigator	Sheena McCormack
MRC CTU Project Leader	Sheena McCormack

TRIAL SCHEMA

Figure 1. Trial Entry, Randomisation and Treatment



TRIAL ASSESSMENT SCHEDULE

X means mandatory, (X) means if indicated

	Prior to Enrolment	Day 0 (Baseline)	Months 1,2,4,5,7,8,10,11 13,14,16,17,19,20,22,23,	First month on PrEP Immediate: m1 Deferred: m13	Months 3, 9, 15, 21	Months 6, 18	Months 12, 24
Informed consent		X					
Eligibility check	X[a]						
Inclusion/exclusion criteria		X					
Randomisation		X					
Baseline HIV/STI/demographics		X					
Visit/Contact case record form				X	X	X	X
SAE assessment				X	X	X	X
Dispensing and Pill count		X[b]		X[b]	X[b]	X[b]	X[b]
Daily diary[c]		←	―	―	―	―	→
Short Behaviour Questionnaire[c]		X	X	X	X	X	X
Long Behaviour & Lifestyle Questionnaire[c]		X					X
Acceptability Questionnaire							X
In depth interview (IDI)[d]		X		X	X	X	X
HIV test	X[a]	X			X	X	X
STI screen	X[a]	(X)		(X)	(X)	X[f]	X[f]
Urinalysis for Protein		X			X	X	X
Serum Creatinine		Immediate		(X)[e]	(X)[e]	(X)[e]	X
PK sample collection[d]				(X)	(X)	(X)	(X)

[a] Eligibility will be determined on the basis of routine data such as sexual behaviour, HIV and hepatitis B status, STI screening
[b] Immediate group months 0-24; deferred group months 12-24
[c] The diaries and questionnaires will be completed by participants and posted to MRC CTU, or entered directly online
[d] The IDIs and PK samples will be in a selected subset in the first instance, and thereafter on the recommendation of the Trial Steering Committee
[e] At these visits clinics will monitor renal function according to their routine practice which will be serum creatinine or urinary protein:creatinine ratio
[f] urine/urethral swab and rectal swab for neisseria gonorrhoea and chlamydia trachomatis and blood for syphillis

CONTENTS

ABBREVIATIONS

AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ANRS	Agence Nationale de Recherche sur le SIDA
AR	Adverse reaction
CF	Consent Form
CI	Confidence interval
CLRN	Comprehensive Local Research Network
CRF	Case Record Form
CTA	Clinical Trials Authorisation
CTU	Clinical Trials Unit
DPA	(UK) Data Protection Act
DSUR	Development Safety Update Report
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FGD	Focus Group Discussion (group discussions)
FU	Follow-up
FTC	Emtricitabine
GCP	Good Clinical Practice
GP	General Practitioner
GUM	Genito-Urinary Medicine
HE	Health economics
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
ICER	Incremental Cost Effectiveness Ratio

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDI	In-depth interview (one to one discussions)
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified Intention-to-treat
MRC	Medical Research Council
MRC CTU	Medical Research Council Clinical Trials Unit
MREC	Main Research Ethics Committee
MSM	Men who have sex with men and transgender women
NHS	National Health Service
NIHR	National Institute for Health Research
OD	Once daily
PBMC	Peripheral blood mononuclear cells
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
PEP	Post-exposure prophylaxis
PPI	Patient and Public Involvement
PrEP	Pre-exposure prophylaxis
QMC	Quality Management Committee
RAI	Receptive anal intercourse
R&D	Research and Development

REC	Research Ethics Committee
RGF	Research Governance Framework (for Health and Social Care)
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of Product Characteristics
SSA	Site-specific approval
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UPC	Urinary protein:creatinine ratio
URAI	Unprotected receptive anal intercourse

GLOSSARY

Truvada® - fixed dose combination of emtricitabine (200mg) and tenofovir disoproxil fumarate (300mg)

1 BACKGROUND

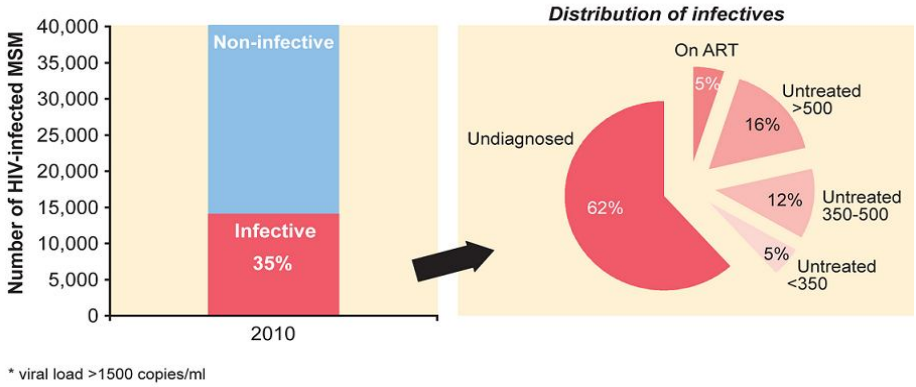
1.1 THE STATUS OF THE HIV EPIDEMIC IN UK

In the UK, HIV remains a disease of major importance with an estimated 91,500 individuals living with HIV at the end of 2010, of whom one-quarter are unaware they are infected[1]. Since the introduction of new therapies in the late 1990's, HIV has been transformed from a fatal illness to a manageable chronic infection. Today, individuals who are diagnosed early in the course of infection have an excellent prognosis with life expectancy approaching that of the general population.

The decline in HIV and AIDS-related mortality and continuing high levels of new infections has resulted in an unremitting increase in the prevalence of HIV, providing a pool of infected individuals to sustain transmission and, since treatment is life-long, an inexorable increase in NHS costs. Estimated treatment and care costs in the UK were £762 million in 2010 and the average life-time cost of treating one HIV infection is estimated to be £280,000 - £360,000[2]. From a cost perspective alone, disregarding impairment on quality of life, it is critical to reduce the incidence of HIV infection.

The population most at risk of acquiring HIV in the UK are men who have sex with men (MSM), who are estimated to number over 500,000 (3.6% of the male population). The estimated prevalence of HIV among MSM aged between 15 and 44 years old is approximately 5%. There is a wealth of evidence of high, and possibly, increasing rates of transmission in this population. This is supported by a concomitant increase in reported high risk behaviours such as unprotected anal intercourse, from 24.3% to 36.5% of the cohort surveyed in London gyms in 1998 and 2008 respectively[3] . In 2010 the highest ever number of new HIV diagnoses (3,000) among MSM was reported[1] and 85% of these were estimated to have been acquired in the UK.

The majority (80%) of those diagnosed start anti-retroviral therapy within a year. Almost all (90%) achieve undetectable virus. Therefore the largest fraction (62%) of the estimated 14,000 infectious MSM in the population, as defined by a HIV viral load > 1500 copies/ml, are the undiagnosed fraction[4]



* viral load >1500 copies/ml

According to surveillance data, over 48,000 MSM of an unknown or HIV-negative status attended a genitourinary medicine (GUM) clinic in 2010, of whom approximately 9,000 were diagnosed with an acute STI indicative of unprotected sex. Intensive efforts to increase the proportion of MSM tested for HIV have met with success, with 90% of MSM attending GUM clinics accepting a test in 2010.

However, there is still room for improvement and new interventions are needed for HIV negative populations to reduce their individual risk and minimise the number with undiagnosed HIV in the community.

1.2 PRE-EXPOSURE PROPHYLAXIS

1.2.1 EVIDENCE OF EFFICACY

The US Food and Drug Administration approved the use of daily oral Truvada (a tenofovr/emtricitabine combination pill) for pre-exposure prophylaxis to reduce sexual acquisition of HIV in otherwise healthy individuals who are at high risk of infection on the 16th July 2012, following an earlier recommendation from an expert advisory panel. This decision was primarily based on the findings of two double-blind placebo-controlled trials which assessed once-daily oral Truvada PrEP: the iPrEx study of gay and bisxual men and transgender women, and the Partner's PrEP study of heterosexual men and women whose partner was HIV infected (Table 1.1). The reduction in HIV incidence associated with allocation to PrEP in these studies was 44% and 73% respectively. The data from all the oral PrEP studies are not unanimous, however: the FEM-PREP study of Truvada, and the two tenofovir arms of the VOICE study in heterosexual women were halted early due to futility, and the oral Truvada arm in the VOICE trial showed no benefit (Table 1.1).

The most likely explanation for these discrepant findings is variability in levels of adherence. In the FEM-PREP study, only 38% of specimens from control patients (non-seroconverters in the Truvada group) had detectable levels of tenofovir, suggesting no or minimal exposure in the previous 1-2 weeks. In VOICE, only 35% of women had detectable drug in a sensitive assay at any timepoint. This figure was higher in iPrEx (51%) and Partner's PrEP (82%), but taken together confirm that adherence to daily dosing was substantially less than 100%. However, it is possible that some participants made logical dosing decisions related to their sexual activity. In iPrEx, for example, the majority of participants had no unprotected anal sex in the 12 weeks preceding a clinic visit on at least one occasion (personal communication, David Glidden, Trial Statistician for iPrEx). Nested case-control substudies within the trials have found a clear correlation between efficacy and the presence of detectable drug (Table 1.1).

As well as demonstrating efficacy, these trials have confirmed the excellent safety profile of Truvada in HIV-negative individuals, consistent with data in HIV positive individuals. In the large numbers exposed to the drug, the only safety concerns to date have been mild gastro-intestinal discomfort at an early stage of follow-up, and mild elevations of creatinine. Only 7 out of 4,500 participants had to stop Truvada because of toxicity.

TABLE 1.1: SUMMARY OF STATUS OF RELEVENT PREP TRIALS INCLUDING THOSE PLANNED

TRIAL	POPULATION	INTERVENTION	TRIAL STATUS/FINDINGS
CAPRISA 004	889 women from urban and rural populations in South Africa	1% tenofovir gel applied before and after sex	Results reported July 2010. Tenofovir gel reduced risk of HIV infection by 39%.[10]
iPrEx	2,499 MSM and transgender men in South America, the US and South Africa	Daily oral truvada	Results reported November 2010. Truvada reduced risk of HIV by an average of 44%. 51% specimens had detectable drug[5]
FEM-PREP	1,950 women at high risk in Kenya, South	Daily oral truvada	Stopped for futility in April 2011 with 28 infections in each arm. Full results expected in

	Africa and Tanzania		early 2012. 38% specimens had detectable drug[6]
CDC4370	2,400 intravenous drug users	Daily oral tenofovir	Reported a 49% reduction in HIV. (www.cdc.gov/nchhstp/Newsroom/docs/PrEP-IDU-factsheet-508.pdf)
VOICE	5,000 women from urban and rural general populations in South Africa, Uganda, Zimbabwe	Daily oral tenofovir or truvada or daily 1% tenofovir vaginal gel	Reported no benefit in oral TDF or Truvada arms or vaginal TDF compared to matched placebo arms.[7]
Partners in PrEP	4,700 Sero-discordant couples in Kenya and Uganda	Daily oral tenofovir or truvada	DSMB review in July 2011 showed oral TDF reduced risk of HIV by an average of 62%; daily Truvada reduced risk of HIV by an average of 73%. As a result placebo arms have discontinued but the trial is ongoing. Additional data expected 2013. 81% specimens had detecable drug.[8]
TDF2	1,200 heterosexual men and women in Botswana	Daily oral truvada	Results released in July 2011. Truvada reduced risk of HIV infection by an average of 63%.[9]
IPERGAY	300 MSM in France for pilot. Expanded to 1,900 MSM.	Oral truvada before and after sex	Pilot phase started Feb 2012.
FACTS-001	3,150 women in South Africa	1% tenofovir vaginal gel applied before and after sex	Started enrolling Oct 2011. Results expected 2013.
IMP 027		Dapivirine delivered via an intra-vaginal ring	Started enrolling Jun 2012

Only one of the completed trials explored an intermittent regimen, in which women were advised to apply one dose of tenofovir 1% vaginal gel within 12 hours of sex, to apply a second dose within 12 hours after sex, and no more than two doses in any 24 hour period[10]. This regimen reduced HIV incidence by 39% (95% CI 6-60%), a level similar to that achieved in iPrEx with daily dosing. The 'before and after' regime will be assessed again in two placebo-controlled trials: one will use the vaginal gel, and, a second will assess Truvada taken before and after sex in MSM in France (FACTS-001 and ANRS IPERGAY respectively). In both trials, the comparison will be placebo and results are expected in 2015-16. Therefore to date, efficacy has only been confirmed for daily oral Truvada.

1.2.2 HUMAN PHARMACOLOGY AND ANIMAL CHALLENGE DATA

The pharmacokinetic properties of Truvada suggest that this drug is a good choice for target populations whose highest risk is receptive anal intercourse. Oral dosing achieves higher levels of tenofovir diphosphate and emtricitabine triphosphate in the rectal fluid and tissue than in plasma and peripheral blood mononuclear cells [11,12], possibly due to drug that has not been absorbed higher up the gastro-intestinal tract.

The half-lives of tenofovir diphoshpate and emtricitabine triphosphate are estimated to be 6.25 and 1.6 days respectively, which permits once daily dosing and provides 'pharamcokinetic forgiveness' with sub-optimal adherence. However, this also means that it takes longer to reach steady state[13]

and levels in rectal tissue may be sub-optimal during this period. Macaque studies suggest that whilst emtricitabine triphosphate is detectable in rectal tissue within 2 hours of oral dosing, tenofovir diphosphate takes longer and reaches a peak about 24 hours later [14] .

1.2.3 LACK OF EVIDENCE ON EFFECTIVESS AND COST-EFFECTIVENESS

All of the trials to date assessing Truvada have been placebo-controlled, to avoid confounding by differences in behavioural characteristics. While this has clearly established biological efficacy for an individual, this does not equate to the level of protection that PrEP will provide at the population level when used in a "real life" context i.e. its effectiveness. In particular, the perception that PrEP protects against infection may lead to reduced use of condoms or riskier sexual practices ("risk compensation"). If this phenomenon exists, the efficacy estimates from the trials to date will exaggerate the actual protective effect of PrEP; if it is a strong phenomenon it could render PrEP ineffective at an individual and population level. This was one of the concerns expressed by the European Medicines Agency in a consultation document, in which they indicated that further trials might be needed[15].

Also, for expensive interventions (the cost of daily Truvada is currently £418.50 per month), it is increasingly recognised that reliable cost-effectiveness estimates should inform the decision on whether the intervention should become widely available. This point was cogently made in a recent editorial: "Whether or not cost considerations are considered relevant to decisions about regulatory approval, decisions about health coverage should reflect judgments of cost-effectiveness. Failure to honestly face the challenge of treatments that provide insufficient therapeutic value to justify their expense is a principal reason for the burgeoning cost of health care ….. Even if decisions about approval and coverage are made without any explicit consideration of cost-effectiveness, high cost ought to be relevant to the assessment process. When treatments are likely to be very expensive, and their clinical benefits are uncertain based on current knowledge, it becomes all the more important to develop sufficiently rigorous evidence about their risks and benefits."[16] It is noted that reliable estimation of cost-effectiveness requires knowledge of the real-life reduction in HIV incidence that PrEP will achieve, data which do not currently exist.

1.2.4 SELECTION OF STUDY POPULATION AND PREDICTED UPTAKE

The MSM population is the only risk group in the UK in which HIV incidence is sufficiently high to enable the conduct of a large scale HIV prevention trial with clinical endpoints.

Data are available from two recent UK surveys on the likely acceptability of the intervention among MSM in the UK. In the first, conducted in 2011 in over 1,000 men recruited in gay commercial venues in London, less than 2% of MSM reported ever using PrEP, although 58% reported they would be willing to take a pill on a daily basis to prevent HIV infection[17] . The second, conducted through the Sigma panel of 1,800 MSM that participate in a monthly questionnaire, found a similar level of interest in taking PrEP (60%), with a preference for a daily regimen over a peri-coital regimen in a ratio of approximately 2:1[18]

Despite this willingness to take PrEP it is unlikely that large scale provision will be possible in the UK in the forseeable future given its prohibitive expense and competing demands on the health care budget. Gilead had agreed to provide sufficient drug to provide coverage on 500 MSM for up to two years (daily dosing). This provides a window of opportunity to prescribe the drug within a clinical research project, as advocated by BHIVA/BASHH, to inform public health decision making[19] .

1.3 RATIONALE FOR THE PROPOSED STUDY

To fill the evidence gap on the real-life effectivess and cost-effectiveness of PrEP, the ideal would be to conduct a large, pragmatic, open-label trial which mimics how PrEP will be delivered in the routine health setting. An open-label design is essential to assess the potentially crucial influence of risk compensation. The randomisation would be to immediate PrEP or PrEP after 12 months follow-up. The primary outcome would be the acquisition of HIV infection in the first year; the difference between the groups will reflect the net effect of the biological efficacy of PrEP and its impact on behaviour. Cost-effectiveness analyses would be conducted to estimate the cost per infection averted and cost per QALY. We estimated that a trial of approximately 5000 participants would be required to generate a sufficient number of primary endpoints for reliable statistical inference.

There are inherent risks and opportunity costs in carrying out such an ambitious study. The main threats to its feasibility are the acceptability of randomisation and the willingness of otherwise healthy men to regularly attend clinic for follow-up visits. This protocol describes a pilot study, whose principal rationale is to assess the feasibility of conducting the main trial. Its design is identical to that envisaged for the main trial but with fewer participants from a selected number of sites. It will also provide an opportunity to test that the trial procedures are acceptable and sustainable in participating clinics, and to optimise data collection tools.

2 SELECTION OF SITES/CLINICIANS

As this is a pilot, the number of sites will be limited. The sponsor has overall responsibility for site and investigator selection, but the decision to include a site will be taken jointly between MRC CTU and the PHE.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

For the pilot sites:

- 500 or more MSM seen per year for HIV test.
- 50 or more HIV positive participants in current follow-up
- Experience with prescribing Truvada

In addition each clinical trial site and PI must fulfil a set of basic criteria, covering PI qualifications and PI and site responsibilities and minimun resources required during the pilot. These criteria have been agreed by the PROUD Trial Management Group (TMG) and are formalised in the signed Investigator agreement,

All approvals and contracts will be in place and all site required documenation and training completed before MRC CTU will open a site to the protocol.

3 SELECTION OF PARTICIPANTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

3.1 PARTICIPANT INCLUSION CRITERIA

1. Born to male gender, age 18 years or more
2. Previously attended the enrolling clinic on at least one occasion
3. Completed a screen for HIV and STIs
4. HIV negative by a routinely used assay within 4 weeks prior to or on the day of randomisation
5. Reported unprotected anal intercourse (UAI) on more than one occasion within the 90 days prior to randomisation
6. Likely, in the opinion of the volunteer, to have UAI in the next 90 days
7. Willing and able to comply with the visit schedule throughout the follow-up period
8. Willing and able to provide written informed consent

3.2 PARTICIPANT EXCLUSION CRITERIA

1. An acute viral illness that could be due to HIV seroconversion
2. Any contraindications to Truvada according to the current package insert
3. Treatment for hepatitis B infection indicated or ongoing
4. Unlikely, in the opinion of the clinician, to comply with the randomised allocation

3.3 NUMBER OF PARTICIPANTS

500

3.4 CO-ENROLMENT GUIDELINES

Participants cannot enrol in this study more than once.

Participation in other studies may be permitted but this must first be discussed with the MRC CTU.

Participants with confirmed HIV seroconversion (i.e. have fulfilled the primary endpoint) may enrol in other studies.

3.5 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Routine data will provide the information required prior to the randomisation visit.

Written informed consent to enter into the trial and be randomised must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed (see Sample Consent Form - **Appendix II**).

Signed consent forms must be kept by the investigator and documented in the CRF and a copy given to the participant. With consent, a letter should be sent to the general practitioner (GP) informing him/her of the trial and the participant's involvement in it (see **Appendix III**).

4 RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

The randomisation method is described in Section 9.1.

RANDOMISATIONS
Follow the Working Instructions to access the website
Or
Call or fax MRC CTU, Monday to Friday 08:30 to 17:00
Tel: 020 7670 4783 or Fax 020 7670 4659

A manual randomisation process will be set up to cover any instances when the electronic system is not working. This will be detailed in the trial Working Instructions.

4.2 PARTICIPANTS WITH REGULAR SEXUAL PARTNERS

Volunteers whose regular sexual partner is also HIV negative, will be encouraged to enrol together, and the randomisation will be managed to ensure that they are allocated to the same group to minimise the possibility of drug-sharing, and to facilitate mutual support to remain HIV negative.

5 TREATMENT OF PARTICIPANTS

5.1 INTERVENTION

The drug to be used in this trial is Truvada, which is licensed for the treatment of HIV infection in Europe and is widely used. This once daily film-coated tablet contains 245mg of tenofovir disoproxil (TDF) and 200mg of emtricitabine (FTC), both of which are nucleot/side analogue HIV-1 reverse transcriptase inhibitors. It should be taken orally with or without food. The most common adverse reactions in HIV positive individuals taking Truvada as part of combination therapy, occurring in 10% or more, are diarrhoea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams and rash. Further information on Truvada in HIV positive individuals is available in the SmPC.

The investigational medicinal product (IMP), Truvada, will be manufactured and supplied by Gilead Sciences, Inc from clinical trial supply. It will be labelled for clinical trial use with MHRA approved Annex 13 compliant labels. The Truvada supplied is identicial in composition to the commercially supplied Truvada used in HIV clinics across the UK. If circumstances arise that require dispensing of Truvada from normal clinic stocks this is allowed as long as this is documented appropriately.

5.2 TREATMENT PROCEDURES

Those allocated to an IMMEDIATE offer of Truvada on the day of randomisation will continue to have access to the drug for the duration of the study.

Those allocated to a DEFERRED offer will have access to Truvada from 12 months after enrolment.

5.2.1 TREATMENT SCHEDULE

The treatment schedule is a once daily regimen.

5.2.2 DISPENSING

The Principal Investigator will ensure that Truvada is dispensed in accordance with the protocol and local procedures as appropriate. Local Working Instructions will be reviewed at site initiation. Truvada will be stored in a secure, limited access storage area under the specified storage requirements.

The Principal Investigator will ensure that records are maintained showing the receipt, dispensing and destruction of all Truvada. A drug accountability log will be kept to record the identification of the participant to whom the Truvada was given and the date they received drug. The aim will be to provide sufficient to last beyond the next scheduled visit. Any unused Truvada that is returned will also be documented.

It may be necessary for a member of the clinic study team to dispense Truvada at times when a pharmacist is not present. Where this is the case the Principal Investigator will ensure a robust system is in place to capture all required dispensing information.

It may be necessary for drug to be posted to ensure continued supply. When this is the case the Principal Investigator will ensure a robust system is in place to capture the result of the HIV test and urinalysis.

5.2.3 DOSE MODIFICATIONS AND INTERRUPTIONS

Truvada must be interrupted if a participant suffers a serious adverse event that could be a drug reaction, or if their renal function is confirmed to be abnormal, pending further investigation or specialist referral. Renal function will be assessed using either serum creatinine (in the absence of protein supplements) to estimate glomerular filtration rate, or urinary protein to creatinine ratio according to clinic practice.
Truvada can be reintroduced at the discretion of the clinician, following a discussion with the participant. Should the event recur, Truvada must be discontinued.

5.2.4 TREATMENT DISCONTINUATION

Treatment may be stopped early for any of the following reasons:

- HIV infection
- Unacceptable toxicity or adverse event
- Any change in the participant's sexual behaviour or circumstances that justifies the discontinuation of treatment in the clinician's opinion
- On the recommendation of the Trial Steering Committee/termination of the study by the Sponsor

The participant is free to interrupt or discontinue Truvada. They will be discouraged from doing so if they are continuing to have unprotected anal intercourse.

Even if participants are no longer taking Truvada, every attempt should be made to maintain them in the study. Participants who have confirmed HIV infection do not need further HIV tests but should continue, provided they are willing, to complete the sexual behavioural data and have the STI screens. If a participant is withdrawn from follow-up, refer to Section 6.6 - Early Stopping of Follow-up.

5.3 OVERDOSE OF TRIAL MEDICATION

An overdose is defined as

- 2 or more tablets a day for three or more consecutive days OR
- more than 3 tablets in one day

In the event of an overdose, trial treatment will be interrupted and the participant monitored for evidence of renal toxicity until resolution, after which Truvada can be recommenced. The precise frequency of monitoring will be determined by the time that has elapsed since the overdose and whether or not there is any evidence of clinical or laboratory toxicity.

5.4 ACCOUNTABILITY & UNUSED DRUGS

The amount of drug given to the participant, and the date, will be recorded on the case record form as well as the amount of drug unused at each study visit. If there is an excess of residual drug or unexpected shortage, an explanation will be sought by the clinic study team. Actual drug dispensed will be compared to expected drug as part of the central monitoring.

All unused trial drug will be collected at the final visit, which will be 24 months in the majority.

5.5 COMPLIANCE & ADHERENCE

Information will be provided to all participants on Truvada to ensure comprehension of and compliance with the instructions.

Blood will be collected from up to 50 participants allocated to immediate Truvada during their first 6 months of the study.

The various measures of adherence will be compared on an aggregated and, where possible an individual level. The adherence results , as well as the barriers and facilitators to adherence identified during the one to one discussions , will be reviewed by the Trial Steering Committee who will advise on the need for further sampling.

5.6 NON-TRIAL TREATMENT

5.6.1 POST-EXPOSURE PROPHYLAXIS

In the event that a sex act involving anal intercourse is not protected by a condom or Truvada, participants may take post-exposure prophylaxis according to national guidelines [20].

5.6.2 MEDICATIONS THAT ARE NOT RECOMMENDED FOR CONCOMITANT USE

The following medications are not permitted:

- drugs containing emtricitabine or tenofovir disoproxil fumarate including Atripla, Emtriva and Viread
- Adefovir dipoxil
- Lamivudine and other cytidine analogues
- Didanosine
- Cidofovir and other medicinal products that compete for active tubular secretion
- Drugs that reduce renal function

The named medications are not cited in the information sheet as they are not prescribed by General Practitioners, and not available over the counter.

5.6.3 MEDICATIONS TO BE USED WITH CAUTION

Co-administration of Truvada with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, or the co-administered drug.

5.6.4 TREATMENT AFTER HIV SEROCONVERSION

Participants who seroconvert stop Truvada, and will be managed according to national guidelines. They will continue in follow-up see Section 6.5.4 - In the event of seroconversion

5.6.5 TREATMENT FOR ACTIVE REPLICATION OF THE HEPATITIS B VIRUS

If daily Truvada is required to treat active replication of hepatitis B acquired after enrolment, then this will take precedence over the randomised allocation. Participants may continue in follow-up.

6 ASSESSMENTS & FOLLOW-UP PROCEDURES

6.1 PRIOR TO ENROLMENT

Potentially eligible men and transgender women (MSM) will be identified during a routine GUM clinic visit at which they report UAI on more than one occasion in the last 90 days, or recognise that they are eligible when they find out about the trial through outreach activities, community organisations and social media. Staff in participating venues who conduct the pre-HIV test counselling will include information on pre-exposure prophylaxis (PrEP) at the same time as post-exposure prophylaxis (PEP) during the enrolment period. Interested men will be able to download the information sheet from the study website or be provided with this (**Appendix I**). A note will be made of the clinic number on a Pre-Screening Log, if given out by clinic staff.

MSM who are interested will have an opportunity to discuss the information sheet with a member of the study team and to ask for any clarification, either during a visit or on the telephone.

The eligibility check prior to enrolment will be done using the GUM clinic records as MSM attending sexual health clinics in the UK are asked about their sexual behaviour and undergo the following investigations as recommended in the Standards for the management of STIs 2010:

- HIV
- Urethral, rectal and pharyngeal chlamydia (nucleic acid amplification test)
- Urethral, rectal and pharyngeal gonorrhoea (nucleic acid amplification test)
- Syphilis RPR/TPHA

Hepatitis B status is checked at the first visit to a clinic. Immunisation against hepatitis B is promoted and delivered in sexual health clinics, and a response confirmed by checking for hepatitis B surface antibodies.

If there are no reasons for exclusion based on the available information, and the subject wishes to proceed to a trial visit, an appointment will be made and they will be asked to make a note of their sexual behaviour (number of partners and number of episodes of UAI).

6.2 TRIAL SPECIFIC ASSESSMENTS & PROCEDURES

6.2.1 ENROLMENT VISIT (MONTH 0)

6.2.1.A Pre-randomisation procedures

The study staff will ascertain that the information sheet has been fully understood and obtain written informed consent.

There will be a clinic interview, during which baseline demographic, clinical and behavioural data relevant to the eligibility criteria in Section 3.1 and 3.2 will be collected onto a case record form. The behavioural and lifestyle information provided by the individual and available in the clinic record will inform the development of a personalised plan for reducing their risk. A screen for sexually transmitted infections and point of care test for HIV will be performed if these are indicated, according to routine clinic practice. A specimen of urine will be collected for analysis in clinic.

The study staff will explain how to complete the diary and behavioural questionnaires and make sure the questions are clear. Participants will then be asked to complete the short (last 30 days) and a

long (last 90 days, lifestyle and well-being) behavioural questionnaires, in private, and to place these in a sealed envelope and hand them in to study staff in the clinic, to be sent on to MRC CTU for data entry.

6.2.1.B Randomisation procedures

Randomisation should be performed on the day of the enrolment visit while the participant is present in the clinic, and after the eligibility check described above. If there are eligibility queries, these should be clarified with a member of staff at MRC CTU before randomisation.

Randomisation will be performed using a computer-generated randomisation list. Clinic staff will be able to go through the randomisation checks online, or in circumstances when this is not available by phone/fax to the MRC CTU. The participant's trial number, allocation and the date of randomisation will be entered into the Trial Register at the clinic and at the MRC CTU.

6.2.1.C Post-randomisation procedures

All participants will receive support to adhere to the agreed plan to manage their personal risk, and counselling about the importance of adhering to the agreed schedule of visits. All participants will be provided with sufficient monthly questionnaires to last until the next visit, and stamped addressed envelopes if they have selected to complete these manually. A diary will also be provided to record acts of anal intercourse and condom use, different partners, and pill taking when applicable.

A blood sample to confirm HIV status using an antigen/antibody assay should be collected and processed according to the clinic routine. In the event of an indeterminate or positive result, the participant will be recalled for further investigation.

For participants allocated to IMMEDIATE Truvada, the clinician and participant will go through the instructions for use of with Truvada (see Sections 5.2.1 Treatment Schedule). They will be issued with 1 bottle, containing 30 tablets, and the next clinic appointment will be made before they could run out of drug. They will be asked to tick the days they take drug on the diary. The clinician will ensure that the participant understands that

- it takes two weeks before drug has reached a steady level in the tissues and that the drug may be less effective during this period
- their risk may not be reduced if they have missed 3 or more tablets in the week before unprotected anal intercourse
- starting or restarting Truvada when they have caught HIV increases the chance of resistance to Truvada

The clinician will use this information to advise participants on the circumstances in which they should consider post-exposure prophylaxis.

A blood sample will be collected to determine renal function, using serum creatinine to estimate the glomerular filtration rate.

6.2.2 FOLLOW-UP AFTER ONE MONTH ON TRUVADA: MONTH 1 (IMMEDIATE) OR MONTH 13 (DEFERRED)

This assessment, which can take place in the clinic or by telephone, is required for

- **participants randomised to IMMEDIATE Truvada** at month 1
- **participants randomised to DEFERRED Truvada** at month 13.

There will be an interview to see if the participant has experienced any side-effects sufficient to interrupt Truvada, and how they are managing to fit the daily pill into their routine schedule. Urine will be collected for analysis in clinic. In the presence of 1 + of protein in the urine of a participant

who is taking Truvada, and the absence of nitrites which makes a urinary tract infection less likely[21], a blood or urine sample will be collected to check renal function according to clinic routine.

Study staff will check that the short questionnaire and diary are being completed, and if not, seek a reason for this. If the participant is willing a short questionnaire will be completed during the clinic visit, and placed in a sealed envelope to be sent to MRC CTU.

A blood specimen may be collected for the analysis of drug levels.

Unused pills will be recorded on the case record form, and checked directly if the participant bought these to clinic. Sufficient drug will be dispensed to last beyond the next appointment approximately two months later. If the study assessment was conducted on the telephone, the participant will need to attend to collect their drugs.

6.2.3 QUARTERLY CLINIC FOLLOW-UP (MONTHS 3, 6, 9, 12, 15, 18, 21, 24)

These 3 monthly visits are required for **all participants.** During the deferred period, these visits may be conducted on the telephone supported by data collected in another clinic.
There will be an interview to review the participant's personal risk reduction plan and determine whether additional support is required. The clinician will check that the questionnaires and diaries are being completed, and if not, seek a reason for this. If the participant is willing a monthly questionnaire will be completed during the clinic visit, and placed in a sealed envelope to be sent to MRC CTU.

During periods in which the participant is taking Truvada, the clinician will ascertain whether there have been any side-effects sufficient to lead to interruption of drug, and any serious adverse events.

During this visit the following investigations will be performed according to clinic routine:
- HIV test
- Urethral, rectal and pharyngeal swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoea*
- serology for syphilis
- Urinalysis

If these tests have been collected proximal to the due date according to the schedule, either at the enrolling clinic or another clinic, the results already available will be used, and tests only collected on the day of the visit if clinically indicated.

In the presence of 1 + of protein in the urine of a participant who is taking Truvada, and the absence of nitrites which makes a urinary tract infection less likely[21], a blood or urine sample will be collected to check renal function according to clinic routine.

A blood specimen may be collected for the analysis of drug levels.

Unused pills will be recorded on the case record form, and checked directly if the participant bought these to clinic. Sufficient drug will be dispensed to last beyond the next appointment approximately three months later.

6.2.4 MONTHS 6 AND 18 CLINIC FOLLOW-UP

These visits are required for **all participants**.

These visits will be performed as Quarterly Visits, except that the following screen for sexually transmitted infections will be collected regardless of whether or not this would be done routinely

- Urine/urethral swab and rectal swab for *Chlamydia trachomatis* and *Neisseria gonorrhoea*
- serology for syphilis

If these tests have been collected proximal to the due date according to the schedule, either at the enrolling clinic or another clinic, the results already available will be used, and tests only collected on the day of the visit if clinically indicated.

6.2.5 ANNUAL CLINIC FOLLOW-UP AND EXIT (MONTH 12, 24)

These visits are required for **all participants.**

Annual visits will be performed as Quarterly Visits.

In addition participants will be asked to complete a long behaviour and lifestyle questionnaire in private in the clinic, and place this in a sealed envelope to be sent to MRC CTU. The following will also be performed:

- Urine/urethral swab and rectal swab for *Chlamydia trachomatis* and *Neisseria gonorrhoea*
- serology for syphilis
- serum for creatinine

If these tests have been collected proximal to the due date according to the schedule, either at the enrolling clinic or another clinic, the results already available will be used, and tests only collected on the day of the visit if clinically indicated.

A blood sample to confirm HIV status using an antigen/antibody assay should be collected and processed, regardless of whether or not this is indicated according to the clinic routine.

If the participant is willing, an acceptability questionnaire will be completed during the clinic visit, and placed in a sealed envelope to be sent to MRC CTU.

6.3 PROCEDURES FOR ASSESSING HIV SEROCONVERSION

Presumptive HIV infections should be confirmed according to criteria developed by UK Standards for Microbiology Investigations[22]. A repeat sample should be obtained and reactivity confirmed by a sensitive HIV RNA assay.

6.4 PROCEDURES FOR ASSESSING SAFETY

Participants will be asked one month after starting Truvada and quarterly whether they have had any admissions to hospital, or suffered any significant illnesses that stopped them undertaking their usual daily activities and required medical intervention. A clinical member of the team will determine whether or not an illness that interfered with usual daily activity meets the definitions for Serious Adverse Event (SAE) provided in Table 7.1: Definitions. SAEs should be reported to MRC CTU within 24 hours of the investigator becoming aware of this. Participants will also be asked whether they have had any side-effects sufficient to interrupt or stop their Truvada.

Glomerular filtration rate will be estimated at baseline, 12 and 24 months. Urinalysis for protein will be assessed at these and interim visits and the presence of 1+ or greater protein that cannot

otherwise explained will trigger an additional investigation according to routine clinic practice for patients taking Truvada (either a further creatinine measurement to estimate glomerular filtration rate, or urinary protein:creatinine ratio). In the event that that estimated glomerular filtration rate (eGFR) is less than 50mL/min, or the ratio of protein: creatinine (UPC) greater than 20, the participant will be recalled, their dietary supplements and pill taking reviewed, and a repeat test performed in the absence of any protein supplements. If the eGFR is confirmed to be < 50 mL/min or the UPC > 20, then Truvada will be interrupted pending further investigation and/or referral for specialist opinion. In the event that this leads to discontinuation of Truvada, this meets the definition of 'another important medical condition' as described in Table 7.1: Definitions, and should be reported to MRC CTU within 24 hours of the investigator becoming aware of the event.

6.5 OTHER ASSESSMENTS

6.5.1 SELF-REPORTED BEHAVIOUR

Self-reported sexual and adherence behaviours will be collected in the daily diary and short and long questionnaires.

The **diary** will be a simple record for noting acts of anal intercourse, whether or not a condom was used throughout, and whether or not a pill was taken each day. The facility to enter this information directly into a database held at MRC CTU will be available for participants that have access to the web, and wish to do this. Data will be identifable to CTU staff by trial number and date of birth only. Participants that record the diary manually will be asked to post these to MRC CTU or to bring them to their next clinic visit.

Participants will be asked to summarise their sexual and adherence behaviours in the **short (last 30 days) questionnaire** each month including baseline, in private. As with the diaries these can be entered electronically by the participant or manually and placed in a sealed envelope.

A **long (last 90 days) questionnaire** that includes lifestyle and well-being questions as well as sexual behaviour will be completed during the clinic visits at baseline, 12 and 24 months in private.

In depth interviews (one to one discussions) will be conducted in a subset of participants (approximately 50 in the first instance) in clinics with access to staff trained in the technique who are independent of the clinic team. Selection will be directed by MRC CTU together with Professor Horne having reviewed the quantitative data collated from self-report and dispensing returns together with biological data such as drug levels (if available) and STIs. Participants will be selected on the basis that they are representative of various combinations of high/low risk and adherence behaviours. An individual trained in IDI techniques will be provided with a summary of the group data and the pattern of behaviour that the participant being interviewed has followed, although not the specific quantitative detail. They will interview men about sexual and adherence behaviours and PrEP acceptability using the one to one discussion guide (see **Appendix VI)**). The one to one discussion will be explained to the participants using the Supplementary Participant Information Sheet (Appendix VII). Written informed consent will be collected prior to participation using the Supplementary Informed Consent Form (Appendix VIII). One to one discussions may be facilitated in person, over the phone or via virtual networks (such as secure web based discussion forums).

6.5.2 SEXUAL BEHAVIOUR

The number of partners (any and new) with whom the participant had anal sex in the last 30 (short) or 90 (long) days, as well as more specific questions about the most recent episode(s) of anal intercourse will be collected in the questionnaires.

The number of acts of anal intercourse, and whether or not a condom was used will be recorded in the diary.

Markers of unprotected intercourse such as urethral or rectal gonorrhoea, urethral or rectal chlamydia, early syphilis will be collected every 6 months.

6.5.3 ADHERENCE BEHAVIOUR

Doses taken and missed in relation to unprotected anal intercourse will be provided by the diary.

Participants' perception of their adherence and missed doses in the weeks before and after the last anal sex act without a condom will be recorded in the short questionnaire.

Dispensed drug and unused drug will be recorded on the case record form.

Plasma and/or peripheral blood mononuclear cells will be collected from a sub-set of participants on the IMMEDIATE arm (up to 50 participants). Further samples at additional time points in a larger number of participants may be recommended by the Trial Steering Committee (TSC).

Approximately 100 participants at clinics with this resource will be invited to use a Medication Event Monitoring System (MEMS) cap to record the date and time when they open their pill bottles during the study.

6.5.4 IN THE EVENT OF SEROCONVERSION

In the event of a seroconversion, information about all sex acts since the previous negative result, number of new partners, characteristics of partners, and adherence to condoms will be collected as is routine practice. Information regarding adherence to Truvada will also be elicited, if applicable.

Participants should continue, provided they are willing, to complete the short and long questionnaires and have the STI screens, although these can be collected at their routine HIV clinic visits if more convenient.

In accordance with national guidelines for newly diagnosed individuals, a genotypic drug resistance test should be performed to identify mutations which may have been transmitted from the infecting partner or acquired as a result of exposure to Truvada. This test should be performed on the earliest possible sample after seroconversion and a copy of the result sent to MRC CTU for data entry.

6.5.5 ACCEPTABILITY

Men's attitudes regarding the acceptability of the study and PrEP will be collected in the **acceptability questionnaires** at or after the 12 and 24 month follow-up visits. After reviewing the quantitative data, a guide on acceptability will be developed for group discussions.

Group discussions will be conducted with a subset of participants who have experienced PrEP (approximately 10 group discussions with approximately 8 participants per group by staff trained in the technique who are independent of the clinic team). Some participants will be purposefully selected for participation in group discussions and others will be invited on an ad hoc basis. Selection will be directed by MRC CTU together with Professor Horne having reviewed the quantitative data collated from self-reported acceptablity and adherence questionnaires. The group discussion will be explained to participants using the Supplementary Participant Information Sheet (**SPIS Appendix VII)**. Written informed consent will be collected prior to participation using the Supplementary

Informed Consent Form (**Appendix VIII)**. Group discussions may be facilitated in person or via virtual networks such as secure web based discussion forums.

The acceptability questions focusing on PrEP will be informed by the findings of the group discussions and may result in modifications to the questionnaires.

Field notes will be collected about study acceptability during the course of the study by individuals trained in ethnographic participant observation techniques, as described by this group previously[2,3]. Typically, these will note conversations observed or initiated by the recorder with and between participants, non-participants, clinic staff and community workers. The notes will be anonymous and recorded using the field notes template (**Appendix IX**).

6.6 EARLY STOPPING OF FOLLOW-UP

If a participant chooses to discontinue their trial treatment, they should be encouraged to continue in follow-up; if they do not wish to remain on trial follow-up, every effort will be made to establish an acceptable means to ascertain their HIV status at 12 and 24 months from enrolment; however, their final decision must be respected and the participant will be withdrawn from the trial completely should this be their wish, and the appropriate case record form completed.

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

Participants who stop trial follow-up early will not be replaced.

6.7 PARTICIPANT TRANSFERS

If a participant moves from the area, every effort should be made for the participant to continue on the allocated arm, either by transfer to another site that is taking part in the trial, or by collecting the routine HIV/STI results through a non-participating clinic. In the event of a transfer, a copy of their CRFs should be provided to the new site and the participant will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the participant; until this has been done, responsibility for the participant lies with the original site.

6.8 LOSS TO FOLLOW-UP

Participants who fail to attend will be contacted by telephone and/or email, according to the permissions granted at routine clinic registration.

Participants will not be considered lost to follow-up until the trial has ended, unless they have left the UK with no plans to return, and with no means to ascertain HIV status. Efforts will be made throughout the trial to retain participants, with particular efforts in relation to visits at months 12 and 24.

Interviewers may invite participants who chose to leave the study, to take part in a one to one discussion in order to understand their decision to stop participating in part or all of the study. The standard one to one interview guide would be used in these circumstances as well as the supplementary participant information sheet and consent form.

7 SAFETY REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. Section 7.1 - Definitions lists definitions, Section 7.3 - Investigator Responsibilities gives details of the investigator responsibilities and Section 7.4 - MRC CTU Responsibilities provides information on MRC CTU responsibilities.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial protocol. These definitions are given in Table 7.1: Definitions.

TABLE 7.1: DEFINITIONS

TABLE	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: ▪ Results in death ▪ Is life-threatening* ▪ Requires hospitalisation or prolongation of existing hospitalisation** ▪ Results in persistent or significant disability or incapacity ▪ Consists of a congenital anomaly or birth defect ▪ Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a medical event that leads to the permanent discontinuation of Truvada; an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 MEDICINAL PRODUCTS

The IMP in this study is Truvada.

Adverse reactions include any untoward or unintended response to all drugs. Reactions to an IMP must be reported appropriately.

7.1.2 EXEMPTED ADVERSE EVENTS

Adverse Events include:

- Any event that leads to the interruption or discontinuation of Truvada, regardless of relationship
- Any event the Investigator considers important to the safety evaluation of Truvada, including bone fractures, renal events and unexplained abdominal pain or headaches
- Overdose of Truvada without signs or symptoms

and any Serious Adverse Event that is:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected after trial drug administration (even though it may have been present prior to enrolment)
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, eg, elective cosmetic surgery, social admissions

7.1.3 OTHER STUDY-SPECIFIC REQUIREMENTS

Blood will be collected for creatinine at baseline, 12 and 24 months follow-up.

Urine will be tested at each clinic visit for the presence of protein according to routine clinic practices. Creatinine will be checked if protein ≥ 1+ on dipstick, in order to estimate glomerular fitration rate, or a urine specimen sent for analysis of urinary protein:creatinne ratio (see Section 6.4).

Weight will be checked at each visit.

7.2 OTHER NOTABLE EVENTS

Other notable events include the sexually transmitted infections captured through laboratory screening.

7.2.1 PREGNANCY

The trial will only recruit individuals born to the male gender.

7.3 INVESTIGATOR RESPONSIBILITIES

SAEs and SARs should be notified to the MRC CTU within 24 hours of the investigator becoming aware of the event.

7.3.1 INVESTIGATOR ASSESSMENT

7.3.1.A Seriousness

The investigator should determine at each visit, or telephone contact where this substitutes for a visit, whether or not a Serious Adverse Event has occurred since the previous record, using the definition given in Table 7.1: Definitions.

If the event is serious, then an SAE Form must be completed and the MRC CTU notified within 24 hours.

7.3.1.B Severity or Grading of Serious Adverse Events

The severity of all SAEs and/or SARs in this trial should be graded using the toxicity gradings in **Appendix IV**.

7.3.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 7.2: Assigning Type of SAE Through Causality. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

TABLE 7.2: ASSIGNING TYPE OF SAE THROUGH CAUSALITY

RELATIONSHIP	DESCRIPTION	SAE TYPE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment and drug is interrupted, refer to Section 5.2.3 - Dose Modifications, Interruptions & Discontinuations.

7.3.1.D Expectedness

If there is at least a possible involvement of the trial treatment, the investigator must assess the expectedness of the event. An unexpected adverse reaction is one not previously reported in the current Summary of Product Characteristics (SPC) or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in Table 7.1: Definitions. Please see **Appendix V** for a list of expected toxicities associated with the drug being used in this trial. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.3.1.E Notification

The MRC CTU should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.3.2 NOTIFICATION PROCEDURE

1. The SAE Form must be completed by the investigator (the consultant named on the Signature List and Delegation of Responsibilities Log who is responsible for the participant's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed by a member of the site trial team, signed and faxed or emailed as appropriate. The responsible investigator should subsequently check the SAE Form, make changes as appropriate, sign and then re-fax to the MRC CTU or email as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting and why the event is considered serious.

2. The SAE Form must be sent by fax to the MRC CTU
   Fax: 020 7670 4659 or email information to **PROUD@ctu.mrc.ac.uk**

3. Follow-up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further SAE Form, indicated as 'Follow-up' should be completed and faxed to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be deleted from any test results.

4. Staff should follow their institution's procedure for local notification requirements.

SAE REPORTING
Within 24 hours of becoming aware of an SAE, please fax a completed SAE form to the MRC CTU on:
Fax: 020 7670 4659 or email information to **PROUD@ctu.mrc.ac.uk**

7.4 MRC CTU RESPONSIBILITIES

Medically-qualified staff at the MRC CTU and/or a medically-qualified delegate will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the MHRA, research ethics committees and Gilead Sciences, Inc as appropriate. Fatal and life-threatening SUSARs must be reported to the MHRA within 7 days of the MRC CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

The MRC CTU, as Sponsor, will submit Development Safety Update Reports (DSURs) to the MHRA, Ethics Committees and Gilead Sciences, Inc.

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations will be reviewed throughout the study based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. The risk assessment will be used to devolp and amend the trial Quality Management Plan.

There are risks already identified which have been addressed within the protocol and trial procedures. Participants may believe themselves completely protected by Truvada and take risks they would not otherwise have done. Determining the extent of this is an important outcome measure in the pilot. Investigators and other members of the clinic study team will help participants to consider Truvada as one component of their overall risk reduction strategy, they will emphasise the limitations of Truvada and the importance of adherence. Participants will need to provide sensitive information on a regular basis, however the questions do not differ substantially from those routinely asked in GUM clinics and all information will be held in compliance with the Data Protection Act, and linked using only their trial number at MRC CTU, and GUM clinic numbers at PHE. Date of birth and soundex will be used to cross check the new HIV diagnoses database at PHE 3..

Although there is a risk of mild to moderate side effects when taking Truvada the more serious side effects of renal tubular dysfunction and lactic acidosis have not been reported in HIV negative populations. There is a small risk of resistance arising from continued treatment with Truvada following seroconversion.

8.2 CENTRAL MONITORING AT MRC CTU

MRC CTU staff will review the reports generated from the database that list inconsistencies and missing data with regard to

- Eligibility criteria
- Follow-up schedule
- Trial specific procedures including collection of outcome data

Other essential trial issues, events and outputs will be detailed in the Monitoring and Quality Management Plan that is based on the trial-specific Risk Assessment.

8.3 ON-SITE MONITORING

The frequency, type and intensity of routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring and Quality Management Plan.

8.3.1 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

8.3.2 CONFIDENTIALITY

We plan to follow the principles of the UK Data Protection Act.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Randomisation will be performed centrally at the MRC CTU using a computer algorithm based on random permuted blocks stratified by site.

9.2 OUTCOME MEASURES

9.2.1 MAIN OUTCOME MEASURES

Time to accrual of 500 participants
Retention at 12 and 24 months from randomisation

9.2.2 OTHER OUTCOME MEASURES

- HIV infections acquired between trial entry and 12 months, and between 12 and 24 months

- Safety
  - Serious Adverse Reactions attributable to Truvada
  - Any adverse event leading to interruption or discontinuation of Truvada
  - Renal function estimated using serum creatinine at 12 months
  - Presence of viral resistance mutations likely to have been selected by Truvada (K65R, M184V) in participants who acquire HIV infection.

- Adherence:
  - Proportion of doses taken estimated from self-report
  - Proportion of days covered according to dispensing records for the daily schedule
  - Presence of drug as expected in a subset of selected participants

- Risk Compensation:
  - Number of sexual partners with whom had UAI, UIAI and URAI (unprotected defined as without a condom) between trial entry and month 12 and month 12 to month 24
  - Number of acts of AI, protected and unprotected by a condom, between trial entry and month 12 and month 12 to 24
  - Proportion of acts of AI protected by either condom, PrEP or both between trial entry and month 12 and month 12 to 24
  - Sexually transmitted infection (STIs) acquired between trial entry and month 12
  - Sexually transmitted infection (STIs) acquired between month 12 and month 24

- Other:
  - Facilitators and barriers to adherence to a personal risk reduction plan in a subset of selected participants

9.3 SAMPLE SIZE

The target of 500 participants (250 per treatment arm) for the pilot is a pragmatic choice, to guide whether 5000 participants can be enrolled over 2 years, as this is the anticipated target for an

adequately powered effectiveness trial in this population. It is also informed by the number of participants clinics have agreed to recruit to the pilot.

9.4 INTERIM MONITORING & ANALYSES

The Trial Steering Committee for the PROUD Pilot study agreed that it was appropriate for key study outcomes to be monitored by an independent individual expert rather than a formally constituted IDMC. Key study outcomes will be monitored by the Independent Data Monitor. Their role will be dictated in the Terms of Reference for the independent monitoring of the PROUD Pilot study.

9.5 ANALYSIS PLAN

The analyses will be described in detail in a full Statistical Analysis Plan. The primary aim of the pilot is to demonstrate the feasibility of an adequately powered trial. The rate of recruitment will be assessed by individual centre. Participant retention at 12 months, in particular in the deferred arm, will be compared with the assumption used in the sample size calculation for the full trial. Secondary analyses will compare sexual behaviour between the two groups as allocated, censoring patients at either HIV infection or, for participants with incomplete follow-up, at their last negative HIV test.

10 ANCILLARY STUDIES

Although the pharmacokinetic analyses, MEMS caps, one to one and group discussions will only be conducted on a sub-set of participants, these are considered integral to the pilot study rather than ancillary.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The pilot complies with the principles of the Declaration of Helsinki (2008).

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

11.1.2 SITE COMPLIANCE

All participating sites are in the UK and will therefore comply with the above.

An agreement will be in place between the site and the MRC CTU, setting out respective roles and responsibilities (see Section 13 - Finance).

The site will inform the Trials Unit as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the pilot, or
- The scientific value of the pilot

11.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for at least 2 years after the end of the pilot. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, and other relevant parties, with suitable notice. The data may be subject to an inspection by the competent authorities.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

There is strong evidence from placebo-controlled trials reported to date that Truvada is biologically effective in reducing the risk of the acquisition of HIV infection (see Section 1.2), and, in the light of this evidence, it has been argued that further placebo-controlled trials would not be ethical[24]. However, as discussed in Section 1.3 it is not known whether an increase in high-risk sexual behaviour may outweigh the protective effects of PrEP, thus rendering the intervention ineffective at an individual and population level. Thus, there remains equipoise around the use of PrEP in a "real life" context. Representatives from the gay community in the UK have been closely involved in developing the study concept. Further, accumulating data in the pilot will be monitored by an Independent Data Monitoring Committee (Section 14.3), who can recommend closure of the pilot if there is early evidence of harm.

There is a risk that PrEP will not be available at the end of the pilot to participants, if funding still has not been identified to support access through the public health programme. This will be made clear in the informed consent process.

11.2.2 ETHICAL APPROVALS

Before initiation of the pilot at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to the ethics committee for approval. Any further amendments will be submitted and approved by the same ethics committee.

The rights of the participant to refuse to participate in the pilot without giving a reason must be respected. The participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his future management.

11.3 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site. A copy of the local R&D approval and of the Participant Information Sheet (PIS) and Consent Form (CF) on local headed paper should be forwarded to the MRC CTU before participants are entered.

12 INDEMNITY

The MRC is the sponsor. The MRC is not insured but it has indemnity arrangements in place such that public funding is provided to meet claims.

The MRC accepts that it might face claims for damages in cases where:

- it sponsors the research;

and

- the MRC, or any of its employees, or any person formally acting with the MRC's authority, has been negligent or has failed to adhere to the relevant guidelines/guidance, legislation or procedure on good practice in relation to medical research;

and

- that negligence or failure to adhere to legislation, etc has caused or has materially contributed to the personal injury suffered by the individual making the claim.

The MRC also sets out below instances where it might make ex gratia payments without any admission of liability.

- In relation to instances where the MRC is the sponsor of research, the MRC may consider making an ex gratia payment when a significant adverse reaction in the form of a personal injury has occurred which is likely to have been caused by, or materially contributed to, by participation in a research study. In deciding whether to make such a payment, the MRC will not require the research participant to demonstrate that the personal injury has been caused by a breach of any duty of care that may have been owed by the MRC.

13 FINANCE

The Pilot which will enrol up to 500 men, is funded through a competitively acquired Investigator-led award from Gilead Sciences, supplemented by MRC CTU and PHE (formerly HPA) core funds. CLRN support will also be available, provided that the network adopts the Pilot in the portfolio.

Gilead Sciences will provide MRC with Truvada free of charge. MRC will control distribution of the drug, and a small grant to participating sites based on milestones.

Routine clinical services will be reimbursed through the usual scheme.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the pilot And these are detailed below.

14.1 TRIAL MANAGEMENT GROUP (TMG)

A TMG will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU). The TMG will be responsible for the day-to-day running and management of the pilot. It will convene at least once a month, and more frequently when required. The full details can be found in the TMG Charter.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the joint Chairs (clinical and community). The role of the TSC is to provide overall supervision for the pilot and provide advice to the sponsor through the independent Chairs. The ultimate decision regarding the feasibility of the trial, lies with the TSC. Further details of TSC functioning are presented in the TSC Charter. Gilead Sciences will be represented on the TSC.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The Trial Steering Committee for the PROUD Pilot study agreed that it was appropriate for key study outcomes to be monitored by an independent individual expert rather than a formally constituted IDMC. Key study outcomes will be monitored by the Independent Data Monitor. Their role will be dictated in the IDMC Terms of Reference

14.4 ROLE OF STUDY SPONSOR

The Sponsor is responsible for expedited reporting of serious adverse events and breaches according to the guidance and timelines set out in national legislation, and for the preparation of DSURs that include all Suspected Unexpected Serious Adverse Reactions. The Sponsor is also responsible for notifying the authorities within 90 days of the final participant visit that the pilot has closed, or within 15 days of a decision to close the pilot prematurely, and for provision of a summary report within one year of closure. These responsibilities will be carried out by the MRC CTU.

14.5 PARTICIPANT INVOLVEMENT

In line with the MRC Clinical Trials Unit Patient and Public Involvement (PPI) Policy and international guidelines, participants will be invited to comment on the running of the pilot study and in planning subsequent studies. Participant involvement meetings will be facilitated in person and via secure web-based discussion forums

15 PUBLICATION

The preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for presentation, oral or written, to a learned society or symposium will be discussed on the Trial Management Group calls.

The TSC will be notified of this intention through the Chief Investigator and the TMG notes.

Every effort will be made to allow the Trial Steering Committee and other relevant parties involved in the pilot and named in the clinical trial agreements prepared by the Sponsor, 30 days to comment before any results are submitted. This timeline will be strictly observed for peer-review journals, but may be more difficult to adhere to for conference presentations. Approval from the Chief Investigator, the Trial Statistician, representatives from the clinical site Principal Investigators and a representative from Gilead Sciences must be obtained as a minimum before submission to a conference.

Authorship should reflect work done by the investigators and other personnel involved in the analysis and interpretation of the data, in accordance with generally recognised principles of scientific collaboration.

16 PROTOCOL AMENDMENTS

After the protocol has been approved by the REC and the MHRA, no changes may be made without the documented agreement of both the investigators and the Sponsor.

Version 1.1 10-September-2012

CTA & REC numbers added

At request of MHRA:

Section 7.1.2 updated to include bone fractures, and events in HIV negative study populations which were reported by 2% or more of Truvada subjects, and more frequently than placebo recipients.

Deleted from "adverse events do not include"

- An event that does not meet the definition of Serious as defined in Table 7.1: Definitions other than events that lead to the interruption or discontinuation of Truvada

Weight will be checked at each visit.

Version 1.2 05 Aug-2013

At the request of the Investigators:

The updates are to provide recent relevant results (section 1), clarify that the recruitment strategies will be broader than clinics and that follow-up data can be collected within the GUM clinic network as this is more convenient for the participants (section 6), and to provide additional detail on the quantitative and qualitative data collection (section 6). Section 5 has been updated as it may be necessary to post drugs. In Section 6 we provide further detail about one to one and group discussions and have included the related PIS, IC and one to one interview guide. The Investigators wish to clarify that discontinuation of Truvada is only a Serious Adverse Event when the clinician decides they would never prescribe Truvada again (section 7), and that soundex will be needed in addition to date of birth to cross-check the PHE database for HIV endpoints (section 8). In line with MRC CTU and international guidelines, we have expanded the oversight to include Participant Involvement meetings, and clarified the independent data monitoring that we have implemented on the recommendation of the Trial Steering Committee (section 14).

The version number and date have been updated on the cover page and in the header.
The HPA has now become the PHE and logo & details updated accordingly
ISRCTN number has been added
Dr Mitzy Gafos, the Social Science Lead, has been added to the MRC CTU staff on pii
Contact details, the contents and abbreviations have been updated piii, and p 11, 12,13.

Additional detail has been added

- with respect to the trials that have now reported in section 1.2 p16-17 and section 17 references p53
- to describe the outreach recruitment of participants and the intention to use data collected throughout the GUM network in support of study visits to assess eligibility and follow-up in sections 6.1 p27, 6.2.3, 6.2.4, 6.2.5 p29-30.

- to describe the acceptability questionnaires, one to one and group discussions, MEMS caps and field notes in sections 6.5.1 p31, 6.8 p34 and in the new section 6.5.5 p32-33.

A new section 6.5.5 Acceptability has been added. As well as describing the purpose and relationship between the questionnaires and the group discussion, there is a description of the field notes to be collected in a range of venues p33.

Clarification that:

- the TSC will review all the adherence data available and advise on further sampling for pharmacokinetic analyses section 5.5, p26
- discontinuation of Truvada due to a medical event must be permanent to qualify as a Serious Adverse Event serction 7, p36.
- An Independent Data Monitor has been appointed in place of an IDMC.

Addition of a new section 14.5 under Oversight & Trial Committees, to describe the participant oversight in line with MRC CTU and international guidelines p49.

Version 1.2.1 14 October 2013

The version number and date have been updated on the cover page and in the header.

The trial schema and trial assessment table have been revised to indicate acceptability questionnaire to be completed at months 12 and 24.
The acceptability questionnaires description, in sections 6.2.4 moved to section.6.2.5

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