An HIV Self-testing Public Health Intervention

Part of a NIHR programme grant for Applied Research: PANTHEON (Prevention And Testing for HIV: Economics and Outcomes of Novel Approaches)

PROTOCOL
Version: 4.0
Date: 17-Dec-2019

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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 5.0. The MRC CTU at UCL endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the SELPHI trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients/participants into it.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) and the UK Data Protection Act (MRC CTU at UCL DPA number: Z6364106).

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the SELPHI trial to the MRC CTU at UCL. Queries relating to UCL sponsorship of this trial should be addressed to Max Parmar, MRC CTU at UCL Director, MRC CTU at UCL, 90 High Holborn 2nd Floor London WC1V 6LJ or via the trial team.

FUNDING

SELPHI is funded as part of an NIHR programme grant for Applied Research No: RP-PG-1212-20006 - A comprehensive assessment of the cost-effectiveness of HIV prevention and testing strategies, including HIV self-testing, among men who have sex with men (MSM) in the UK (PANTHEON).

AUTHORISATIONS AND APPROVALS

This trial was approved by UCL Research Ethics Committee.

TRIAL REGISTRATION

Registration with the ISRCTN Clinical Trials Register, is ISRCTN20312003.

TRIAL ADMINISTRATION

Please direct all queries to the Trial Manager at the coordinating site in the first instance; clinical queries will be passed to the Chief Investigator as appropriate.

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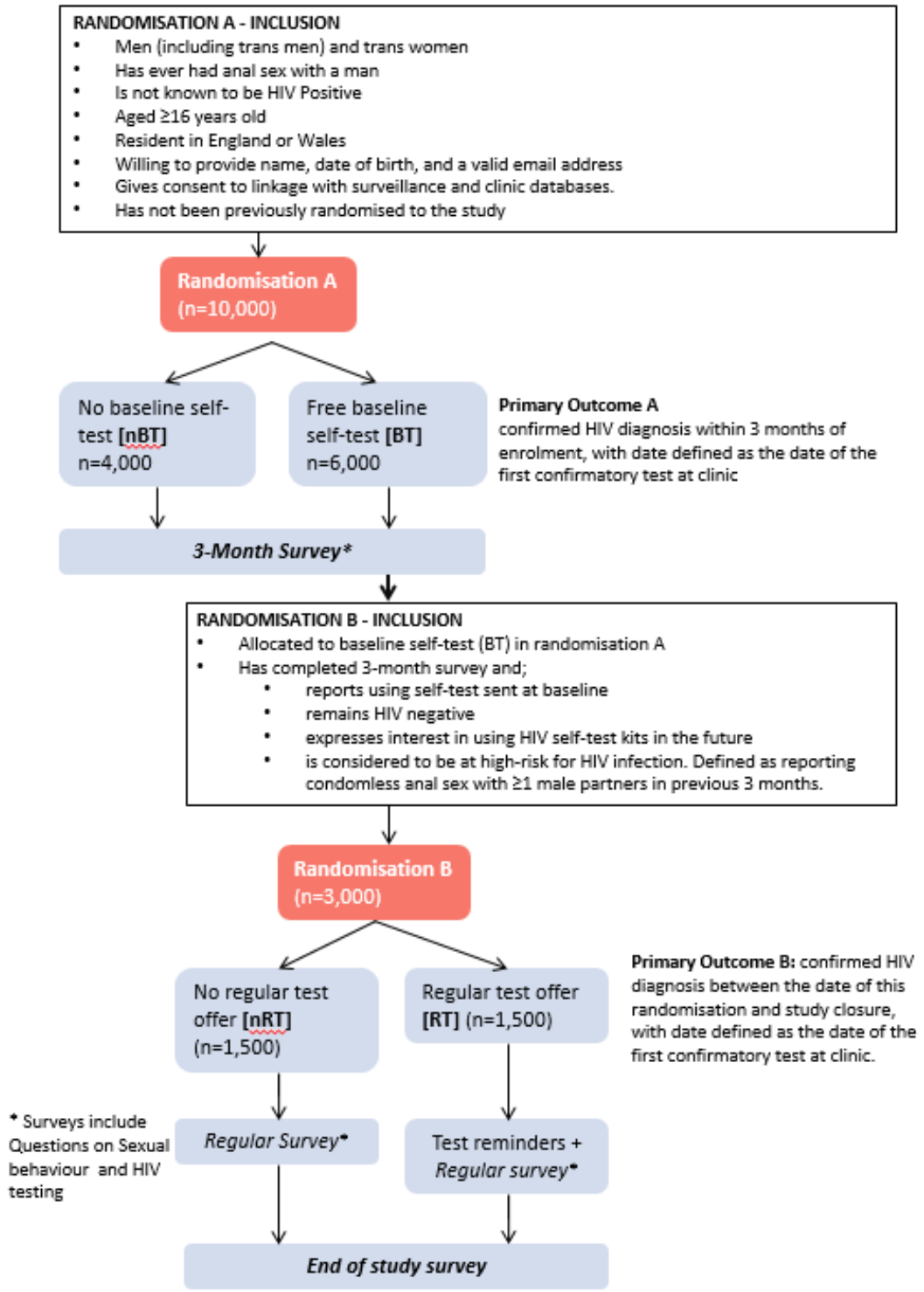
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM (or Short Title of Trial)	SELPHI
Long Title of Trial	An HIV Self-testing Public Health Intervention
Version	4.0
Date	17-Dec-2019
Study Design	Parallel group, randomised trial with two phased randomisations to free HIV self-testing kits
Number and Type of Participants to be Studied	10,000 HIV-negative men (including trans men) and trans women who have sex with men.
Setting	Internet-based study with eligible participants living in England or Wales
Interventions to be Compared	At enrolment, the offer of a single, free baseline HIV self-test (**BT**) versus no free baseline HIV self-test (**nBT**) At 3 months, amongst those from the BT group who are eligible, regular offers of free self-tests every 3 months (**RT**) versus no offer of free self-tests (**nRT**).
Study Question	To assess if access to self-testing for HIV offered at no cost via the internet leads to increased rates of HIV diagnosis compared with standard-of-care. Specifically: ▪ Does the offer of a single, free self-test increase the likelihood that individuals with undiagnosed-HIV at study enrolment will be diagnosed and linked to clinical care, compared with current standard-of-care for HIV testing? ▪ Amongst individuals without HIV at study enrolment, does the offer of regular free self-tests increase the frequency of testing and reduce the average interval between the acquisition of a new HIV infection and linkage to clinical care?
Primary Outcome Measure(s)	The primary outcomes for each randomisation are as follows: ▪ Randomisation A is a confirmed HIV diagnosis within 3 months of enrolment. ▪ Randomisation B is time (from the time of randomization when they are HIV negative) to confirmed diagnosed HIV, measured from the date of this randomisation. Data will be censored on the date of study closure.
Secondary Outcome Measure(s)	▪ The overall frequency of HIV testing irrespective of testing modality i.e. where and how individuals test ▪ Frequency of STI screening ▪ Markers of the recently of infection at the time of HIV diagnosis, where available e.g. CD4 count, antibody avidity assays. ▪ Frequency of condomless sex (self-reported) ▪ New STI diagnosis
Randomisation	Unstratified, with different allocation ratios depending on specific randomisation.
Duration	Surveys continue for a minimum of 18 months after last enrolment, but cross-checks against the national database will continue through to the end of 2021.
Sponsor	UCL
Funder	NIHR
Chief Investigators	Professor Sheena McCormack & Professor Alison Rodger
MRC CTU at UCL Project Leader	Professor Sheena McCormack

TRIAL SCHEMA

Figure 1 Trial Schema



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ABBREVIATIONS

ABBREVIATION	EXPANSION
AIDS	Acquired Immune Deficiency Syndrome
APR	Annual Progress Report
ART	Anti-retroviral Therapy
BT	Baseline Test. The intervention group for randomisation A.
CAB	Community Advisory Board
CE-marked	Conformité Européene" which literally means "European Conformity
CI	Chief Investigator
CI	Confidence interval
CTU	Clinical Trials Unit
DMP	Data Management Plan
DPA	(UK) Data Protection Act
EMIS-II	The European MSM Internet Survey
GCP	Good Clinical Practice
GP	General Practitioner
GUMCAD v3	Genitourinary medicine clinic activity dataset
HARS	HIV and AIDS reporting section
HIV	Human Immunodeficiency Virus
HIVSS	HIV Self-Sampling
HIVST	HIV Self-test
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISO/IEC	International Organization for Standardization/International Electrotechnical Commission
ISRCTN	International Standard Randomised Controlled Trial Number
IVD	In-vitro testing Device
LHSTM	London School of Hygiene and Tropical Medicine
MSM	Men who have sex with men
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London
nBT	No Baseline Test. The control group for randomisation A.
nRT	No Regular Tests. The control group for randomisation B.

ABBREVIATION	EXPANSION
NHS	National Health Service
NRES	National Research Ethics Service
PANTHEON	Prevention And Testing for HIV: Economics and Outcomes of Novel Approaches
PEP	Post-exposure Prophylaxis
PHE	Public Health England
PrEP	Pre-exposure Prophylaxis
PSC	Programme Steering Committee
PY	Person-years
QA	Quality Assurance
QC	Quality Control
QMAG	Quality Management Advisory Board
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee
RT	Regular Tests. The intervention group for randomisation B.
SD	Standard deviation
SELPHI	An HIV Self-Testing Public Health Intervention
SOP	Standard operating procedure
SSL	Secure Sockets Layer
STI	Sexually Transmitted Infection
TCP/IP	Transmission Control Protocol/ Internet Protocol
TGW	Transgender women
THT	Terrence Higgins Trust
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
UKCRN	UK Clinical Research Network (now the NIHR CRN)
URL	Uniform Resource Locator

1 BACKGROUND

1.1 HIV TRANSMISSION, LOW RATES OF TESTING & LATE DIAGNOSIS IN MSM AND TGW THE UK

The HIV epidemic in men who have sex with men (MSM) continues to grow with around 3,000 new infections estimated to occur in the UK per year despite prevention efforts [1,2]. This is likely due to modest increases in condomless anal intercourse among MSM since the late-1990s, coincident with realisation of the long term health benefits of ART[3-5] and as HIV infection was seen as less of a threat to health[6]. This is also against a background of HIV-positive people being shown to be dramatically less infectious if they are using effective ART[6].

There are no reliable data on HIV prevalence or incidence among trans women or men in the UK as historically gender identity has only been captured as male or female, although Public Health England are currently revising the gender identify categorisation. Meta-analysis of studies in USA, six Asia-Pacific, five Latin American, and three European countries suggests a 49% higher likelihood of becoming HIV positive for transgender women, in comparison with all other populations of reproductive age; this equates to an estimated 19% global prevalence of HIV in trans women[7].

HIV testing uptake and frequency remains sub-optimal in the UK, with recent community surveys suggesting that approximately 25% of MSM have never tested for HIV, between 50-60% have not tested in the previous year and less than a quarter of MSM at higher risk of HIV infection are testing at the recommended frequency of every three months[8,9]. Approximately 25% of HIV-positive MSM are unaware of their HIV infection and disproportionately contribute to onward transmission (60% to 80% of new HIV transmissions come from people not diagnosed)[10] as well as presenting late with consequent increased risk of death. An estimated 14% of diagnoses made in MSM in the UK are diagnosed late in the course of their HIV infection with advanced immunodeficiency[11]. Again there are no reliable data on HIV testing among trans women or men but clinical reports from cliniQ, a trans-led service in London, indicate a disproportion number of transgender women presenting in clinic with AIDS defining health conditions. Increasing HIV testing and reducing late diagnosis is therefore a UK public health priority.

1.2 HIV TESTING

Whilst there is research describing low HIV testing and repeat testing rates among UK MSM[10], there is little evidence about effective and innovative interventions to expand and increase testing options outside traditional clinical settings. Currently most HIV tests are conducted in genito-urinary medicine (GUM) clinics. Recent initiatives offer HIV self-sampling which involves an individual taking their own test sample (blood or saliva) which they post back to the relevant laboratory for testing and are subsequently contacted with the result. Since November 2015, England and Wales have a national HIV self-sampling (HIVSS) service offering blood based self-sampling for HIV[12].

A further approach is to offer HIV self-testing (HIVST) where the person not only takes the sample but also processes it themselves, so they are aware of the result. A potential advantage is that, by removing structural and social barriers to testing and increasing associated privacy and convenience HIVST, could increase initial and repeat testing rates and therefore diagnosis. A further potential advantage is that such testing is cheaper than testing at clinics. There is also the possibility for prevention synergy with HIVST i.e. PrEP requires frequent HIV-testing which could be facilitated by HIVST, although test sensitivity on ART is as yet unclear. The PrEP trial in Thailand reported that participants receiving tenofovir took longer (191 days) to develop a reactive oral fluid HIV self-test

result than those receiving placebo (17 days)[13]. Therefore, among people using PrEP, a blood-based HIV test may be an appropriate choice.

There is also the potential for HIVST to reduce risk behaviours and the potential for harm reduction strategies such as disclosure of serostatus to partners or to inform practices, such as serosorting and seropositioning. There is little research in these areas to date. However, HIVST could also potentially increase HIV transmission through missed opportunities for STI screening and risk behaviour counselling. There are also limitations of test performance with lower sensitivity and a more prolonged window period than laboratory based 3rd or 4th generation tests in early infection or if on ART. This could lead to condomless sex following a negative HIVST test within the window period with increased risk of transmission[14].

Evidence suggests that HIVST is acceptable to MSM and other key populations at risk of HIV globally both in high and low-income settings[15-17]. Data suggests that MSM appreciate the confidentiality and privacy afforded by HIVST but there is the potential for harms associated with HIVST. These include the potential social and emotional harms of a reactive test in the absence of counselling services. Also very few studies have evaluated post-test linkage with counselling and support or with treatment outcomes, but there is little evidence that HIVST leads to unintended harm or any other significant unintended outcomes[17-19]. In terms of evidence that HIVST can increase testing frequency or diagnosis there is little currently available. There are few current RCTs in MSM in high-resource settings; currently there are 3 in the US and one in Australia. All use self-reported frequency of testing as the primary outcome comparing HIVST to standard-of-care.

Acceptability and willingness to use self-tests has been high among trans-women included in studies in Peru and San Francisco. However, both studies showed that trans-women may be less likely to access care after a positive self-test and therefore that additional support to link to services may be necessary [20,21]. Acceptability of HIVST has not been evaluated among transgender men who have sex with men, but in a recent global survey trans MSM reported significantly lower odds of perceived access to HIV testing than cisgendered MSM[22,23]. HIVST could offer transgender women and men who have sex with men an opportunity to increase their testing frequency in the absence of appropriate clinic based services.

In the UK, self-testing was made illegal in the UK in 1992 because of concern among others, that a person could discover they had HIV without ready access to counselling which may lead to self-harm. With the new climate ART has engendered, HIVST was legalised in April 2014, with the first CE-marked HIV self-testing kits released to the UK market in April 2015. These kits use a whole blood sample and are marketed under the name BioSURE® HIV Self Test.

Despite the theoretical potential of HIVST, there is an absence of robust evidence on the potential impacts of self-testing approaches in the UK and limited qualitative data to inform how such interventions will be perceived, used and experienced among MSM and TGW at risk of HIV infection in the UK. A key question also arises as to whether the NHS should provide free HIV self–testing. Information is lacking in key areas to inform this decision, including what is the impact of self-testing on testing and HIV diagnosis rates and linkage to treatment and care. There are also no existing data on the effectiveness of offering self-testing for HIV in terms of increased diagnosis rates or reduction in time from infection to diagnosis in MSM and TGW, despite its importance, potential role and recommendations under new guidelines[24]. The WHO presents “HIV self-testing (HIVST) as an innovative strategy with great potential to contribute to achieving the United Nations (UN) 90–90– 90 targets by 2020”[25].

To address the key question above there is a need for a study to estimate the effect of offering free self-testing on HIV testing and diagnosis rates to use as the basis for a cost effectiveness assessment.

1.3 PANTHEON PROGRAMME

SELPHI is conducted as part of a programme of work funded by NIHR, which includes a comprehensive assessment of cost effectiveness of HIV prevention strategies among men who have sex with men; PANTHEON (Prevention And Testing for HIV: Economics and Outcomes of Novel Approaches).

The main research questions for the pantheon programme are:

- Does provision of free HIV self-testing increase the rate of diagnosis in MSM?
- Which HIV prevention initiatives for reducing HIV incidence are most cost-effective?

Formative work conducted to inform this study suggests that HIVST is highly acceptable to MSM who value its convenient and accessible nature, and the associated confidentiality and privacy. Concerns within this group relate to the possibility of (self) harm following a positive result, and an increase in bacterial and other STIs due to the dislocation of HIV testing from other clinical sexual health interventions. Our formative work also suggests that men are most likely to use HIVST as supplementary testing option between clinic tests when seeking reassurance of a continuing HIV-negative status, rather than as a primary testing method following a risk event. HIVST is perceived to be exceptionally useful in meeting norms of regular HIV testing which are deeply held by many gay and bisexual men.

Interviews with key informants suggest that HIVST has particular applications for MSM who are not gay identified and those who do not have easy access to clinical interventions such as individuals living in rural areas, or areas with sub-optimal service delivery. Key informants tended to believe that (free) HIVST would initially attract significant interest among MSM, with diminishing numbers of individuals accessing the technology when its use becomes normalised. Concerns around clinical pathways into care and support were universal among this group.

1.4 EVALUATING THE COST-EFFECTIVENESS OF HIV PREVENTION INTERVENTION OPTIONS

Condom use has long been the main prevention approach used by MSM and TGW and behaviour change interventions (including alcohol and drug interventions) promoting condom use remain important. Other prevention approaches include promotion, pre-exposure prophylaxis (PrEP; (where HIV-negative people at high risk take HIV drugs regularly to prevent infection), recommending immediate treatment in all people with diagnosed HIV (which is now known to be of benefit to individual health)[26], and interventions prioritising partner notification of newly diagnosed cases. However, it is unclear which offer the greatest benefit for cost. Most existing cost-effectiveness studies are either non-UK focussed and/or implicitly exclude MSM.

In practice, assessing the cost-effectiveness of these prevention interventions can only be done through modelling, by synthesising the relevant evidence in order to quantify the long term impact of reduced HIV population spread[27]. Our individual-based model simulates the UK population of MSM from the start of the epidemic, tracking detailed levels of condomless anal sex with long term and casual partners and hence risk of HIV acquisition[1]. This model will be used for our evaluation of cost effectiveness of different HIV prevention approaches and it is in this context that the cost effectiveness of our self-testing intervention will be assessed.

1.5 HIV-SELF TEST KIT

BioSURE® UK is a UK-based company specialising in the provision of rapid in-vitro testing devices (IVDs). The BioSURE® HIV Self-Test is the only licensed CE marked HIV Self Testing device in the UK. Released in the UK market in April 2015, it allows the user to determine their HIV status in a place of their choice at a time that is convenient to them. The test is easy to perform, requires a tiny drop of blood and gives a simple to read result in 15 minutes.

The BioSURE® HIV Self-test comprises a paper test strip inside a plastic barrel. The test is performed by mixing a small drop of blood with a liquid contained in the buffer pot. The mixture is absorbed by the paper strip. When the test is completed, two lines can appear on the paper strip. The upper line (the Control line) will only become visible if the test has been performed correctly. The lower line (the Test line) will only become visible is the applied sample contains antibodies to HIV.

Figure 2 BioSURE® HIV Self-Test

The BioSURE® HIV self-test contains a unique combination of a specific antibody binding protein which is conjugated to gold nano-particles and HIV 1/2 antigens which are held in a test membrane. The whole blood sample is applied to the capillary tip of the tube, which draws a tiny amount (2.5µl) into the test device. The tube tip is then inserted in to the buffer solution which is provided in a sealed vial (buffer pot). The buffer combines with the sample and the test reagents. The blood/buffer mixture migrates along the test strip. If the sample contains antibodies to HIV, the antibody/gold conjugate particles are captured and immobilised by the antigens already in the test strip and this produces a line (the TEST line). In a non-reactive (negative) sample, there are no antibody proteins present and there is nothing for the antigens to capture, therefore, this test line is not produced. There is a control line on each test strip to make sure the sample and reagents have been properly applied and have migrated up the test strip. The control line will always be produced if the test has run correctly.

The sensitivity of the BioSURE® HIV self-test kit to detect infection with HIV-1 was evaluated using 614 specimens from individuals known to be infected with HIV-1 and from 776 individuals at high-risk for infections. 648 individuals were identified as positive for infection with HIV-1 using a licensed confirmatory assay, and/or FDA approved NAT assay. Of these, 646 specimens tested reactive on the BioSURE® HIV self-test. The calculated sensitivity of BioSURE® HIV self-test in these studies was 99.7% (95% CI 98.9-100).

Table 1 BioSURE® test specifications

	BIOSURE®
Device	3rd generation
Specimen	Finger-prick
Commercial availability	Sold in UK & Europe
Regulatory Status	CE marked
Sensitivity	99.7% (98.9-100)
Window period	3 months*
Specificity	99.9% (99.6-100)
PERFORMANCE IF 10,000 SELF-TESTS PERFORMED	
Population Prevalence	False Positive
High (2.0%)	2 (1:100)
Low (0.2%)	2 (1:10)
*25-35 days based on published studies[28]	

2 TRIAL RATIONALE AND DESIGN

2.1 RATIONALE

As reviewed in **Section 1.2**, previous and ongoing studies of HIV self-testing have generally been small and qualitative. SELPHI is a large, randomised trial whose primary aim is to measure the impact of self-testing on new confirmed HIV diagnoses linked to clinical care.

2.1.1 PRIMARY OBJECTIVES

- Is the online promotion and postal delivery of free HIV self-test kits (with testing reminders) feasible and acceptable?
- Will the offer of a single free HIV self-test at enrolment lead to the confirmed diagnosis of prevalent HIV infections and entry to standard HIV clinical care?
- Among seronegative individuals at high risk of acquiring HIV Infection, will the offer of regular free self-tests with testing reminders result in more rapid confirmed diagnosis of an incident HIV infection and entry in to standard HIV clinical care?
- Generate data to inform key parameters for cost-effectiveness models.

2.1.2 SECONDARY OBJECTIVES

- Comparison of the following between those allocated to received free HIV self-test kits and those not:
  - frequency of HIV testing
  - how individuals access testing options (e.g. testing with a healthcare professional, self-sampling or self-testing)
  - frequency of STI screening.
- frequency of condomless sex (either self-report or as reflected in new STI diagnoses).
- Reported usage of HIV self-testing kits.
- Acceptability of HIV self-testing.
- Assess post-test linkage with counselling and treatment services including attendance for confirmatory HIV test
- Assess the extent to which demographic, socio-economic, health-related factors, sexual risk behaviours use predict testing behaviours

2.2 DESIGN

SELPHI is an internet-based study; participants will be recruited via social media, and in gay and trans friendly online and social environments. Participants will be directed to the study website which will provide information about self-testing and describe the study. The study has two randomisations (**Figure 1**).

Randomisation A takes place at enrolment. After consent, assessment of eligibility and completion of baseline data collection (**Appendix A**), participants will be randomly allocated to the offer of a free baseline HIV self-test (**BT**) versus no offer of a free baseline HIV self-test (**nBT**). All test-kits will be delivered to the participant's nominated address (within England and Wales only) by the kit provider (BioSURE®). The inclusion criteria for this randomisation are broad (**Section 3.2**). Participants randomised to BT will be sent a brief survey at 2 weeks' post-randomisation to check if the test kit has been received and utilised. All participants will be asked to complete an online survey at 3 months' post-randomisation. At this point Randomisation B occurs amongst those who are eligible.

Randomisation B is more restrictive and is open only to participants allocated to the **BT** group who meet the additional eligibility criteria for this randomisation (**Section 3.3**). This randomisation will take place immediately after participants in the BT group have completed the Randomisation A 3-month survey. Eligible participants will be randomised to receive regular (immediately and then every three months thereafter) HIV testing reminders and the offer of a free HIV-self test kit (**RT**) versus no regular self-test (**nRT**).

Participants in the **RT** group will be contacted every three months to ascertain if the previous self-test kit was used and what the result of that test was (participants who report testing positive will be directed to HIV care options). Participants who remain negative will be reminded it is time to test again and that they can receive another free self-test kit if they wish.

Follow-up surveys will continue until the last participant randomised in Randomisation B is followed for a minimum of 18 months.

Follow-up in terms of cross-matching against the national HIV database will continue until the end of 2021.

3 SELECTION AND RECRUITMENT OF PARTICIPANTS

3.1 RECRUITMENT STRATEGY

SELPHI is an internet-based study; participants will be recruited via social media, and in gay and trans friendly online and social environments. Participants will be directed to the study website where they will be asked to answer questions to determine their eligibility for the study. Recruitment will take place via a dedicated web page. A number of marketing campaigns will be issued over the recruitment period (Recruitment is estimated to take around 12 months). Adverts will be tailored to attract individuals in our target population.

3.2 RANDOMISATION A INCLUSION CRITERIA

1. Men (including trans men) and trans women
2. Has ever had anal sex with a man
3. Is not known to be HIV-positive
4. Aged ≥16 years old
5. Resident in England or Wales
6. Willing to provide name, date of birth, and a valid email address
7. Consent for linkage of survey responses to surveillance and clinic databases held by PHE.
8. Has not been previously randomised to the study

3.3 RANDOMISATION B INCLUSION CRITERIA

1. Allocated to baseline self-test (BT) in randomisation A
2. Has completed the 3-month survey and:
    a. reports using self-test sent at baseline
    b. remains HIV-negative
    c. expresses interest in using HIV self-test kits in the future
    d. is considered to be at high-risk for HIV infection. Defined as reporting condomless anal sex with ≥1 male partners in previous 3 months.

3.4 NUMBER OF PARTICIPANTS

The study aims to recruit 10,000 participants to Randomisation A with 6000 allocated to the BT arm. and predict that around 3,000 will be eligible to be recruited into Randomisation B (i.e. half of the participants allocated to BT). See **Section 5.3** for sample size justification.

3.5 INFORMED CONSENT PROCESS

Participants interested in registering for the study will be presented with information about the study, its aims, methods, benefits and potential hazards. Systems will be in place to ensure that the responses given by the participant cannot be altered by any third party and ensure that participants who are not willing to participate (having read through the information of what is required) are not included in the study. Information will also be supported by a frequently asked question section of the study website.

Consent to the study will be obtained online using an easy to navigate series of questions to the participant about various specific points requiring consent to assess their willingness to participate. Participant consent materials can be found in **Appendix A**.

3.5.1 KEY ELEMENTS OF INFORMED CONSENT PROCESS

Potential participants will be informed of the following:

- the study objectives
- about both randomisation A and B at enrolment by being informed that they will be randomised to receive no tests or one or more tests (60% chance that they will receive at least one test).
- about the completion of online surveys and the receipt (or not) of free-self test kits in the post.
- information on the self-test kit being offered by the study (BioSURE®). Information on the BioSURE® test will highlight the need for a blood sample. A link to a video about the use of the test will be provided (https://youtu.be/WdoMwzTguV0).
- that in order to participate they must be prepared to provide their name and date of birth in order for the study to link their data to PHE and clinical datasets to assess linkage to clinical care (the need to provide accurate answers will be stressed so as not to undermine data integrity).

3.5.2 USER VALIDATION

Registration to the study will involve a user validation process whereby the participant is required to respond to a verification URL sent to their preferred mode of contact. This will be used to establish that:

- the participant's contact details are genuine and the participant is contactable.
- the participant has not previous registered for the study.

Receipt of a response to the verification URL will be the final step in verifying a participant's willingness to participate in the study.

3.5.3 WITHDRAWAL

Participants will be provided with the facility to inform the trial team that they wish to withdraw (or "unsubscribe") from the study at any time (**Section 4.5**).

4 PROCEDURES

All trial processes will be implemented as part of a trial website and customised online survey system developed by the trial team in partnership with Demographix Ltd. Trial registration, randomisation and follow-up data collection will be based around a series of online surveys that users will complete after reminders that will be sent via email. The flow of participants through the study is shown in **Figure 3** and **4**. Content of the individual surveys and information provided to participants is provided in **Appendix A.** Information on the method of randomisation can be located in **Section 5.1**.

Figure 3 Randomisation A schema

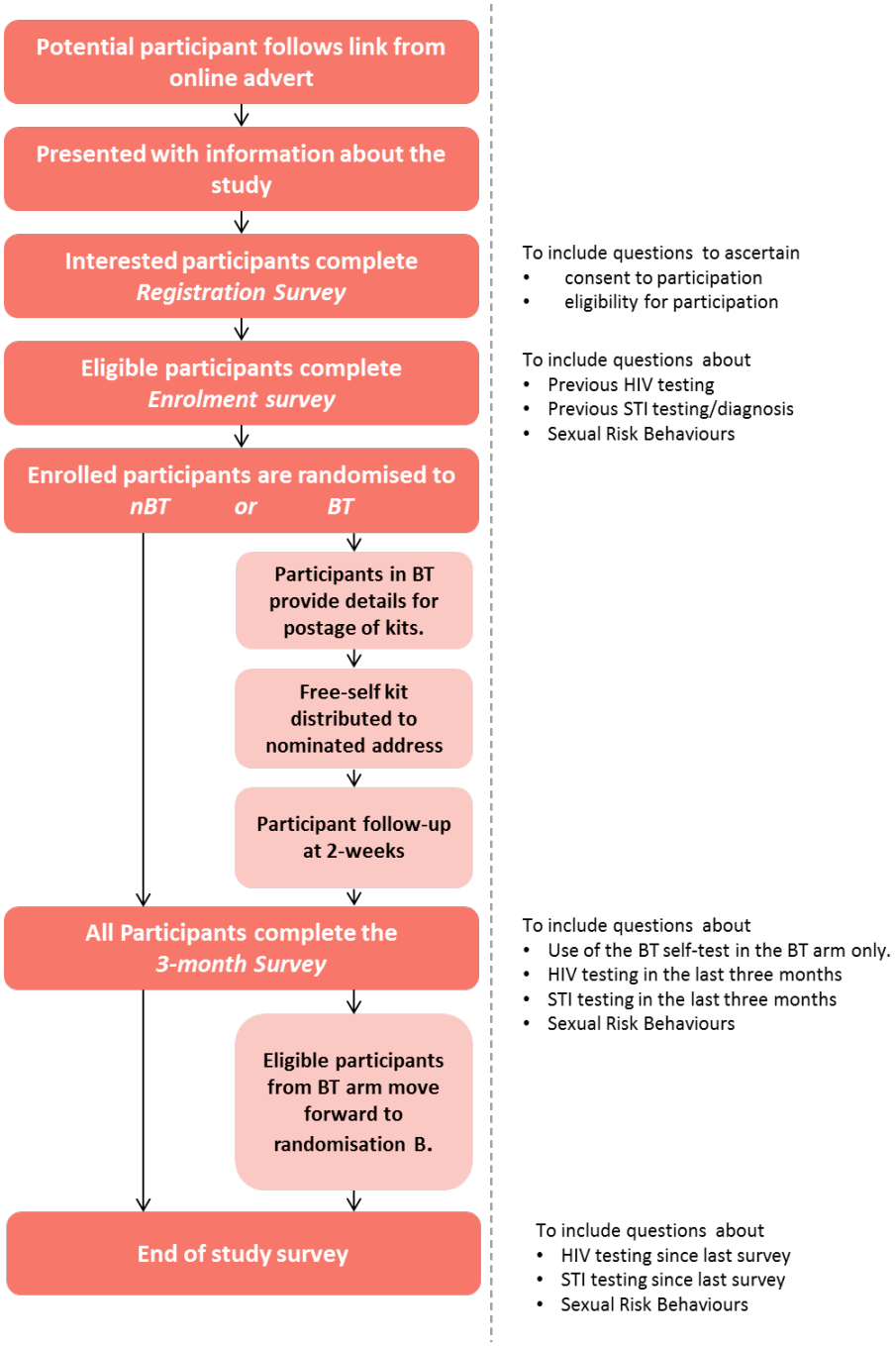
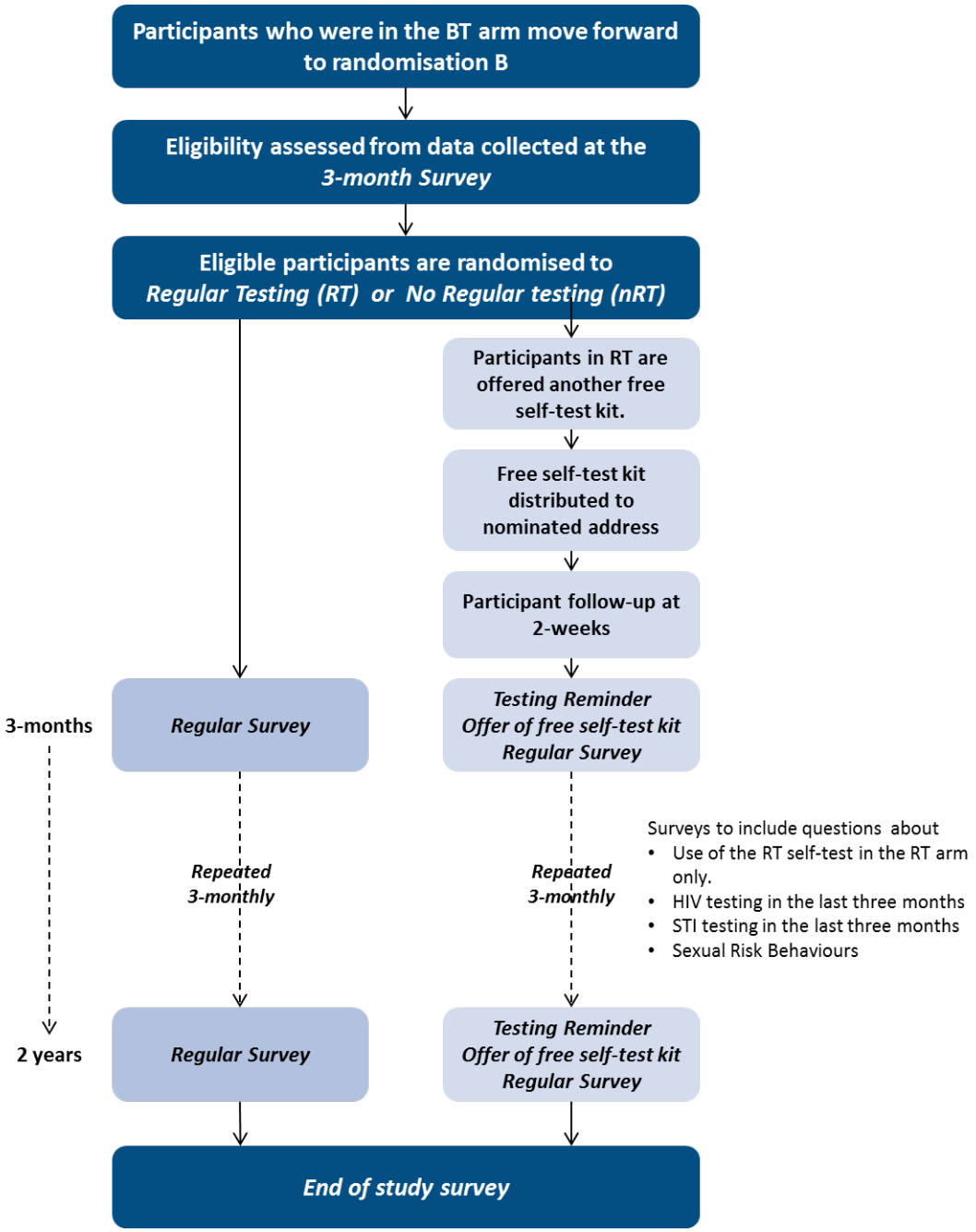


Figure 4 Randomisation B schema



4.1 PARTICIPANT SURVEYS

At registration, the participants will be asked to agree to provide details outlined in the **Registration Survey** (this will include a valid email address). All subsequent surveys throughout the study will be accessed using the unique personalised URL links which will be included in the reminder email sent to participants (**Appendix A**). Responses to questions within the surveys will determine the participant's next step in the study. For example, if a participant responds at any stage to inform the study that they have tested positive for HIV they will be exited from the study and directed to a specific page on the study website with advice on testing positive and next steps (**Section 4.6**).

4.2 RANDOMISATION A

Participants will be accessed for eligibility against criteria outlined in **Section 3.2**. Randomisation A will be performed after completion of the **Registration Survey** and **Enrolment Surveys**. Those participants who do not complete both surveys will not proceed to randomisation. Participants who are offered a self-test will be informed of this and then directed to the BioSURE® website to provide their postal address details. They will be informed that all identifying information they provide to BioSURE® (including address) will be confidential and not communicated to the study team. BioSURE® will not be permitted to use any information provided to them by participants in the study for commercial purposes included marketing activities. Participants who are not offered a self-test will be thanked for their contribution and provided information about other options for HIV testing including how to buy a self-test kit.

All participants registered in the study will also be asked if they are willing to be contacted to participate in qualitative research involving personal contact (**Section 7**).

At 2-weeks randomisation participants randomise to **BT** will be sent an email/text inviting them to participate in the **2-Week Survey**. This survey will serve to ascertain whether the participant has received and used their free HIV self-test.

At 3-months after randomisation all participants will be sent an email/text inviting them to participate in the **3-Month Survey**. This survey will ask those in the BT group about their use of the free self-test kit and will ask participants in both groups about sexual behaviour, use of PrEP, and other HIV and STI testing. Participants will be sent reminders in the case of non-completion.

A final end-of-study survey will be administered to capture information on testing during Selphi, use of PrEP and whether participants have experienced any negative effects or harms following a self-test (Appendices A and N).

4.3 RANDOMISATION B

Participants who meet the eligibility criteria (**Section 3.3**) will be automatically entered into Randomisation B following completion of the randomisation A 3-month survey. It is currently assumed, without hard evidence, that 50% of participants will meet the inclusion criteria. This parameter will be closely monitored during the study. If more than 50% meet the inclusion criteria, then randomisation to B will be closed once 3,000 participants have been randomised. If fewer than 50% meet the inclusion criteria the TMG will consider actions to increase this figure such as a re-focussing of social advertising or a relaxation of the inclusion criteria.

4.3.1 REGULAR TESTING (RT) GROUP

Participants randomised to regular further self-tests (RT) will be informed that they have been selected to receive further free self-tests and they will be reminded about this via emails sent 3-monthly (**Appendix A**). Participants are not obliged to accept any further free-test kits. Following this they will be directed to the BioSURE® website where they will confirm/change postal address details.

The surveys served to those in the RT group will address a number of purposes:

A. the intervention itself - being defined as the offer of a free HIV self-test kit with regular reminders to test for HIV.
B. questions posed to answer the study research questions
C. questions posed to answer the process evaluation questions

Via the Regular Survey every three months', participants will be:

A. Informed that another free-HIV test kit is available to them. The participant can choose whether they wish to accept another free self-test kit or not.
B. Asked questions about other sexual risk behaviours and STI and HIV testing behaviours and linkage to care (for those who test positive having tested for HIV).
C. Asked questions on usage and experience of using their previous test.

Questions are colour coded in **Appendix A** to link with coloured categories above.

4.3.2 NO REGULAR TESTING (NRT) GROUP

Those randomised to no regular testing (nRT) will be informed that they will continue receiving 3 monthly surveys.

These regular surveys will include:

B. Questions about other sexual risk behaviours and STI and HIV testing behaviours and linkage to care (for those who test positive having tested for HIV).

4.3.3 END OF STUDY

End of study is defined as the end of 2021 as cross-matching against the national HIV database will continue through this time, although surveys will cease at the end of 2019 .

All participants who have not tested positive during the study will be sent an email/text at the end of the study inviting them to complete a final survey and to thank them for their participation. The main purpose of this survey is to capture any unrecorded HIV diagnoses, participants have experienced any negative effects or harms following a self-test, views to inform potential roll out of free HIVST nationallyand use of PrEP during Selphi (Appendices A and N).

As and when the study is informed that a participant has tested positive they will be exited from the study **(Section 4.6**)

4.4 PROCEDURES FOR ASSESSING OUTCOME MEASURE

Data on HIV diagnosis in the UK are compiled from voluntary laboratory and clinician reports of newly identified HIV antibody positive individuals. This is reported to PHE to populate the national HIV surveillance database which has a very high level of coverage (~95%). Cases are reported using the individual's date of birth and Soundex (a phonetic algorithm based on surname). All participants will be required to provide date of birth and surname for entry in to SELPHI. The combination of these two variables map to a unique individual with a high probability, ascertainment of the primary outcome will be primarily based on linkage to the HIV and AIDS reporting section (HARS) database. Other linkages for secondary outcomes will be made to the PHE Genitourinary medicine clinic activity dataset (GUMCAD v3).

4.5 EARLY STOPPING OF FOLLOW-UP

A participant is free to stop participation in the study at any time. For example, a participant may register for the study and be randomised, but may choose to not use the HIV self-test that has been issued to them. Equally, they may use the test but may choose not to share the result of this with the study team. The study team will continue to attempt to communicate with the participant in the ways specified in this protocol until such time that the participant instructs the study to stop. This will be done by including an "unsubscribe" option on all emails sent to the participant and by having a feature on the website that allows the participant to email the trial team to express their wishes. They will be asked why they wish to withdraw in order to access how/if the study processes can be improved (although they are not obliged to provide their reasons).

4.6 PROCESS FOR PARTICIPANTS TESTING POSITIVE DURING THE STUDY

During the study, some participants are likely to test positive for HIV infection. In this event, (provided the participant chooses to provide this information to the study) participants will be provided links to information on where to find support (e.g. Terrence Higgins Trust (THT) forum for new diagnoses, NHS clinic finder). Any participant who tests positive will stop receiving regular surveys about testing and if randomised to RT will stop receiving the offer of free test kits.

If participants report a reactive HIV test but no link to care, then a clinician will contact them directly through email.

5 STATISTICAL CONSIDERATIONS

5.1 RANDOMISATION

Simple randomisation, based on a random number generator, will be used. The large sample size dictates that any chance imbalances should be minor and any efficiency gains from a more complex randomisation method negligible. In Randomisation A, participants will be randomised in a 3:2 ratio to the offer of a free baseline HIV self-test (**BT**) versus no offer of free baseline self-test (**nBT)**. An unequal randomisation ratio is being used to increase the number of participants who are eligible for Randomisation B. In Randomisation B, participants will be randomised in a 1:1 ratio to the offer of regular further tests (**RT**) versus no offer of regular further tests (**nRT**).

5.2 OUTCOME MEASURES

The primary outcome for both randomisations is a confirmed HIV diagnosis, with date of diagnosis defined as the date of the first confirmatory test at clinic. Diagnoses will be primarily identified through linkage with PHE New Diagnoses Database, although will be supplemented with outcomes identified via GUMCADv3, and by patient self-report (verified against documented results).

The primary outcomes for each randomisation are as follows:

- Randomisation A is a confirmed HIV diagnosis within 3 months of enrolment.
- Randomisation B is time between randomisation and date of confirmed HIV diagnosis. Data will be censored on the date of study closure allowing for delays in reporting from clinics to PHE.

Secondary comparative outcomes are:

- The overall frequency of HIV testing irrespective of testing modality i.e. where and how individuals test
- Frequency of STI screening
- Markers of the recently of infection at the time of HIV diagnosis, where available e.g. CD4 count, antibody avidity assays.
- Frequency of condomless sex (self-reported)
- New STI diagnosis

5.3 SAMPLE SIZE

As there is considerable uncertainty around a number of key parameters (for both randomisations) statistical power has been estimated over a range of plausible values. All calculations allow for the non-identification of 10% of primary outcomes e.g. linkage failure to PHE New Diagnoses Database.

5.3.1 RANDOMISATION A

A total of 10,000 participants will be randomised: 6,000 to **BT** and 4,000 to **nBT**. The primary analysis will compare the proportion of participants who have a confirmed HIV diagnosis within 3 months of the date of randomisation (sensitivity analyses will examine delayed diagnoses). The power of this comparison is a function of underlying HIV seroprevalence and the proportion of HIV seropositive participants who meet the primary outcome measures in each group (we ignore the influence of the small expected number of seroincident infections). Plausible ranges for these parameters are explored in **Table 2**. HIV seroprevalence rates of between 1.5% and 2.5% are plausible based on HIV self-sampling in the UK[29], suggesting that between 150 and 250 HIV seropositive but undiagnosed men in total will be randomised. The proportion of seropositive participants in the **nBT** group who

will receive a confirmed HIV diagnosis by using an HIV test outside of the trial (e.g. in clinic, self-sampling, paid self-test) is highly uncertain – values between 20% and 50% were examined. Not all participants in the **BT** group who are sent a self-test kit will use it and not all participants with a reactive result will link to clinical care. We assume that between 50% and 80% of participants who self-test positive in the **BT** group will have a confirmed HIV diagnosis. Note that this parameter (or the corresponding value in the **nBT** group) will not be estimable from the observed data as we do not know the denominator of the total number of seropositive individuals.

5.3.2 RANDOMISATION B

The primary outcome measure is the time between randomisation (to Randomisation B) and confirmed diagnosis of HIV. A simulation study (with 1,000 simulations) was performed to estimate the power of the primary analysis based on a log rank test, based on empirical epidemiological data and assumptions about the uptake of the intervention. Ranges of values have been explored for two key parameters, HIV incidence and the interval between infection and diagnosis in the **nRT** group.

1. Total of 3,000 participants randomised in a 1:1 ratio to **RT** and **nRT**. This assumes that 50% of those enrolled in the **BT** group meet the eligibility criteria for Randomisation B. This assumption will be closely monitored in the early stages of the trial.
2. Uniform recruitment over 9 months (to Randomisation A (i.e. approximately 1,100 per month).
3. Last enrolled participant followed for two years
4. HIV incidence between 1.5 and 3.0 per 100 person-years (PY). No directly relevant data were available, but the incidence among MSM attending GUM clinics in England has been estimated to be 2.7 per 100 PY[30].
5. Interval between infection and diagnosis in **nRT** group follows a Weibull distribution with a shape parameter of 0.4 and a median between 1.0 and 2.5 years. The "shape" parameter was selected arbitrarily to produce a higher initial rate of detection of infection. Modelling by Phillips et al.[31] and Birrell et al.[2] on the general MSM HIV epidemic in the UK suggests a median time to diagnosis of approximately 2 to 3 years. We have also explored values below this range since individuals who agree to participate in the trial – with an implicit interest in testing themselves for HIV – are unlikely to be representative of the general MSM population.
6. 10% of participants in **RT** who get a reactive self-test do not link to care and thus do not get a confirmed HIV diagnosis.
7. Participants randomised to **RT** will be offered self-test kits every 3 months, but 20% of these offers are rejected or kits are posted and not used by the participant (in a random manner).

Table 2 Randomization A. Power to detect a difference between the proportion of participants diagnosed in the BT and nBT groups (chi-squared test, 2α=0.05)

HIV SEROPREVALENCE (%)	NBT(%)[1]	BT(%)[1]	POWER (%)
1.5	20	50	81
		60	95
		70	99
		80	100
	30	50	42
		60	71
		70	89
		80	97
	40	50	13
		60	35
		70	62
		80	83
	50	60	11
		70	30
		80	55
2.0	20	50	91
		60	99
		70	100
		80	100
	30	50	53
		60	83
		70	96
		80	99
	40	50	16
		60	45
		70	75
		80	92
	50	60	14
		70	39
		80	68
2.5	20	50	96
		60	100
		70	100
		80	100
	30	50	63
		60	91
		70	99
		80	100
	40	50	19
		60	54
		70	84
		80	97
	50	60	16
		70	47
		80	78

[1] Proportion of seropositive participants who get a confirmed HIV diagnosis within 3 months

Table 3 shows the power of the trial under these assumptions, along with the expected number of endpoints. The power of the trial appears to be satisfactory except when both HIV incidence is low and the time to HIV diagnosis in the **nRT** group is short.

Table 3 Randomization B. Power to detect a difference in the time to HIV diagnosis between the RT and nRT groups (log rank test, 2α=0.05)

HIV Incidence (per 100 PY)	Median time to diagnosis (years) in nRT group	Power (%)	Estimated HIV infections per group	Median number HIV diagnoses (nRT/RT)	Median hazard ratio (RT versus nRT)
1.5	1.0	56	53	24/40	1.73
	1.5	72	53	21/40	1.91
	2.0	82	53	19/40	2.08
	2.5	87	53	18/40	2.21
2.0	1.0	75	71	30/53	1.70
	1.5	83	71	28/52	1.94
	2.0	91	71	26/52	2.08
	2.5	93	71	24/51	2.20
2.5	1.0	83	89	38/66	1.73
	1.5	93	89	34/65	1.92
	2.0	96	89	32/65	2.09
	2.5	98	89	30/64	2.25
3.0	1.0	89	107	46/78	1.74
	1.5	96	107	41/77	1.92
	2.0	98	107	38/77	2.09
	2.5	99	107	36/77	2.23

5.4 INTERIM MONITORING & ANALYSES

The Trial Management Group (**Section 12**) will oversee monitoring of data, including recruitment, retention, overall event rate, the completeness and quality of data, and report to the Programme Steering Committee (PSC). The PSC may request unblinded analyses but the reports of such analyses will be restricted to the PSC, the Chief Investigators, and Professor Phillips (and, clearly, the statisticians who produce the reports). If agreed by the PSC, the TMG may decide to present the findings from Randomisation A (primary outcome collected 3 months after randomisation) while follow-up to Randomisation B is ongoing.

5.5 STATISTICAL ANALYSIS PLAN

A full statistical analysis plan will be developed, detailing the methods of analysis for primary and important secondary outcomes. All main analyses will be intention-to-treat i.e. irrespective of whether the offer of a self-test resulted in its actual usage. However, the following individuals will not be included in primary analyses:

- Trans women and transmen, since the number recruited is too small for reliable statistical inference. Instead, additional qualitative research will focus on this group and use trial data to develop a mixed method study in trans people and use of HIVST.
- Participants who are identified by PHE as having an HIV diagnosis date that precedes enrolment to the trial. This contradicts information given by participants at enrolment that they have never had a positive HIV test (one of the eligibility criteria). The presumption is that the participant gave inaccurate information in order to possibly secure a free HIV self-test. In some cases this presumption will be incorrect i.e. the PHE matching algorithm was incorrect. However, on balance, it is considered more important to exclude some participants unnecessarily than include participants who cannot possibly achieve the primary endpoint.

Standard analytical methods will be used for the primary analyses of Randomisation A (chi-squared test for comparison of proportions) and Randomisation B (Kaplan-Meier and Cox regression analysis for time-to-event data). For Randomisation B it is noted that we are interested in the extent to which self-testing reduces the interval between infection and diagnosis rather than the interval between randomisation and diagnosis. However, the time of infection is not generally observed. Indirect information on the duration of infection will be available on some participants from CD4 counts, antibody avidity tests, and nucleotide ambiguity scores assessed at diagnosis. We intend to develop methods to obtain estimates of the interval between infection and diagnosis, possibly using a convolution approach assuming the same underlying HIV incidence in the two trial groups.

6 REGULATORY & ETHICAL ISSUES

6.1 ETHICAL CONDUCT OF THE STUDY

6.1.1 ETHICAL CONSIDERATIONS

The potential adverse consequences of a positive test, such as a deterioration in mental health, were considered during the process of obtaining CE-marking for the self-test kit, and also during development of the materials and information that accompanied the kit for Selphi participants who received a kit. But the benefit of an individual knowing that they had HIV was considered to outweigh the small risk of harm. The BioSURE® test is already available commercially in the UK, having satisfied the regulatory authorities. Based on the information collected in the first year, the risk-benefit analysis is substantiated, but Selphi will ask about participants experience of negative effects or harms from HIVST in the end of study surveys and explore this further through in-depth interviews (Appendices A, N, O and P). The second potential adverse consequence is that people do not engage with care following a reactive result. One of the Selphi clinicians will contact participants who report a positive self-test without reporting that they have linked to HIV servicesfor confirmatory HIV testing and if positive for further management and ongoing care. .

The survey questions are of necessity sensitive, and it will be necessary to store personal identifiers as part of the study data until the final cross-check has been completed. This is because there are different systems for creating the Soundex in the clinic network, and they may evolve during SELPHI. We will comply with the Data Protection Act, and the sensitive and personal data will be stored in a Data Safe Haven managed by Rackspace, a recognised leader in the field or in the UCL data Safe Haven (when data are with UCL). We will provide this information during the informed consent and explicitly collect a statement of understanding as we recognise that people rarely read the Terms and Conditions thoroughly when they sign up to online services. Those members of the research team who are conducting statistical analyses will not be able to link the sensitive and personal data.

As the trial has a complex design, participants will consent to be randomised to one or more self-tests rather than an explicit and separate consent for Randomisation A and Randomisation B (see Participant Information Sheet). This aspect of the trial was extensively discussed by the PPI group, who were satisfied that randomisation B was consistent with the information and consent for randomisation A in terms of one or more test, and that it was preferable to avoid information overload.

6.1.2 ETHICAL APPROVALS

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent information and other relevant documents e.g. advertisements, as well as the survey questions. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File held at MRC CTU at UCL.

An annual continuing review approval form will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The Chief Investigator will notify the REC of the scheduled end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

The rights of the participant to refuse to participate without giving a reason will be respected. After

the participant has registered, they are free to withdraw from the study as they wish (**Section 4.5**).

6.2 REGULATORY COMPLIANCE

The trial complies with the principles of the 1996 version of the Declaration of Helsinki. It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) and the UK Data Protection Act (DPA number: Z5886415).

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU directive 2001/20/EC. Therefore, a Clinical Trial Authorisation is not required.

This study is also not defined as a clinical investigation of a medical device trial. The HIV self-test kit being used in the study has CE-marking and the study is not designed to establish that the performance claimed by the manufacturer can be adequately demonstrated, and that the device is judged to be safe to use on patients.

Before initiation of the trial, the protocol, all informed consent documentation, information materials and survey questions to be given to the prospective participants will be submitted to the ethics committee for approval. Any further amendments will be submitted and approved by the ethics committee.

6.3 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been 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. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), which will be separately reviewed by the Quality Management Advisory Group (QMAG).

7 PROCESS EVALUATION

As part of the PANTHEON grant the process evaluation of the intervention will be assessed by Sigma Research at LHSTM.

7.1 PROCESS EVALUATION

RCTs identify whether interventions are effective in the time and place when they are delivered. Process evaluation linked to RCTs allows fuller interpretation of these findings and understanding of how they might be applied elsewhere. Embedding process evaluation within RCTs enables evaluators to limit biases in estimating effects when applying the trial findings in new contexts, while developing the detailed understandings of context, implementation and mechanisms of action that can support a policymaker, practitioner or systematic reviewer in interpreting effectiveness data[32,33]. Thus, estimating an effect size in an RCT is fundamentally important, but not sufficient alone to inform future policy and practice. Process evaluation is necessary to understand the factors which shape outcomes[32,33].

Informed by the MRC guidance on process evaluation[33] and developing and evaluating complex interventions[32], as well as the wider implementation science literature[34-36], the SELPHI process evaluation will investigate the following key domains: implementation of the planned intervention; mechanisms of impact for the intervention and contextual factors that affect impact and potential normalisation of the intervention with the target population.

Realist evaluation principles posited by Pawson and Tilley[37] will be used to investigate how the SELPHI intervention works. For the purposes of the process evaluation, there are two broad areas of interest in terms of SELPHI implementation: fidelity and reach & acceptability.

7.1.1 FIDELITY

Understanding what is implemented and how it is implemented is integral to explaining how an intervention works. The process evaluation captures what is delivered in practice in order to avoid dismissal of sound intervention theories due to a failure to implement them effectively[38]. The focus will be on the "form" of delivery in terms of whether this represents fidelity to what was intended to be delivered, as well as measuring the dose and reach of delivery. The SELPHI intervention includes standardised inputs and processes with no local or regional tailoring. Therefore, our approach to evaluating implementation focusses very clearly on fidelity of form rather than fidelity of function.

Fidelity of form refers to the standardised features of our intervention. Standard structures and processes of the SELPHI intervention are outlined in **Figure 3** and **4**. We hypothesise that, for the intervention to be optimally effective, all the essential elements should be delivered as planned. The process evaluation will examine the extent to which these standardised intervention components were implemented with *fidelity of form*.

Where deviations from *fidelity of form* occur we will assess whether these were intentional adaptations (and if so what motivated them), unintentional drift or simple omission; and whether the adaptation runs with or against the logic of the interventions theory of change.

Fidelity of function considers the extent to which locally-decided actions are consistent with the theory of change. This is not an issue in SELPHI as the intervention will be delivered nationally from a single hub, utilising online ordering and postal delivery – hence local or regional variation in the means of delivery cannot occur. In relation to *fidelity of function* it is also worth noting that the

intervention is relatively unique as it is not modelled on a pre-existing HIVST distribution intervention because of the recency of the release of a blood-based HIV self-test kit. The recently commissioned national HIV self-sampling (HIVSS) kit distribution mechanisms – which also utilise online promotion and ordering for postal delivery, and a reminder system for second and subsequent test kits – has, however, been examined in order to better understand how systems should be configured and to identify any likely problems that might arise.

7.1.2 REACH AND ACCEPTABILITY

Reach is the extent to which the target audience come into contact with the intervention[33]. The process evaluation will include quantitative assessment of reach, in terms of, for example, proportions of the target audience who are aware of the intervention and who came into contact with it[33].

Assessing awareness of HIVST and the reach of SELPHI across the whole population of MSM in England and Wales would require a large-scale community-recruited survey. While such a survey is not budgeted for within SELPHI, some questions will be added to EMIS II, a pan-European online survey of gay men and other MSM which Sigma Research have been commissioned to run in late 2017. With an intended number of recruits of at least 15,000 MSM resident in England or Wales, EMIS II will allow assessment of reach (coverage) across key demographic groups known to have an impact on testing behaviours (for example, age, sexual orientation and ethnicity[39]).

Acceptability refers to how intervention participants, providers or other stakeholders received or engaged with the intervention[40]. Interventions may initially generate resistance from the target group, which in some cases dissipates with skilful delivery[33,41].

The likely acceptability of the HIVST intervention has already been demonstrated within the formative phase of PANTHEON involving qualitative work with MSM[42] and key stakeholders such as clinical staff, HIV health promoters and policy advocates. Acceptability however needs to be considered as a dynamic characteristic and will be continually assessed during the trial, both through the surveys of participants and the sub-set of in-depth qualitative interviews with participants, including interviews with participants who report experiencing harms or other negative effects through HIVST (Appendices N, O and P) . Using both means of data collection the reach and acceptability across key demographic groups of MSM will be examined as well as what contextual factors that appear to affect this.

7.2 DATA COLLECTION MECHANISMS

The primary aim of the process evaluation is to assess if the online promotion and postal delivery of free HIV self-test kits is feasible and acceptable to gay men, other MSM (including transgender men) and trans women in England and Wales. The process evaluation will utilise four distinct data collection methods to address this question which are described below.

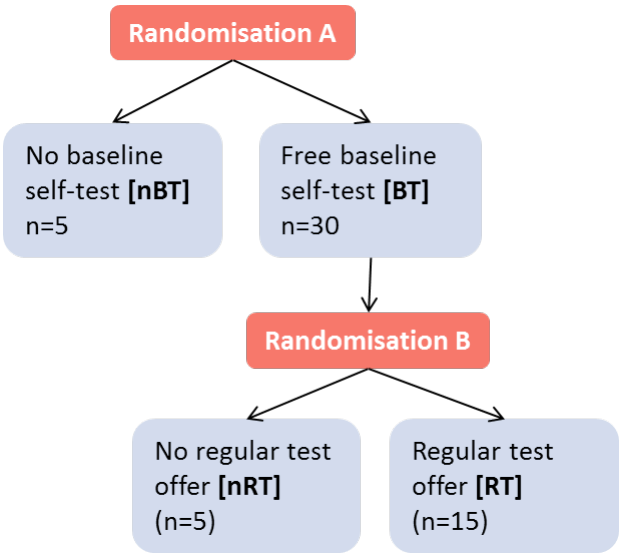
7.2.1 DATA COLLECTED AS PART OF THE MAIN STUDY

The 3 monthly (and end of study) surveys for **all participants** includes questions specific to the process evaluation mainly concerned with their experience of self-tests including negative effects and participation in the trial.

7.2.2 QUALITATIVE SUB-STUDY INTERVIEWS

Qualitative in-depth interviews with trial participants at various points in the trial process will be conducted (**Figure 5**). Interviews will take no more than 40 minutes and a small incentive (in the form of cash or a shopping voucher worth no more than £30, may be offered. In the initial phase of recruitment 15 in-depth interviews will be undertaken with participants to assess any deviations from the planned intervention and to gauge intervention acceptability. Subsequently, selection for interview will be guided by the quantitative data.

Figure 5 Qualitative follow-up interviews



Interviews with participants will examine HIV testing history, experiences of participation in the trial and of using HIVST, and their perceptions of the support available. Acceptable strategies for risk-reduction messaging will also be explored, as will other approaches to increase HIV testing to place self-testing in context. These interviews will also help to develop relevant process evaluation questions for the last participant survey in the study.

At enrolment all participants will be asked if they are interested in taking part in further qualitative studies. A purposive sample of individuals who express interest will be selected based on previous testing history, health service use and demographic factors associated with sub-optimal testing for HIV[8,42]. This will include participants who experience a positive (reactive) self-test to assess emotional responses and linkage to standard HIV care and support. Participants who identify as trans gender, those who report experiencing harms or other negative effects and those who self-report that they are from black or other minority ethnic (BME) groups will also be amongst those invited for interview (Appendices N, O and P).

All participants selected will be offered a Participant Information Sheet and required to sign a Participant Consent Form (**Appendix B**) or record verbal consent (if being interviewed remotely) at interview. Topic guides for interviews can be found in **Appendix C**.

7.2.3 DATA COLLECTED OUTSIDE OF THE MAIN STUDY

EMIS II is a pan-European online survey of gay men and other MSM, including approximately 15,000 in England and Wales, which Sigma Research have been commissioned to run in late 2017. In order to assess the reach of the intervention, questions relating to SELPHI will be added to EMIS II and analysed as a key mechanism to describe the coverage and reach of the SELPHI trial and its promotional strategies.

7.2.4 DATA COLLECTED FROM KIT MANUFACTURER

BioSURE® have agreed to provide on a monthly basis a data report on the volume of kits ordered, dispatched, and any notifications of problems with, or failure of, delivery.

8 DATA HANDLING AND CONFIDENTIALITY

8.1 DATA COLLECTION IN MAIN STUDY

The study will use www.demographix.com"Panelwise" software:

- To compile auto-routing web surveys and host them
- To establish and maintain a record of participants in the study
- To record informed consent to the study
- To allow the addition of new participants to the study and to remove those who no longer wish to take part

Demographix is registered with the Information Commissioner's Office (No. Z1244335) as both a Data Controller for their own data and as a Data Processor for customer data. All client data is stored on servers at data centres certified to the international standard for information security – ISO/IEC 27001:2013 – and is subject to external assessment and auditing.

Demographix provides a maximum security option, which ensures that our automatic data capture on the internet does not include internet protocol addresses (TCP/IP) or any other details that could identify the source of any data.

All data access using Demographix is sent over a Secure Sockets Layer (SSL) connection protected by a Norton/Verisign Certificate. Survey data submitted by participants is sent over an SSL Link. Survey data is held on servers in a secure data centre managed by Rackspace in the UK. Physical access to the servers is protected by numerous measures including biometric security. All data are stored, backed up and replicated across multiple servers in multiple locations with comparable security. Data are not stored, backed up or replicated outside the UK.

Data collected through these means and held by Demographix will be downloaded to password protected encrypted computers at MRC CTU for analysis and will not be attached to first name and email contact data but linked only through a unique code number for each participant. This unique number will allow linking of various elements of participation in the study by individuals while ensuring that contact information is separated from and not included in data sets.

At the end of the study data Electronic data will be stored for 15 years and paper documentation for a minimum of 15 years from the end of the trial in accordance with MRC CTU policies.

8.2 DATA COLLECTION IN QUALITATIVE SUB-STUDY

Qualitative interviews with trial participants will occur on the telephone and face-to-face as convenient. Digital recordings and pseudonymised transcripts will be maintained in a password protected database on password protected LSHTM desktop computers. On transfer, the audio data will be deleted from the digital voice recorder. Digital recordings will be transcribed by a professional transcription company that provides secure encrypted data transfer within the UK, and has been deemed to meet LSHTM's data protection requirements. Anonymised transcripts that require co-coding between staff based outside of LSHTM will be sent via email as encrypted password protected files. No identifying data will be kept with the transcripts. Participants will be pseudonymised. Personal details may be modified if there are concerns regarding participant identification. Care will be taken to ensure that no identifying data are included in the presentation of any qualitative data.

At the end of the project, qualitative data will be stored by *Sigma Research at the LSHTM for 7 years, and then transfer it to the secure LSHTM data archive in line with GDPR legislation.*

8.3 BIOSURE®

The postal details for participants who are randomised to receive free HIV self-test kits will be sent securely to BioSURE® who will dispatch test kits. Address details will only be utilised by BioSURE® for issuing kits as per protocol, personal data will be retained by BioSURE (not electronically) for regulator purposes for 3 months after the end of the study for regulatory purposes. These details will not be used in any other way including marketing activities. BioSURE® have agreed to provide on a regular basis a report on the volume of kits ordered, dispatched, and any notifications of problems with, or failure of, delivery. Ideally, this data will include a unique identifier that allows us to connect this data to each participant in the trial. MRC CTU at UCL will inform BioSURE of any reports of non- delivery or faulty kits reported directly to the SELPHI team.

8.4 LINKAGE WITH PHE DATASETS

Linkage to PHE datasets (**Section 4.4**) will be carried out by providing PHE with the following personal identifiers:

Soundex (a phonetic algorithm based on surname)
Initials
Postcode
Date of Birth
Gender Identity
Gender at Birth
Ethnicity
Country of Birth
GUM Clinic ID

PHE staff will use a matching algorithm and will extract any matched data from the PHE new HIV diagnoses database. This will include CD4 count at diagnosis and viral load, if available. If participants have provided a GUM clinic ID, this can be used to extract information from the GUMCADv3 database on HIV and STI testing and diagnoses. Information extracted from PHE databases will be linked with the main trial database.

8.5 DATA ANALYSIS

Data analysis will be conducted at MRC CTU at UCL. Subsets of the trial data (selected participants and/or variables) may be transferred to collaborating institutions for specific analyses. Such data will be fully anonymised and transferred using secure methods.

Where participant personal identifiers are stored on UCL systems these will be held in the UCL data safe Haven. This service provides a technical solution for storing, handling and analysing identifiable data. It has been certified to the ISO27001 information security standard and conforms to the NHS Information Governance Toolkit. Built using a walled garden approach, where the data is stored, processed and managed within the security of the system, avoiding the complexity of assured end point encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely.

9 INDEMNITY

The sponsor of the trial is the University College London (UCL) and the trial is coordinated by the MRC CTU at UCL, a department of UCL.

UCL holds insurance against claims from UK participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's Insurers, via the MRC CTU at UCL.

10 FINANCE

SELPHI is a randomised controlled trial which is part of a NIHR programme grant for Applied Research (No: RP PG 1212): PANTHEON - A comprehensive assessment of cost-effectiveness of HIV prevention and testing strategies, including HIV-self-testing, among men who have sex with men (MSM), in the UK.

A variation to contract was granted by the NIHR in June 2019 to extend the NIHR programme grant for Applied Research (No: RP PG 1212) from February 2020 to February 2021.

BioSURE® have provided HIV Self-test kits at a reduced cost for use in the study.

11 PUBLIC AND PARTICIPANT INVOLVEMENT (PPI)

This study has been developed with community input at all stages. Continued involvement from participants and the wider community is planned throughout the research. The PPI leads for the study are Roger Pebody from NAM and Roger Trevelion from HIV i-Base

In addition to contributing to the study design, a community advisory board for the study will advise and comment on all aspects of the study, including the study protocol, informed consent and the surveys. This work is led by a community member of the PANTHEON steering group.

This advisory group includes 20 people with direct experience of issues relating to HIV and HIV testing on a personal and/or organisational level. This group is predominantly made up of gay men and includes representation from the trans community. Recruitment came from an open call for volunteers to help for an HIV testing study that was sent out on community email lists, including to previous participants in the PROUD study[43]. It aims to be representative of the diverse range of experiences of likely participants in the main study. Reimbursement for travel costs and a small honorarium are available for this work.

Community involvement is essential given that, by definition, many of the participants we are hoping to recruit to the main study, have a history of either limited or no active engagement with routine HIV testing, despite belonging to a group at high risk.

The advisory group has autonomy to develop the most appropriate ways to support this study, including to decide the balance between face-to-face meetings and email discussions. It will also be an ongoing resource that the researchers can involve for any practical questions that arise during the research, including over recruitment and retention for the duration of the study, and to help with interpreting and disseminating the results.

An initial meeting enabled individual members to generate a close connection with the research group including to directly talk with the chief investigator and other key members of the steering group. This meeting included input and comment on all study documents. Future meetings will be approximately annual, or as necessary throughout the study. For example, this might include options to hold several open community meetings on HIV and HIV testing that as well as having an educational role, could raise the profile of the study.

The study will also facilitate additional involvement of study participants during the study. This will include the option to join an email list, to join an additional advisory group, and depending on demand, to have additional meetings. This model worked well in the UK PROUD study which was an HIV prevention study in a similar group of people at high risk of HIV.

The study has included a budget for regional community meetings if there is interest from participants for these during the study.

The community partners in this study will be fully involved in the interpretation and dissemination of the final results when they become available. They will also advise and inform how the results are best communicated to the wider community.

12 OVERSIGHT & TRIAL COMMITTEES

There are a number of structures that provide the oversight of the trial these are detailed below.

12.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigators, 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 trial. It will meet at least three times a year at least one of which will be in-person. The full details can be found in the TMG Charter. Representative of Demographix and BioSURE® may be invited to join these meetings as necessary.

12.2 PROGRAMME STEERING COMMITTEE (PSC)

The Programme Steering Committee (PSC) consists of independent members, including the Chair. The role of the PSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the PSC. Committee membership can be found in Appendix D.

12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

There is no plan to form an IDMC for the study because (1) there are no significant safety concerns as the intervention is an approved kite-marked test that can be bought commercially (2) the study places no obligation on participants to use the tests (3) no interim comparative analyses are planned as curtailing the follow-up data would weaken the evidence obtained on the effectiveness of the intervention. If any unexpected concerns arise during the trial the independent members of the PSC will be in a position to provide independent advice to the Chief Investigators.

12.4 COMMUNITY ADVISORY BOARD (CAB)

A community advisory board of around 20 members will include membership that broadly represents the likely participants in the main study - including diversity by geographical regional, age and gender. It will include involvement from key community organisations that are involved in HIV testing and prevention work, as well as individual from key populations.

An ad hoc network of trial participants will be connected by email and may also meet depending on user interest and demand.

12.5 PARTICIPANT INVOLVMENT

In line with the MRC Clinical Trials Unit Patient and Public Involvement (PPI) Policy[44] and international Good Participatory Practice guidelines[45], participants will be invited to contribute to patient and public involvement (PPI) activities. Participants will be invited to sign up to a secure electronic mail distribution list, with the option to unsubscribe at any time. Details of PPI activities will be advertised via the mail distribution list. PPI activities may include discussions via email, web- based discussion forums, teleconferences or in-person meetings.

13 PUBLICATION

The TMG, together with other programme collaborators, will form the basis of the writing committee and decide on the nature of publications. Any presentation or publication will be agreed with the PSC according to the terms of their charter. Publications will be made in line with NIHR, CTU and UCL's Data Sharing and open access policies.

Papers will have named authors determined by the TMG according to the following principles:

- To be as inclusive as possible where this is practicable
- To ensure that there is justification for anyone to be named as an author
- Reasons for nomination for authorship may include: study design; grant holding; day-to-day study oversight (TMG membership); analysis; discussion and interpretation of data; representation for key groups. It should be accepted that the people qualifying for authorship will vary over time. In addition, key positions will vary depending on the nature of the publication: clinical lead for clinical papers, statistician lead for methodology papers. In the event of any dispute related to authorship or data release, the PSC will be responsible for making the executive decision.
- Community engagement with the study, including the community advisory board and the participant groups will advise and inform on how these results are reported to the wider community. This would involve community publications and perhaps and online webcast that includes key researchers involved in the study.

14 PROTOCOL AMENDMENTS

Protocol v1.0 07-Sep-2016 approved by REC 27-Sep-2016	
Protocol v2.0 13-Dec-2016	
Changes made from version 1.0	**Sections updated**
General updates to branding.	Throughout.
Updated to allow inclusion of participants aged 16 and over as approved by ethics committee 27-Sep-2016.	Figure 1 Section 3.2
Schedule amended to include a 2-week follow-up survey in the BT and RT arms, which will be used to ascertain if participants have received their free HIV self-test kits and to allow the offer of support and advice more quickly in those participants testing positive.	Section 2.2 Figure 3 Figure 4 Section 4.2
In order to facilitate matching participants with the HIV new Diagnoses database we have been asked to include more data which will be used in the matching algorithm. It is expected that it will be possible to match the majority of individuals by Soundex initials and data of birth. Additional Data items will be used to supplement matching if it is not the first level matching is not achieved. This change has been reflected in the participant information also.	Section 6.1.1 Section 8.4
Minor clarification added to text relating to process evaluation and the plan to interview participants in the early phase of the study.	Section 7.2.2
As previously described the postal address details of participants will be transmitted to BioSURE for dispatch of the free HIV self-test kits. The protocol has been updated to reflect that fact that BioSURE are required by the regulator (MHRA) to retain personal details on all kits that they distributed in order to facilitate a recall of product for instance. This change has been reflected in the participant information also.	Section 8.3
Appendices *Revised* Appendix A – Consent and Surveys The website pages for each of the surveys have now been built and this has required some changes to the text and ordering or questions. This is reflected in the revised version of appendix A. *New* Appendix F – Participant Information These two documents have been extracted from the original Consent and Surveys v1.0 07-Sep-2016 document and formatted to allow downloaded by the participant from the website once for future reference. These document reflect the same information presented in v1.0 but with a few minor updates. *New* Appendix G – Email Text This appendix contains the emails that will be sent to participants taking part in the study, this provides them with the link to the survey. It also provides the opportunity for participants to withdraw if they wish.	 Appendix A Appendix F Appendix G

New Appendix H – Sleeve text When the BioSURE test kit is shipped to participants it will be sheathed in a cardboard sleeve with some trial relation messaging and directions. *New* Appendix J – Website Text This appendix contains the text that will be utilised on the trial website selphi.org.	Appendix J Appendix K
Protocol v3.0 01-Feb-2019	
Changes made from version 2.0	**Sections updated**
Address for MRC CTU at UCL updated. Staff changes updated (William Cragg no longer working on the project; Denise Ward is the Data Manager; Alison Rodger is a professor)	Trial Administration
Duration modified from at least 2 years to at least 18 months.	Synopsis
Updated to reflect Programme Steering Committee's request to review the data by allocation to determine duration of follow-up.	Section 5.4
Updated to reflect modification of study population for the main analyses. Trans women will be analysed separately due to small numbers, and participants whose date of HIV diagnosis in the Public Health England datasets precedes enrolment will be excluded.	Section 5.5
Appendices *New* Appendix K – 2-Year Survey and E-mail Invitation wording This appendix contains the survey that will be provided to all participants in Randomisation A that did not progress to Randomisation B, and the e-mail invite and reminders that will be served to them. *New* Appendix L – Trans Sub-Study PIS/CF This appendix contains the Patient Information Sheet and Consent Form that will be used for the Trans Sub-Study conducted by LSHTM. *New* Appendix M – Trans Sub-Study Topic Guide This appendix contains the Topic Guide that will be used for the Trans Sub-Study conducted by LSHTM.	 Appendix K Appendix L Appendix M
Protocol v4.0 03-Dec-2019	
Changes made from Version 3.0	**Sections Updated**
Staff changes updated (Michelle Gabriel and Mitzy Gafos no longer working on the project; Yolanda Collaco-Moraes is the Project Manager; Denise Ward is the Trial Manager)	Trial Administration
Duration modified to 31 Dec 2021 for checks against the national HIV database.	Synopsis Section 2.2
Clarifications regarding the End of study survey (also referred to as exit, final and 2 year in places)	Fig 1 Sections 4.2, 4.3.3
Collection of information on the negative effects of testing	Sections 4.3.3, 6.1.1, 7.1.2, 7.2.1, 7.2.2 Appendices N, O, P and Q
Clarification that clinicians will contact participants who report a positive test but no link to care (substantial amendment 26-Feb-2018)	Sections 4.6, 6.1.1
Clarification that there will be purposive interviewing of trans people (substantial amendment 07-Feb-2019)	Section 7.2.2
Clarification regarding the data storage and security arrangements at LSHTM	Section 8.2
Appendices	
Revised Appendix A – Consent and Surveys	Appendix A

2-Year survey for Randomisation A and Exit Survey for Randomisation B added	
New Appendix N – Critical Incidents protocol This appendix contains the protocol for the Critical Incidents Sub-Study for SELPHI	Appendix N
New Appendix O – Critical Incidents PIS and Consent Form This appendix contains the Participant Information Sheet and Consent Form for the Critical Incidents/Harms Sub-Study	Appendix O
New Appendix P – Critical Incidents Topic Guide This appendix contains the following topic guides for the Critical Incidents Sub-Study topic guides for social harms and false positives	Appendix P
New Appendix Q – Critical Incidents Sub-study invitation e-mail This appendix contains the invitation e-mail for participants who meet the criteria for the Critical Incidents sub-study	Appendix Q

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