Evaluating the Home-based Intervention Strategy (HIS-UK) to reduce new Chlamydia infection among young men aged 16-25 years by promoting correct and consistent condom use: What is the cost effectiveness of two different delivery models (face-to-face and digital delivery)?

Evaluation of HIS-UK

- **This protocol has regard for the HRA guidance and order of content**

RESEARCH REFERENCE NUMBERS

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Chief investigator: Professor Cynthia Graham

Sponsor: University of Southampton (UK)

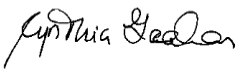
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Chief Investigator:

Signature: 

Date: 15../.02../2023 .

Name: (please print): Cynthia Graham

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Study Statistician:

Signature:



Date: 15/2/23

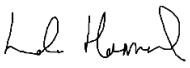
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Name: Stephen Bremner

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For and on behalf of the Study Sponsor:

Signature



Date: .16./.02/.2023

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Name: Linda Hammond……

Position: Head of Research Ethics and Clinical Governance

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ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
BSCTU	Brighton and Sussex Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
NERF	Non-Eligibility Report Form
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SS	Site Staff
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	Evaluating the Home-based Intervention Strategy (HIS-UK) to reduce new Chlamydia infection among young men aged 16-25 years by promoting correct and consistent condom use. What is the cost effectiveness of two different delivery models (face-to-face and digital delivery)?	
Internal ref. no. (or short title)	Evaluation of HIS-UK	
Trial Design	Randomised controlled superiority trial with three-parallel groups (two intervention and one control arm, 1:1:1 allocation), with an internal pilot.	
Trial Participants	Young men aged 16-25 years who are at risk of sexually transmitted infections.	
Planned Sample Size	2231 – Including 135 in the pilot phases.	
Treatment duration	Education and training consultation plus 2 weeks of self-practice sessions at home.	
Follow up duration	12 months	
Planned Trial Period	56 months	
	Objectives	Outcome Measures
Primary	To assess the effectiveness of HIS-UK to reduce new Chlamydia infection as compared to usual condom distribution care.	Chlamydia test positivity rate at 6 months post intervention. Test positivity at 12 months to examine longevity of impact.
Secondary	To assess the effectiveness of HIS-UK to improve correct and consistent condom use as compared to usual condom distribution care.	Monthly changes in the following measures: Condom Barriers Scale Condom Use Errors and Problems Survey Condom Use Self-Efficacy Scale Multidimensional Condom Attitude Scale Sexual Behaviour and Contraceptive Use Cost effectiveness of the two delivery models of HIS-UK compared to usual NHS condom distribution care.

iv. FUNDING AND SUPPORT IN KIND

The trial is funded by NIHR Public Health Research Programme.

v. ROLE OF TRIAL SPONSOR

The trial sponsor (University of Southampton) assumes overall responsibility for the initiation and management of the trial for the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The trial sponsor will ensure that there are robust arrangements for managing, monitoring, and financing the trial in accordance with the U.K. Policy Framework for Health and Social Care Research.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Group (TMG)

The TMG will comprise the CI and all Co-Investigators (clinical and non-clinical) and members of the BSCTU and CRN. The TMG will be responsible for the day-to-day running and management of the trial. It will hold regular teleconferences and face-to-face meetings.

Project Advisory Group (PAG)

The stakeholder and user representative PAG is chaired by the Director of the Centre for Sexual Health Research at the University of Southampton. Members (TBC) will include representatives of organisations with specific interest in the study (for example, Terence Higgins Trust, FPA, Brook, the British Association for Sexual Health and HIV, the Society of Sexual Health Advisors, the Sex Education Forum, Public Health England, and NICE), health promotion professionals, academics, policy makers and user representatives. This group will meet with the investigators quarterly to oversee the execution of the study and provide advice and assistance.

Dissemination Working Group (DWG)

A sub-group of the PAG, along with an additional five user representatives, will form the DWG. Chaired by our PPI Co-investigator, the role of this group is to provide advice and recommendations on our dissemination and impact strategy.

Trial Steering Committee (TSC)

The TSC has membership from the senior members of the TMG, representatives of the research network and independent members (researcher, statistician and clinician, PPI rep). The role of the TSC is to provide overall supervision for the trial conduct and advice through the independent Chair. The TSC will meet biannually.

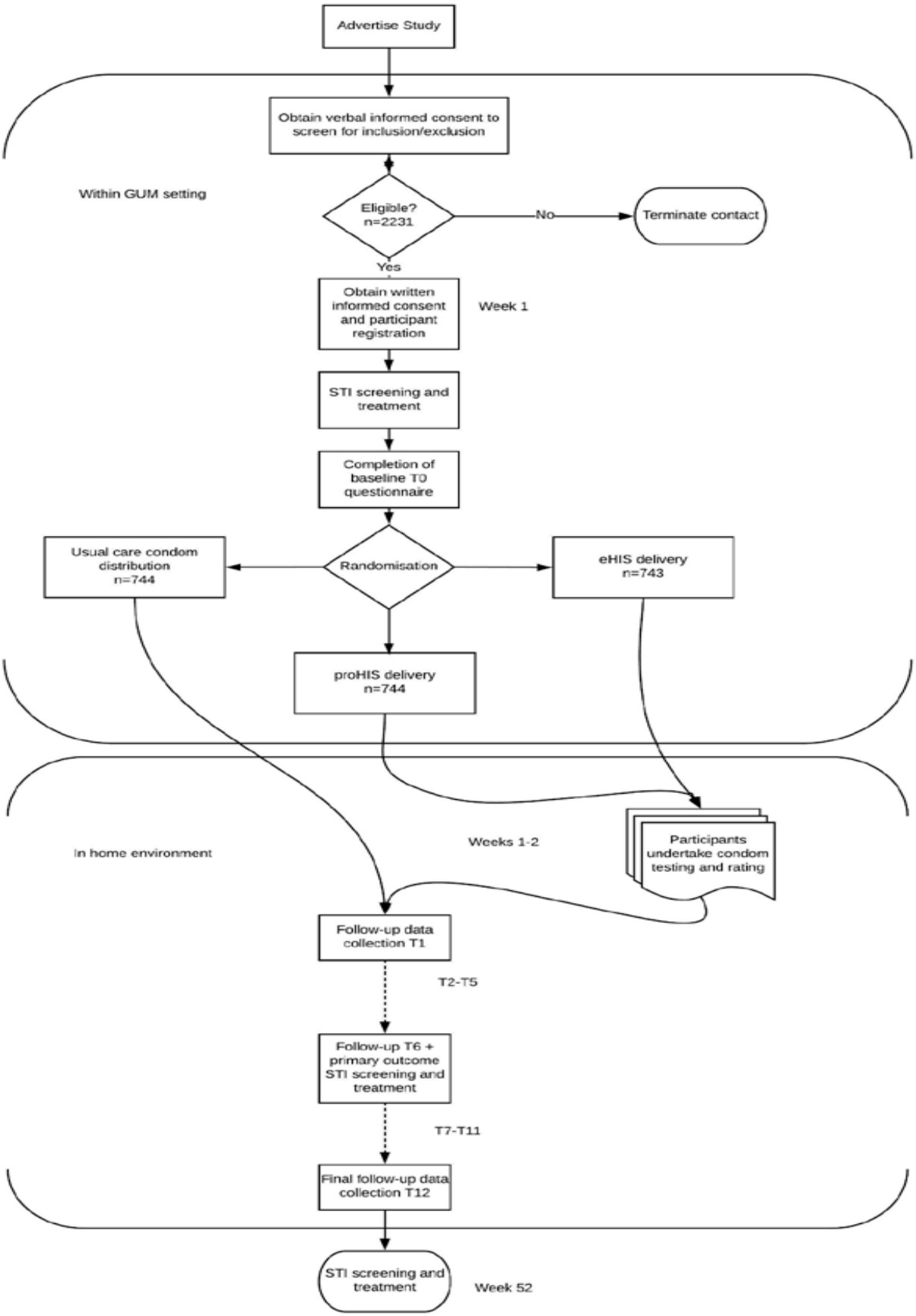
Data Monitoring and Ethics Committee (DMEC)

The DMEC has three independent members, with one having clinical trial expertise, one a researcher in the field, and one an expert trial statistician. The DMEC will meet at least annually (more, if needed). The trial statisticians will produce reports to the DMEC. The DMEC will consider data using the pre-agreed statistical analysis plans and will advise the TSC. The DMEC can recommend premature closure or reporting of the trial or discontinuation of recruitment to any research arm.

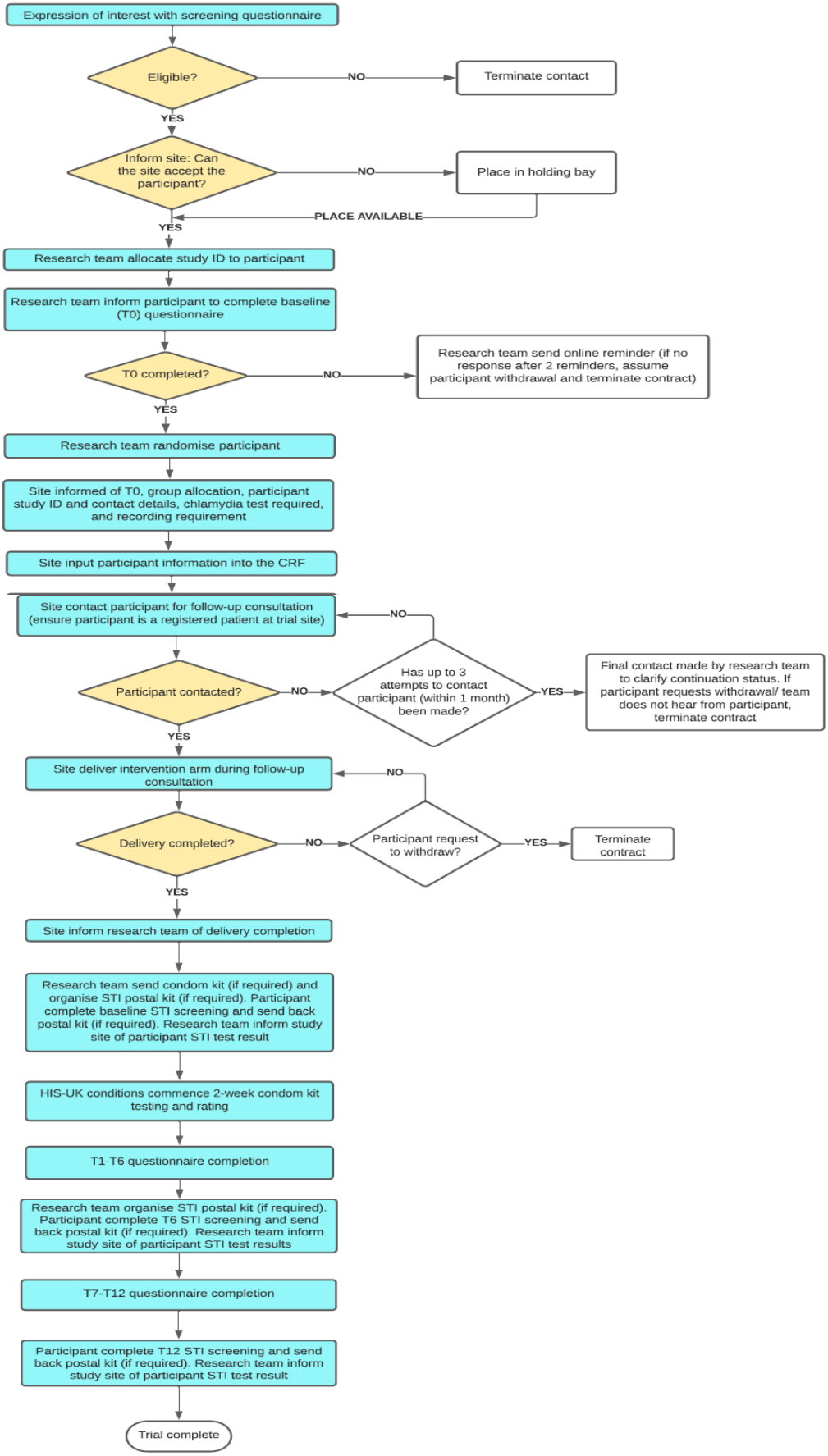
Details of all members can be found on the trial website www.his-uk.net

vii. KEY WORDS: Chlamydia, Condoms, Young Men, Public Health, Digital Health, Behaviour Change Intervention

viii. IN CLINIC RECRUITMENT TRIAL FLOW CHART



ix. ONLINE SELF-REFERRAL TRIAL FLOW CHART



1. BACKGROUND AND RATIONALE

Sexually transmitted infections (STIs) are a major public health concern in the UK. The Department of Health (DoH) has identified the need to reduce STI rates as a priority for decreasing sexual health inequalities and have recognised young male and female heterosexuals and men who have sex with men (MSM) as target 'at-risk' groups [1]. The health, social, and economic costs of STIs are huge and current estimates suggest that treatment costs the NHS £620 million per year [2]. Chlamydia (the most common diagnosis) and gonorrhoea are largely symptomless infections which, left untreated, can result in serious complications, including infertility.

Correct and consistent condom use is the most effective method to reduce STI transmission [3]. Public Health England have recently launched a campaign to protect young people from STIs by using condoms [4]. There is, however, substantial evidence that condoms are often not used properly. There are many reported barriers to condom use such as negative attitudes, decreased sensation and reduced sexual pleasure, fit-and-feel problems, application issues, and erection difficulties [5]. Behaviour change intervention programmes typically try to improve knowledge and skills to increase condom use, but seldom focus on addressing the reasons for condom non-use as important determinants. Issues with the fit-and-feel of condoms are commonly cited by men who report inconsistent or incorrect condom use [6,7] and these negative experiences are highly likely to be responsible for much of the variation in condom use self-efficacy and outcome expectancies known to be related to consistent use [8-10]. In a review of the evidence, we found that only five of 123 studies identified focused on improving condom fit-and-feel [11]. The intervention we propose to evaluate addresses the condom use barriers (including errors and problems) faced by young men by encouraging practice and experimentation. The intervention has already shown promise in feasibility and pilot studies [12-15].

The DoH recommends that evidence-based preventative interventions be used to reduce STI rates [16]. Yet, current national guidelines regarding behavioural interventions to prevent STIs are limited. A review of the evidence on safer sex advice recommended that brief behaviour change interventions targeting individuals and focusing upon skills acquisition, communication competences and motivation to adopt safer sexual behaviours should be provided as part of routine care of those at elevated risk of STIs [17]. In practice, there is scant information about whether such discussions occur and, if so, whether they are effective in reducing risk behaviour. Moreover, many communication and motivational interventions are very resource and cost-intensive. Funding for sexual health services has reduced dramatically, so novel ways of preventing STIs that reduce staff time and clinic attendance are being sought. Indeed, given the increasing use of the internet by young people to obtain health information, NHS England has identified the need to make fuller use of digital technologies [18]. There is therefore a need to develop and evaluate brief behavioural interventions that can be easily implemented without the need for high levels of staff resources.

Recent guidelines from the National Institute for Health and Care Excellence (NICE) include the need to teach young people to use condoms effectively and safely (using education, information and demonstrations) before providing them, and to provide a range of condoms and lubricants [19]. NICE also recommended that future research should explore what behaviour change techniques are most effective for supporting consistent and correct condom use following their distribution [19,20].

Systematic reviews of the efficacy of behaviour change interventions for the promotion of consistent condom use have produced mixed results [21-23]. Poor quality trials and a failure to identify the active components (or behaviour change techniques) of interventions have reduced the ability of studies to inform future development. Yet there is emerging evidence, mainly from US studies, that brief behavioural interventions designed with identifiable and evidence-based components can reduce STI acquisition [9,17,24].

The intervention we want to evaluate meets the above policy and practice recommendations. HIS-UK aims to improve men's condom use skills, self-efficacy, and enjoyment by providing information and guidance on condom experimentation, practice and usage (using a range of different condoms and

lubricants). During its development, we coded the behaviour change techniques and potentially active components of existing promising condom promotion interventions to enable the development of a brief behavioural intervention that is evidence based and theoretically driven [15].

HIS-UK has been adapted from an intervention previously piloted in the US and Canada (The Kinsey Institute Homework Intervention Strategy: KI-HIS). Pilot studies of KI-HIS showed significant improvements in condom use experiences, self-efficacy for condom use, and condom fit and feel, as well as a reduction in breakage and erection problems among heterosexual young men [12] and MSM [13]. Ongoing studies in the US are testing a female and a couple-based version. Preliminary results from the feasibility and pilot testing in the UK has shown a significant increase in reported use of lubricants during condom use, an increase in condom use at last intercourse, an improvement in condom use attitudes, in the fit-and-feel of condoms used, and enhanced sexual enjoyment during condom use [15,25].

HIS-UK has been designed with two delivery models: delivery by a trained health promotion professional[1] (proHIS) or as a digital intervention using an interactive website (eHIS). ProHIS has been designed as an extension of the usual condom demonstration and distribution care model currently practiced by health promotion professionals and offered to young people in condom distribution settings. The purpose of digital delivery (eHIS) is to facilitate improved access to a preventative STI intervention without the need of specialist provider contact. Furthermore, individuals and groups with the greatest need for sexual health services are also those least likely to be able to access them.
Digital interventions (Dis) such as eHIS remove accessibility barriers that contribute to health inequalities and enable participation at a time and location convenient to users, provide anonymity and can reduce fear of stigmatisation. Dis also have the advantage of providing consistency and standardisation in delivery and implementation costs that are typically low compared to other delivery methods.

The development work already undertaken to adapt KI-HIS to HIS-UK, and the two delivery formats of proHIS and eHIS, ensures that the proposed interventions are acceptable to young men and suitable to roll out [15,25]. What we now need to know is whether proHIS and eHIS are effective in promoting behaviour change and reducing STIs, and what is the cost effectiveness of the two delivery models as compared to usual condom distribution care.

2 ASSESSMENT AND MANAGEMENT OF RISK

This trial is categorised as Type A = No higher than the risk of usual medical care.

Condoms are the most effective method to reduce STI transmission. Non-use of condoms during penetrative vaginal or anal intercourse can lead to increased risk of infection.

HIS-UK aims to improve men's condom use skills, self-efficacy, and enjoyment by providing information and guidance on condom experimentation, practice and usage. Participants in this trial are provided with information and training regarding correct condom identification and use and then issued with a range of different condoms and lubricants to try out and test.

The primary philosophy behind HIS-UK is to enhance autonomous motivation for behaviour change by focusing on solitary practice of condoms, similar to the behavioural therapy approach used to treat sexual problems which incorporates home-based exercises. In common with the sex therapy approach, the exercises are designed to increase focus on pleasurable sensations whilst using condoms, thereby challenging beliefs that condoms "spoil" sex.

[1]Condoms are not 'medical treatment' and therefore do not need to be provided by a 'qualified medical practitioner'. The term 'Health Promotion Professionals' represents all trained workers, including non-medical practitioners such as youth workers, working in settings where condom provision can be offered.

The testing of different condoms and lubricants for fit, feel and sensation is not considered to carry any significant risks to the young men who participate in this trial and is comparable to the risks and benefits of the use of condoms and lubricants provided during standard condom distribution care. The benefits to the young men who participate include the chance to try out a range of condom and lubricant types and find the 'best' brand for them.

Young men with a known allergy to latex are excluded from the trial. There is a small but potential risk, however, that a young man registers for the trial and is not aware that they have latex allergy.

The proportion of the UK population with an allergy to latex is not known. Best estimates suggest that in the general population up to five percent are believed to have an allergy although many do not show significant or any symptoms so are probably unaware.

Symptoms of latex allergy typically occur immediately; however, some people have a delayed reaction that is more likely to be an itchy rash. Following screening participants who report that they are "unsure" if they have a latex allergy will be highlighted to the site staff who will then further question the participant to determine level of risk. Men who report previous symptoms will be excluded from the trial, those deemed to be at low risk with no previous allergen history will be allowed to continue but instructed to cease use of all condom products and to contact the site immediately if they experience any adverse reactions.

Condoms and lubricants containing nonoxynol-9 spermicide (N-9) will not be used in the trial as this has been shown to cause damage to human tissue, leading to inflammation and ulceration, which is dose-related.

2.1 COVID-19 RISK ASSESSMENT & PROCEDURES

In response to the COVID-19 pandemic, risk assessments in line with the NIHR restart framework issued in May 2020 (https://www.nihr.ac.uk/documents/restart-framework/24886) performed by the sponsor, funder, research team and sites will continue throughout the study due to the uncertain future of the pandemic. Sites and participants will also follow local COVID-19 guidance in place at each site as required.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Research Question

1) Does the UK Home-based Intervention Strategy (HIS-UK) delivered face-to-face by health promotion professionals (proHIS) and digitally delivered by an interactive website (eHIS) reduce Chlamydia test positivity among young men aged 16-25 years by enhancing condom use experiences and improving correct and consistent condom use as compared to usual condom distribution care?

2) What is the cost effectiveness of the two different delivery models of HIS-UK (face-to-face (proHIS) and digital delivery (eHIS)) as compared to usual condom distribution care?

3.2 Aim

To assess the effectiveness and cost effectiveness of HIS-UK delivered by two intervention delivery models (face-to-face (proHIS) and digital (eHIS)) to reduce test positivity of Chlamydia among young men aged 16-25 years by enhancing condom use experiences and improving correct and consistent condom use, as compared to usual condom distribution care.

3.3 Objectives

1) To assess the effectiveness of HIS-UK among young men aged 16-25 years by comparing face-to-face delivery (proHIS), digital delivery (eHIS) and usual condom distribution care:

- Chlamydia test positivity at 6 and 12 months
- Episodes of condomless anal and/or vaginal sexual intercourse at months 1-12
- Reported condom use errors and problems at months 1-12
- Enhanced condom use experiences ('fit & feel', sensitivity, pleasure and self-efficacy) at months 1-12
- Positive condom use attitudes at months 1-12.

2) To conduct a mixed method process evaluation to explore the ways in which HIS-UK delivered by proHIS and eHIS may work, possible mediators and mechanisms of change, and participants' experiences of engaging with the intervention and trial.

3) To estimate the costs associated with HIS-UK delivered by proHIS and eHIS and their cost effectiveness as compared to usual condom distribution care.

3.4 Outcome Measures

3.4.1 Primary Health Outcome

1. Chlamydia test positivity rate

Chlamydia will be measured at baseline (T0), 6 months (T6) and 12 months (T12) through bio-marker testing and treatment, and at T1-T12 through self-reporting. The primary health endpoint will be test positivity rate at 6 months. To examine longevity of intervention effects, test positivity will be assessed up until twelve-months post randomisation.

3.4.2 Secondary Process Indicators

These will be assessed using the following validated online questionnaires obtained at baseline (T0), and at monthly intervals to 12 months (T1-T12) and supported by qualitative data collected via interviews with participants recruited during wave 1.

2. Condom Barriers Scale [30]

3. Condom Use Errors and Problems Survey [31]

4. Condom Use Self-Efficacy Scale [32]

5. Multidimensional Condom Attitude Scale [33]

6. Sexual Behaviour and Contraceptive Use Survey (sexual partner history, relationship status/type, frequency of intercourse, use of contraception/condoms)

Further outcome data will be collected to inform an economic analysis, as detailed in the table below and in section 9.5.2.

3.5 Table of Endpoints/Outcomes

Objectives	Outcome Measures	Time points
To assess the effectiveness of HIS-UK to reduce new Chlamydia infection as compared to usual condom distribution care.	Chlamydia test positivity rate.	Baseline and then 6&12 months post intervention.
To assess the effectiveness of HIS-UK to improve correct and consistent condom use as compared to usual condom distribution care.	Condom Barriers Scale. Condom Use Errors and Problems Survey. Condom Use Self-Efficacy Scale. Multidimensional Condom Attitude Scale. Sexual Behaviour and Contraceptive Use.	Baseline and then monthly questionnaires to 12 months post intervention.
Assess the cost effectiveness of the two different delivery models of HIS-UK compared to usual care.	EQ5D / SF-12 Costs and resource use.	Baseline and then 6&12 months post intervention.

4 TRIAL DESIGN

To compare the effectiveness of HIS-UK delivered face-to-face by health promotion professionals (proHIS) and HIS-UK digitally delivered by an interactive website (eHIS) to usual condom distribution care we will carry out a randomised, controlled, superiority trial with three-parallel arms (two intervention and one control arm, 1:1:1 allocation), with an internal pilot. We will use a repeated measures trial design with baseline measurement (T0) and follow-up monthly online questionnaires to 12 months (T1-12) post intervention and three STI screening points (T0,T6,T12) for Chlamydia. We will collect health economic data to compare the resource use and cost-effectiveness of delivering HIS-UK by the two delivery models to that of usual condom distribution care.

5 TRIAL SETTING

The trial is multi-centred and will be run in a minimum of six NHS Trust sites. New sites will be added in accordance with REC/ HRA requirements for non CTIMPs via a non-substantial amendment.

Participants will be recruited at selected integrated sexual health (SH) and Genitourinary Medicine (GUM) services and University associated Health Centres/GP practices. Community and educational establishments, youth advisory, information and counselling (YAIC) services, Health Centres, GP practices and community SH/GUM outreach facilities will be used to further advertise the study and signpost interested young men to the recruitment sites or to the study website where young men can submit an expression of interest to participate.

The HIS-UK intervention comprises three key elements:

- Focused condom and lubricant education and training.
- Solitary condom and lubricant experimentation and practice.
- Online ratings of condoms and lubricants.

The first element is designed to be delivered by either a trained health promotion professional or self-delivered in a home environment using the internet. The second two elements are designed to be self-delivered by the participants and undertaken in a home environment.

At 6 months and 12 months post intervention participants will be requested to undertake Chlamydia screening. This can be undertaken in a clinic setting or at home using a Chlamydia screening postal-kit.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Men and people with attributes of a biological male (i.e. a penis).
- Aged 16-25 years.
- Self-reported residency in England.
- At risk of STIs through reporting of condom use errors (i.e. breakage/slippage) or condomless penile-vaginal or penile-anal intercourse with casual/non-regular or new sexual partners during the previous three months.
- Willingness to commit to the trial duration.
- Capable of giving informed consent.

6.2 Exclusion criteria

- People without attributes of a biological male (i.e. a penis)
- A recognised latex allergy.
- No access to the internet.
- Limited written and/or spoken English proficiency sufficient to prevent the following of trial instructions.

7 TRIAL PROCEDURES AND TREATMENTS

Procedure	Location
Advertising	Integrated sexual health and genitourinary medicine (GUM) services Sexual health/GUM community outreach facilities Community and educational establishments Youth advisory, information and counselling (YAIC) services Social Media
Expressions of interest	Online
Recruitment, consent and registration	Sexual health/GUM services University associated Health Centres/GP practices Online
Baseline data – Questionnaire	Sexual health/GUM services University associated Health Centres/GP practices Online

Baseline data – Screening	Sexual health/GUM services University associated Health Centres/GP practices At home (postal kits)
Intervention delivery	Control – Sexual health/GUM services & University associated Health Centres/GP practices (as per standard of care) proHIS- Sexual health/GUM services & University associated Health Centres/GP practices (face-to-face in-clinic or via online video consultation) eHIS- Online
Intervention delivery analytics	Control – Online proHIS – Online
Intervention activities (kit testing)	At home
Intervention activities (rating forms)	Online
Follow-up assessments – Questionnaires	Online
Follow-up assessments – Screening	At home (postal kits) Sexual health/GUM services University associated Health Centres/GP practices

7.1 Recruitment

The trial will recruit participants through targeted advertisements and opportunistic direct approach.

7.1.1 Participant identification

Participants will self-identify to the trial through publicity (e.g. posters, fliers/leaflets, online and digital adverts, trial website, targeted social media adverts and direct text-messaging) and/or via direct approach in recruitment sites by trained site staff (SS).

Furthermore, targeted advertisements, posters and fliers placed in health, community and educational settings will be used to advertise the trial and signpost interested young men to appropriate sites to register or to the study website where young men can submit an expression of interest to participate in the trial.

Young men who are signposted to recruitment site settings from external trial adverts will identify themselves to reception staff on arrival and be introduced to the recruiting staff for eligibility screening.

7.1.2 Screening

No laboratory testing or diagnostic screening will be required to meet any noted inclusion or exclusion criteria.

7.1.3 Payment

To compensate for the “burden” imposed by the research all participants will receive electronic voucher payments totalling £50 (£10 after active participation for three months, £15 after participation for six months, and £25 after twelve months participation).

7.2 Eligibility Checking, Consent and Registration

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site; this includes receiving of informed consent from eligible participants at their site. Authorised, trained and competent staff (SS) will be identified and delegated responsibility by the site Pis to receive informed consent.

Young men can register for the study at a trial recruitment site setting (7.2.1). Alternatively, they can self-register online via the HIS-UK study website once their expression of interest application has been reviewed and accepted by the research team (7.2.2).

Informed consent will be obtained prior to the participant undergoing any procedures that are specifically for the purposes of the trial and are outside standard routine care. Consent will be obtained prior to trial registration, randomisation or the collection of any identifiable participant data.

7.2.1 Registration to the trial

Potential participants will be given sufficient time to read any information provided before deciding whether or not they are interested in finding out more. For those who are interested SS will conduct, with verbal consent, an initial eligibility check using a computer assisted questionnaire administered by *Lifeguide* to ensure relevance of recruitment progression. A count of men who do not meet the eligibility check and for what reason/s will be collated. SS will be required to record the reason for non-eligibility on the site NERF (a tally of the known reported reasons for non-progression).

NOTE: *Lifeguide* is an interactive web-based intervention software platform and secure validated data management system designed to collect participant information and deliver digital interventions (DI) to support health behaviour change. Tablet computers supporting the *Lifeguide* software will be provided to the sites by the trial sponsors. Tablets with 4G connectivity will be provided in sites with poor WIFI.

If eligibility is met, SS will provide full written details (patient information sheet), verbally explain the trial and answer questions. Informed online consent will be taken on the *Lifeguide* platform using the tablet computer on site. A count of eligible men who express an interest in the trial who then do not provide consent will be collected. Reasons for non-participation will be recorded where provided.

Following consent, participants are registered to the trial on the *Lifeguide* platform.

7.2.2 Expressions of interest and participant self-registration

Young men who visit the HIS-UK study website can obtain information about the trial and gain access to the patient information sheet to read before deciding whether or not to participate. Contact details for the study team are also provided to enable potential participants to ask further questions.

Interested young men will be prompted to complete an online expression of interest application administered by *Qualtrics*[1]. The application starts with a series of consent statements regarding the collection of personal data for the purposes of trial recruitment to which young men must agree. Young men then complete a series of eligibility questions which must be completed to ensure relevance of recruitment progression. If eligible, potential participants will be asked to submit their contact details (name, e-mail, mobile number and postal address – for the purposes of site allocation). Reasons for non-eligibility will be recorded within *Qualtrics*. The research team will review all applications and, in partnership with the relevant recruitment site, will identify when young men can register to the trial (to prevent over burden). Trial site will be ascertained from participant postcode (captured on the expression of interest application) and site catchment area. The research team will notify eligible young men when they are accepted onto the trial. A *Lifeguide* weblink will be shared with the potential participant allowing them to complete the trial consent and registration process along with the baseline (T0) questionnaire.

The research team will be informed of completed self-registrations via an automated e-mail generated by *Lifeguide,* and sites will be notified by the research team.

[1] Qualtrics is a University of Southampton approved online survey platform.

Relevant study participant ID numbers and contact details will be shared with the sites via secure e-mail, along with the trial arm allocation (proHIS, eHIS or control) and details of the chlamydia screening required (single or triple). Sites are required to generate a CRF (SR-CRF) for these participants and contact them to arrange an SS consultation.

During the following 4 week period, sites are required to make up to three attempts to contact participants to arrange the SS consultation (telephone, text and/or e-mail may be used). If unsuccessful, final contact will be made by the research team to determine trial participation status.

The purpose of the SS consultation is to determine participant capability, answer participants' questions about the study, obtain verbal informed consent, confirm NHS patient registration and deliver the appropriate trial arm activities (see below).

SS consultations may occur face-to-face in clinic or via a NHS approved video consultation system or for eHIS and Control arm participants, via a telephone call

It should be noted the pro-HIS intervention arm must be performed via a face-to-face clinic or via a NHS approved video consultation system appointment due to the demonstration element on the intervention (see section 7.6.3.1). .

7.2.3 Participant capability

It is a requirement for this trial that all participants are sufficiently proficient in spoken and written English (the eHIS digital intervention is only available as an English language website). It is also the responsibility of the SS to assess the capability of potential participants to provide informed consent – to understand the purpose and nature of the research, what is involved, its benefits, risks and burdens and the alternatives to taking part. They are also required to determine that potential participants have been given sufficient time to make an effective and free decision to participate (a person is assumed to have the mental capacity to make a decision unless it is shown to be absent).

The SS will determine whether participants are able to understand the nature of the trial and what is associated with their participation, are capable of providing consent and therefore fulfil the trial eligibility criteria. If participant registration occurs at a trial recruitment site this will take place during the recruitment, information sharing and consent processes at the recruitment sites. For those who self-register, the assessment will be made during the follow-up SS consultation.

7.2.4 NHS patient registration

All participants are required to be registered patients at a trial site for the purposes of Chlamydia screening data transfer between the trial sites and the research team. If participant registration occurs at a trial recruitment site SS will check the participant is also registered as a patient. If not, a patient registration will be made. For participants who self-register, this check will be made at the follow-up SS consultation. All patient ID numbers will be transferred to relevant CRF for the purposes of screening data transfer.

7.2.5 Right of refusal

The right of a participant to refuse participation without giving reasons will be respected. Participants will be free to withdraw at any time from the trial without giving reasons and without prejudicing further treatment; Participants will also be provided with a contact point to obtain further information about the trial (see the participant information sheet for more details).

The site PI and SS will take responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. In situations where a participant is able to consent initially for the trial but later becomes incapacitated the original consent endures the loss of capacity.

The research team will provide appropriate training for the site PI and SS to undertake all the required activities and process including the trial recruitment and consent processes.

7.2.6 Translation

The eHIS digital intervention is only available as an English language website, and as such trial materials will only be provided in English and no translation service will be offered.

7.3 The Randomisation Scheme

Trial arm randomisation is actioned through an algorithm built-in to *Lifeguide.* The algorithm will use randomly permuted blocks of varying length to preserve concealment and maintain balance within each recruitment setting site, with stratification by site, ethnicity and sexual risk to randomly allocate the participant to a trial arm.

Participants will be allocated to one of the three trial arms at a ratio of 1:1:1.

Following trial registration each participant will be prompted to complete a baseline self-completion computer assisted questionnaire (T0).

On submission of the T0 data participants registering at a recruitment site will be instructed to pass the tablet computer back to the SS. The SS will then be prompted to authorise the T0 submission (on-screen button) which will activate the randomisation algorithm built into *Lifeguide*.

SS will be informed of the outcome of the randomisation process by an on-screen notification message on the tablet computer. The research team will be able to review all randomisation details via the *Lifeguide* database.

For participants who self-register, the randomisation algorithm will be activated on completion and submission of T0. The research team will notify the sites of the trial arm allocation for each study participant (see 7.2.2 above).

Sites are required to

- 'Flag' active trial participants along with their study participant ID on relevant patient records.
- Keep secure all CRFs containing participant IDs and associated patient ID numbers to facilitate data transfer between clinical sites and the research team.

7.4 Blinding

Participants will not be blinded in the trial. Furthermore, trained SS are required to deliver usual care and proHIS and as such are not blinded in the trial.

To avoid bias and potential contamination between trial arms each SS member will be required to demonstrate competency by simulating usual care and proHIS intervention delivery with another SS member or a trial researcher (recorded for independent competency checking) following training. Within each recruitment site, in a 7% random selection of cases (20% during wave 1 recruitment) the interaction with the SS member will be audio-taped and assessed for intervention fidelity by a blinded assessor from the research team, with any discrepancies discussed with a second blinded assessor. Participants will provide consent for this recording to take place.

In all cases where proHIS and usual condom distribution care is delivered, SS will be asked to complete a checklist detailing all training and education activities undertaken (providing valuable analytics of intervention delivery and dosage). Similar questions will also be asked of all participants allocated to the usual care control arm and the proHIS intervention arm by way of a short survey administered by *Lifeguide* after participant registration. Assessors (research team members) of this data will be blinded.

Members of the research team undertaking the data analysis will also be blinded.

7.5 Baseline data

7.5.1 Questionnaire (T0)

Following participant registration each participant will be prompted to complete a baseline self-completion computer assisted (T0) questionnaire (administered via *Lifeguide*). The baseline questionnaire will collect basic demographics (age, ethnicity, postcode, sexual orientation, education, employment and housing), indicators of health-related quality of life and health service resource use. Data will also be collected on a series of behavioural, condom use experience, attitudinal, intentions and self-efficacy outcome measures, along with details of any partnered sexual activity and condom use that had occurred in the previous four-week period. The collection of postcoded data enables each participant to be assigned an Index of Multiple Deprivation Score based on the geographical locality in which they live.

7.5.2 Screening

Each participant is required to provide samples for Chlamydia detection. Participants who report sex with other men (during T0) will be triple tested, as per usual clinical practice (urine sample, and anal and oral swab); all other participants will be requested to provide a single urine test for analysis.

Collection of intimate swabs (anal and oral swabs for men who have sex with men) may cause some embarrassment. Where possible men who have sex with men will be triple tested for Chlamydia; however, if the participant refuses for any reason, a single urine test will be offered rather than removing the participant from the study (see flowchart). Participants who refuse an anal swab but consent to provide an oral swab and urine test will be classed as agreeing to a triple test for the purpose of the study.

If the participant has been tested for Chlamydia within 4 weeks of the baseline visit as part of standard of care, the results from this test may be used for the study and the participant will not be required to provide any samples for Chlamydia detection at the baseline visit. SS will assess and inform the participant when this will be applicable.

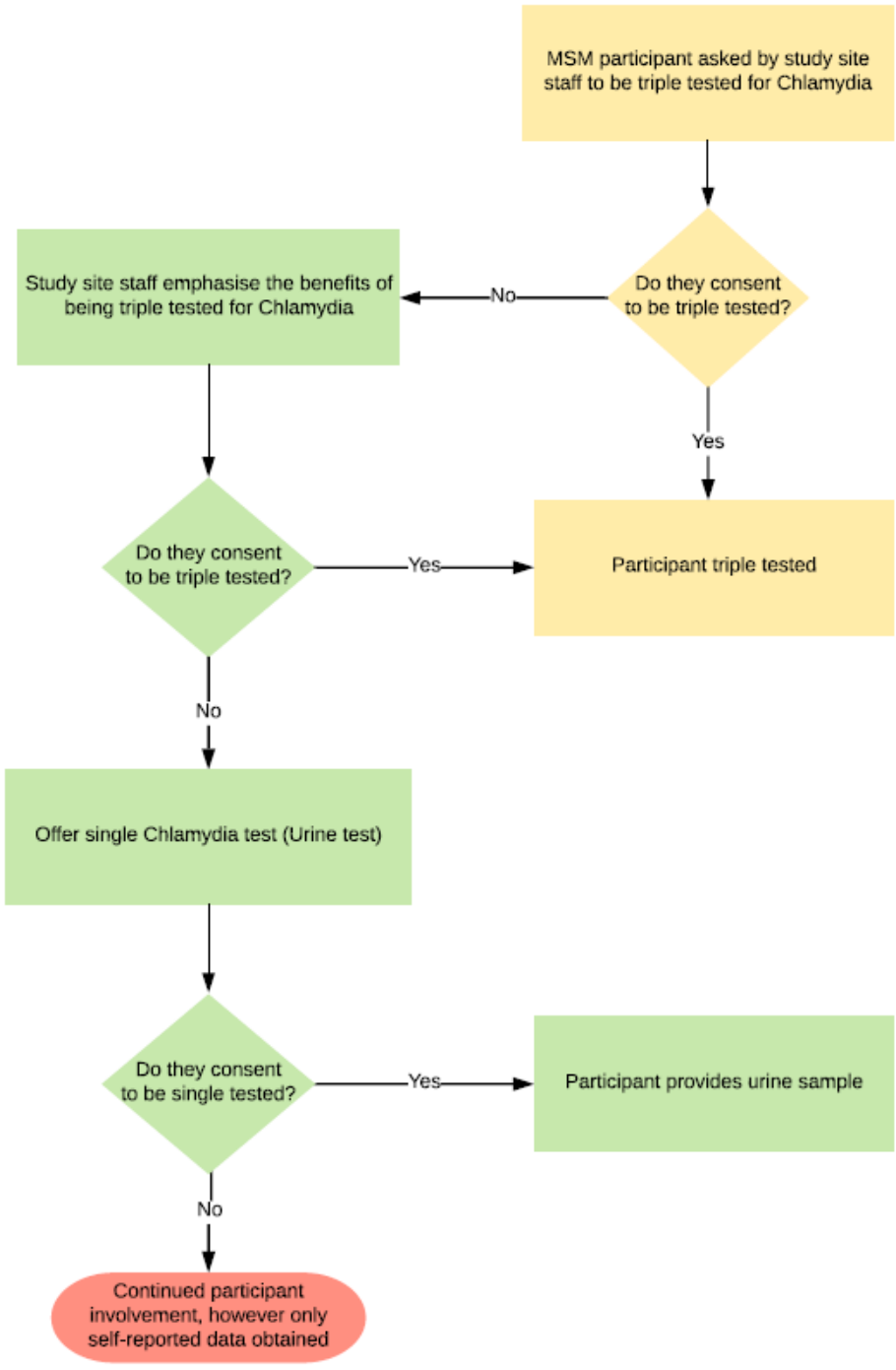
At baseline sites have the option of collecting samples in-clinic or via a postal screening kit.

Sites will be responsible for the laboratory analysis of samples collected in-clinic (or sites can provide a postal kit in clinic to reduce face to face contact time, if required due to the pandemic) and will be required to share the screening outcome data with the research team via the *Lifeguide* platform or the University of Southampton's password secured Encrypted Electronic Safesend Service.

Otherwise, the research team will arrange for postal kits to be mailed out to participants. The research team will be responsible for the collection and laboratory analysis of the samples, and for communicating the test results back to the study site.

All positive Chlamydia tests will be treated as per standard care.

Flowchart: Summary of the triple testing refusal process



7.6 Intervention Delivery and Activities

7.6.1 Control Arm

Usual care is the comparator control condition. Participants randomly allocated to the control arm receive:

i) Standard condom distribution care consultation offered in the recruitment setting.
ii) Details about the *Lifeguide* platform (to complete follow-up T1-T12 questionnaires).

7.6.2 HIS-UK Intervention Arms

The HIS-UK intervention comprises three key elements:

a) Focused condom and lubricant education and training.
b) Solitary condom and lubricant experimentation and practice.
c) Online ratings of condoms and lubricants

This trial compares two delivery models for the HIS-UK focused education and training (element (a)), namely face-to-face delivery by a trained health promotion professional (proHIS) and digital delivery by way of an online website (eHIS).

7.6.3. Education and Training

7.6.3.1 Face-to-Face Delivery: proHIS

Participants randomised to the proHIS intervention arm will receive a face-to-face consultation with the trained SS. These consultations may occur face-to-face in-clinic or via a NHS approved video consultation system. Each participant will receive:

i) A verbal consultation introducing HIS-UK, including the need for and advantages of condom testing and self-practice.
ii) A comprehensive condom application demonstration using a penile demonstrator to teach correct condom use competency. To meet the competency requirement, each participant will be asked to repeat back the demonstration (verbally or actively) to the SS member until no errors are made.
iii) Information about using condoms for pleasure, and how to find the best condom for fit and feel.
iv) Information about lubricants, their benefits, and how to use them.
v) An overview of the condom information and self-practice instruction guide containing details of the home-based exercises and how to rate the condoms and lubricants tested.
vi) A condom kit containing 24 condoms (minimum of eight different types, shapes and sizes) and 12 sachets of lubricant (three different types).
vii) Details about the *Lifeguide* platform with access to the condom/lubricant rating forms and T1-T12 questionnaires.

7.6.3.2 Digital Delivery: eHIS

Participants randomised to the eHIS intervention arm will receive the following:

A condom kit containing 24 condoms (minimum of eight different types, shapes and sizes) and 12 sachets of lubricant (three different types).

i) Details about the *Lifeguide* platform with full access rights to the eHIS website (authorised within *Lifeguide* at randomisation), the condom/lubricant rating forms and T1-T12 questionnaires.

Using interactive digital media (information, videos and serious gaming) the eHIS website will provide:

i) An introduction to HIS-UK, including information about condoms, and the need for and advantages of condom testing and self-practice.

ii) Teaching on correct condom use (how to apply and remove a condom).
iii) Information about using condoms for pleasure, and how to find the best condom for fit and feel.
iv) Information about lubricants, their benefits, and how to use them.
v) Advice on condom self-practice and details of condom use exercises to try out at home.
vi) Details on how to test and rate the condoms and lubricants provided in the condom kit.

7.6.4 Solitary Experimentation and Practice

Following education and training all participants in the two intervention arms (proHIS and eHIS) commence a two-week condom/lubricant experimentation and self-practice period using the contents of the condom kits and following the guided home-based exercises. The aim is for participants to practice applying, using (masturbating with) and removing each of the condoms provided in the condom kit in "low pressure" situations (i.e., not in the presence of a sexual partner) and to try out and experiment with the different lubricants.

As young men try out each condom and lubricant, they are asked to focus on pleasurable sensations in order to build positive associations between condom use and sexual enjoyment.

7.6.5 Condom and Lubricant Rating

After experimentation with each condom/lubricant, participants are requested to complete an online rating and feedback form using the *Lifeguide* platform. The purpose of the rating form is to enable participants to identify the condoms that 'fit & feel' the best, and the lubricant of choice. *Lifeguide* agents facilitate automated texts and e-mails to prompt intervention arm participants to complete the required ratings over the 2-week self-practice period (days 3, 7 and 12). Protocol compliance is defined as a minimum of three submitted rating forms and full compliance as the submission of eight.

At the end of the 2-week rating period, proHIS and eHIS intervention participants who adhere to minimum protocol compliance are offered 12 condoms of their choice and six sachets of their preferred lubricant via the post.

7.6.6 Intervention Delivery Analytics

Participants randomised to proHIS and the control arm will be contacted via *Lifeguide* notification (e-mail/text) sent after delivery of the trial arm to complete a brief checklist survey of the training and education activities that were undertaken during the consultation.

The web pages of eHIS are delivered by *Lifeguide* and managed by a series of intelligent "agents" (interaction, information, instruction, and evaluation). The purpose of the agents is to manage and monitor the learning of individuals by observing and recording e-learning behaviour (i.e., pages visited, instructional videos watched) and triggering automated messages and prompts to guide and assist effective learning (to visit further information pages, undertake tasks, watch video clips) and ensure exposure to all learning elements by participants.

7.7 Long Term Follow-Up Assessments

7.7.1 Monthly Questionnaires

All participants (proHIS, eHIS and control) will receive automated texts/emails every month (via *Lifeguide* agents) for 12 months, prompting them to complete an online assessment questionnaire (T1-T12) as per baseline (T0).

Participants are required to complete each questionnaire within 21 days of first notification. Automated reminder messages (days 3, 7, and 12) will be sent (text and/or email) until completion. Final contact will be made by the research team (personalised telephone call and/or e-mail) between days 15 & 21 to determine the status of trial participation. Following the telephone discussion, if no further questionnaires are completed the participant will have deemed to have withdrawn from the trial.

Following submission of each monthly questionnaire, proHIS and eHIS intervention arm participants who have been sexually active in the previous month will be prompted to order further supplies of condoms and lubricants of their choice should they wish (12 condoms and six lubricants). The research team will be notified of all condom orders and will be responsible for mailing out supplies.

7.7.2 *Chlamydia Screening*

At 6 months and 12 months post intervention, each participant is required to provide samples for Chlamydia detection.

To reduce research 'burden' on trial participants and to minimise attrition, only participants who have reported sexual activity in the previous six months (T1-T6) will be prompted to undertake follow-up screening. Furthermore, if a participant reports Chlamydia screening within 4 weeks of the 6 months and 12 months follow-up time points, the results from this screening may be used for the study and the participant will not be required to provide further samples for detection. Participants will be notified of the need to be screened via an on-screen message following submission of the T6 and T12 questionnaire data using the *Lifeguide* software.

Participants who have reported penetrative anal sex with other men during the previous 6 months (@T6 reporting sex with other men between T1 and T6; @T12 reporting sex with other men between T7 and T12) will be offered a triple test (urine sample, and anal and/or oral swab). All other participants who report penetrative anal or vaginal sex with only women will be requested to provide a single urine test for analysis.

Where possible, men who report sex with men will be triple tested for Chlamydia; however, if the participant refuses for any reason, a single urine test will be offered as an alternative. If a single urine test is refused, the participant will be allowed to continue with the study and their self-reported STI screening data will be used. Participants who are offered triple testing but refuse an anal swab and consent to provide an oral swab and urine test will be classed as agreeing to a triple test for the purpose of the study.

To reduce research 'burden' on trial sites, the protocol for follow-up screening of Chlamydia will vary depending on the ability of each site to provide in-clinic and postal screening (see below).

Following the submission of the T6/T12 questionnaire data a *Lifeguide* on-screen message will offer participants who require follow-up screening the option to receive a postal Chlamydia screening kit or to present for screening at the recruitment site setting in which they registered. Those who opt for postal screening are asked to confirm their personal contact details for the purposes of kit delivery and notification of results.

The research team are informed of participant choices by way of a *Lifeguide* notification.

A. Research team provision of postal kits

The research team will arrange for screening kits to be mailed out to participants who request a postal kit and will be responsible for the collection and laboratory analysis of the samples.

If after three weeks a participant has not returned samples for screening participants will automatically receive a reminder message (text and/or email) to return the postal kit or choose instead to present for screening at the service setting in which they registered.

Final contact will be made by the research team (personalised telephone call and/or e-mail) three weeks later if a screening has still not occurred. If a sample is still not provided the screening outcome data at T6/T12 will be marked as missing.

Outcome data will be entered onto the *Lifeguide* platform by the research team and study participant ID numbers and screening results will be shared with the sites via secure e-mail.

All positive results will be treated as per usual NHS care.

B. Participants choosing to present in person

Participants who opt to return to the recruitment setting are given three weeks in which to present for screening. They are sent three reminders by way of auto generated text messages and/or e-mails sent via *Lifeguide*.

Sites will be notified by the research team of those participants who opt to present in person. Relevant study participant ID numbers will be shared with the sites via secure e-mail, along with the type of kit required (single or triple).

If after three weeks a participant has not presented for follow-up screening, *Lifeguide* will automatically send them a message (text and/or email) repeating the option to receive a postal Chlamydia screening kit or to present for screening at the service setting in which they registered.

A final contact will be made by the research team (personalised telephone call and/or e-mail) three weeks later if a screening has still not occurred. If a sample is still not provided the screening outcome data at T6/T12 will be marked as missing.

All positive results will be treated as per usual NHS care.

7.8 Qualitative Assessments

Consistent with MRC guidance and a person-based approach to the delivery of interventions [49], mixed-methods will be used to examine how the intervention was implemented, possible mechanisms of impact, and contextual factors that may have influenced implementation of the intervention.

Qualitative in-depth interviews will be undertaken with all SS in the recruitment sites following wave 1 participant recruitment. The purpose of these interviews is to explore acceptability of the research design and intervention delivery, including how easy it was to recruit to the trial, willingness of participants to be randomised, ease of acquiring STI screening and data transfer, and issues of intervention fidelity.

To measure process and potential contamination between trial arms qualitative assessments of the delivery of proHIS and the control arm will be undertaken. Within each recruitment site, in a 7% random selection of participant cases (20% during wave 1 recruitment) the consultation interaction with the SS will be audio-taped and transcribed and assessed for intervention fidelity. Randomisation to this recording will occur within Lifeguide. SS will be informed of the outcome of the randomisation process by an on-screen notification message on the tablet computer; research team members will be notified via automated e-mail. Participants will provide consent for this recording to take place.

The research team will then contact SS to organise collection of the digital recorder and recording. Digital recorders containing recordings will be kept secure by SS until a collection has been organised.

At T6 and T12 follow-up, all wave 1 participants will be asked (via *Lifeguide*) if they would be willing to be contacted by the research team and be interviewed about the trial (either face-to-face or by telephone). From those who agree, 20 participants at each time point will be purposively sampled based on baseline characteristics to ensure a range of participant experiences are represented. The purpose of these interviews is to explore 1) trial acceptability, 2) issues of contamination and protocol adherence, and 3) how and why the intervention may/may not be beneficial. We expect that 20 interviews at each time point will be sufficient to reach theoretical saturation; however, if necessary, additional interviews will be undertaken with participants from subsequent waves. All participants will be required to give consent for the interviews to be digitally recorded, transcribed and analysed.

7.9 Withdrawal

Participants have the right to withdraw from the trial at any time without giving a reason. Sites have the right to withdraw participants from the trial if they judge this to be in the participant's best interests following participant behaviour and/or information shared during the SS consultation and intervention delivery.

Participants will be deemed to have withdrawn from the trial if they fail to submit three successive monthly questionnaires (T1-T12) and fail to complete further questionnaires following contact from the research team.

Should a participant decide to withdraw from the trial, all efforts will be made to report the reason for withdrawal as thoroughly as possible (participants will be asked for their consent to be interviewed, or to communicate the reasons for their decision in writing/e-mail). Participants will also be asked if they consent for the reason for their decision to withdraw to be recorded.

Participants will be replaced if they withdraw prior to randomisation.

Data and samples collected up to the point of withdrawal will be used after withdrawal unless the participant informs the research team otherwise.

7.10 Trial progression

The first wave of recruitment will be run as an internal pilot to assess trial acceptability, intervention fidelity, and the feasibility of randomisation and Chlamydia screening for trial continuation.

Assessment of progression will be made based on a pilot cohort of 135 young men, followed up for a period of six months; the findings from in-depth process interviews conducted with all SS and a sub-sample of up to 20 young men; and the assessment of intervention fidelity recordings.

During this period the following questions will be answered:

- Can we recruit eligible young men at a reasonable rate and to the numbers anticipated?
- Are young men willing to be randomised within the trial?
- Is Chlamydia screening at T0 and T6 sufficiently acceptable and feasible to implement?
- Do young men remain in the trial in sufficient numbers at six month follow-up?
- Are the intervention and trial design sufficiently acceptable?
- Are SS able to deliver the intervention with reasonable fidelity?

If the trial is stopped prematurely, participants will be notified by text/e-mail and participant payments honoured.

7.11 Storage and Analysis of Clinical Samples

Samples obtained: Urine / anal and oral swabs.

The collection, analysis, storage and destruction of all biological samples will be as per usual care.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with GDPR (2018). Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.12 Supply and Distribution of HIS-UK Intervention Condoms and Lubricants

<u>Ordering</u>

Condoms supplied in the HIS-UK condom kits and mail-out supplies at T1-T12 will be sourced and supplied by the research team (discounted commercial supply). Reimbursement for the cost of these will be sought from sites through the offset against site research costs unless costs can be covered by other means.

Distribution

The research team will make up and distribute HIS-UK kits to the trial sites. The research team will also be responsible for the postal distribution of kits to HIS-UK trial participants who receive a telephone or on-line video SS consultation, and for the distribution of condoms and lubricants ordered by HIS-UK trial participants at T1 to T12.

At the end of the trial

Any remaining HIS-UK kits may be utilised by the sites at the end of the trial and are not required to be returned to the research team.

7.13 Assessment of Compliance

Participants randomised to the proHIS arm are required to demonstrate condom competency to the SS during the intervention education and training consultation.

SS provide a comprehensive condom application demonstration using a penile demonstrator to teach correct condom use competency. To meet the competency requirement, each participant must repeat back the demonstration (verbally or actively) to the SS until no errors are made. Competency is recorded within *Lifeguide*.

Compliance to the HIS-UK home-based exercises will be monitored and assessed by the research team through the number of condom/lubricant rating forms submitted by eHIS and proHIS participants. Protocol compliance is defined as a minimum of three submitted rating forms and full compliance as the submission of eight.

To examine compliance of the eHIS intervention participants' access to and usage of the eHIS intervention will be recorded within *Lifeguide*. All compliance data will be collated from *Lifeguide.*

7.14 Impact of COVID-19 pandemic

Due to the uncertain future of the pandemic, additional options of online registration and telephone and video consultations have been added. Sites should perform face to face in-clinic consultations when possible and deemed feasible by the site and participant, but this will remain dependent on the pandemic status. Alternative options of online registration and video/telephone consultations will be used when required in order for the study to continue and remain safe for participants and site staff.

The number of sites required to achieve the recruitment targets could also be impacted by the pandemic and the research team will monitor recruitment rates throughout the study. If required, additional sites will be added to improve recruitment, in accordance with REC/ HRA requirements for non CTIMPs via a non-substantial amendment.

8 SAFETY

8.1 Definitions

International Conference for Harmonisation/Good Clinical Practice (ICH/GCP) requires that both investigators and Sponsor to follow specific procedures when notifying and reporting adverse events/reactions in research studies. These procedures are described in this section of the protocol.

For this Non-CTIMP trial only reports of Serious Adverse Events (SAEs) that are:

- **Related** to the trial (i.e. they resulted from administration of any of the research procedures)
- **Unexpected** (i.e. not listed in the protocol as an expected occurrence)

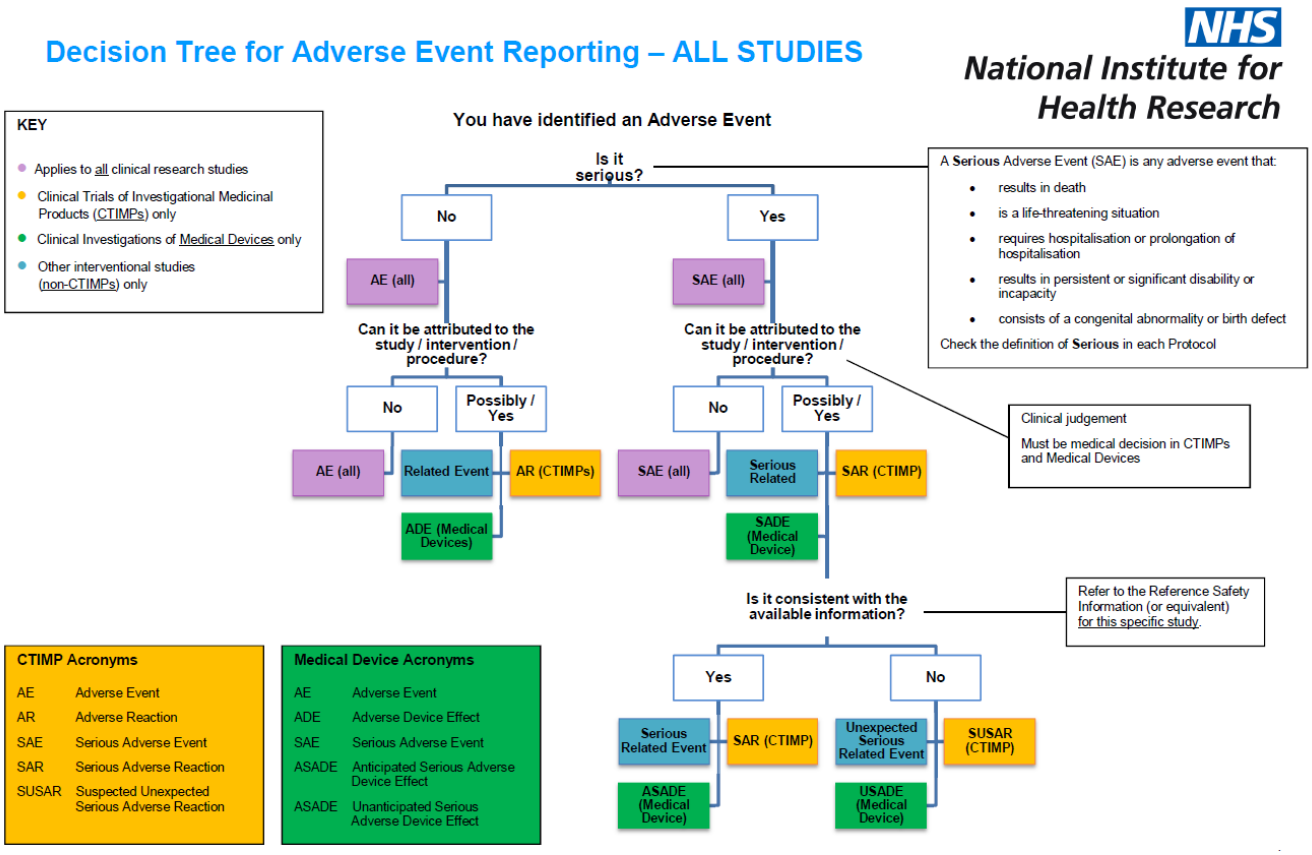
will be submitted to the REC that approved the trial using the Non-CTIMP safety report to REC form. These will be sent within 15 days of the Chief investigator (CI) becoming aware of the event.

Table 1: Definitions applicable in HIS-UK trial

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a trial intervention, whether or not related to that trial treatment.
Serious Related Event or Unexpected Serious Related Event.	Any **related event or unexpected event** that meets the definition below that can be attributed to the trial/intervention/procedure, that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation** or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity (based on clinician's judgement) Will be reported.

Life-threatening (*), in the definition of 'serious', refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

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 (excluding psychosis) including elective procedures that have not worsened do not constitute an SAE.



8.2 Causality and Expectedness

Table 2. Definitions of Causality for Serious Related Events

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship.	Not reported
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Not reported

Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the trial intervention, and there is some possible link to the trial). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	Serious Related Using the reporting form report within 24 hours of being made aware to BSCTUsafety@bsms.ac.uk and to the site PI
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Serious Related Using the reporting form report within 24 hours of being made aware to BSCTUsafety@bsms.ac.uk and to the site PI
Unexpected	It is not consistent with the available information for this trial intervention.	Unexpected Serious Related Event Using the reporting form report within 24 hours of being made aware to BSCTUsafety@bsms.ac.uk and to the site PI

For example, related events may be as follows:

I. Embarrassment, discomfort, anxiety or distress caused by contents of the educational training, booklet or website;

II. Embarrassment, discomfort, anxiety or distress caused by undertaking the HIS-UK home-based exercises;

III. Embarrassment, discomfort, anxiety or distress caused by answering questionnaires or taking part in the interviews;

IV. Disappointment at being allocated to the control arm;

V. Distress caused by concern about data security and confidentiality in the trial (routine text and e-mail messages);

VI. Anxiety or distress caused by concern about risk of sexually transmitted infection and risk taking sexual behaviours;

VII. Others as deemed by the site.

Expectedness

The expectedness of the SAE will be assessed by the local delegated investigator (named PI) and the CI and must be reported to the BSCTU within 24 hours of the site being made aware (BSCTUsafety@bsms.ac.uk).

8.3 Reporting and Responsibilities

Notification Procedure for Serious Related and Unexpected Serious Related Events.

1. The initial form must be completed by a member of the SS team who is on the delegation of responsibilities log.
2. Send the initial form with as much information as possible by email to BSCTUsafety@bsms.ac.uk and the PI as soon as site becomes aware of it. The PI reassess the causality and assess the expectedness. The initial report shall be followed by detailed, follow up reports as appropriate.
3. Follow-up: Patients must be followed-up until clinical recovery is complete, or until the event has resolved. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information must be reported on the follow-up/final report. In the absence of the PI, the form should be completed and signed by another trained member of the site staff team who is named on the delegation log (as designated by local PI). The PI should subsequently check the form, make changes as appropriate, sign and then send to the Brighton & Sussex CTU as soon as possible. The patient must be identified by a study participant ID number. The patient's name must not be used on any correspondence. This final report is then graded on the basis of expectedness judged by the PI and CI.
4. The BSCTU will notify the research ethics committee as per the conditions of the favourable opinion and according to CTUSOP018 within 15 calendar days of the BSCTU first being notified of the event.

It is the responsibility of the BSCTU in collaboration with the CI for:

1. Central data collection and verification of all reported events according to the trial protocol onto a database.
2. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
3. Notifying Investigators of events that occur within the trial.
4. Preparing standard tables and other relevant information for timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

8.4 Urgent Safety Measures

The Sponsor, PI or CI may take appropriate safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. The REC that approved the trial will be notified immediately and in any event within three days, in the form of a substantial amendment that such measures have been taken and the reasons why.

8.5 Notification of Deaths

Only deaths that are assessed to be caused by the intervention will be reported to the sponsor. This report will be immediate.

8.6 Safeguarding of Participants

Safeguarding means protecting a person's right to live in safety, free from abuse and neglect. All NHS staff have a responsibility to safeguard people in their care, but extra care must be taken to protect those who are least able to protect themselves. Children and young people, and vulnerable adults, can be at particular risk of abuse or neglect. A child is a person aged under 18 years. Responsibilities for safeguarding are enshrined in legislation.

Within the NHS clinic setting:

Any allegation received during the study registration process that suggests the participant to be at risk of significant harm (physical harm, emotion and psychological harm, sexual harm and exploitation, neglect) will be dealt with under the NHS safeguarding policy.

Contacts with the research team:

If a participant divulges any worries or concerns in relation to the study during follow-up, the researcher will signpost the young person to a source of advice and support. In the event of a participant divulging information that is considered to pose an immediate risk, such as the intention to harm themselves or allegation of abuse, then any confidentiality agreements will be overridden and the participant will be informed that their information will be passed through the University of Southampton's Safeguarding system so they are supported. Allegations will be discussed with the Principal Investigator, in order to make a risk assessment as soon as possible, and to agree actions and possible contact with external agencies e.g. Police, Social Services. Nominated Safeguarding Officers/Leads and Clinical Leads may also be involved at this stage. The young person cannot refuse for this referral to occur.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample Size Calculation

For the purposes of sample size estimation, the primary health outcome is the test positivity rate of Chlamydia at six months post randomisation.

The effectiveness of HIS-UK delivered by proHIS and eHIS will be analysed with an overall Type I error rate of 5% (2.5% per comparison), comparing test positivity among each of the intervention arms with the control arm (usual care). Data published by the National Chlamydia Screening Programme suggest a test positivity rate of 11% among young men aged 15-24 years in England tested in specialist sexual health services. [28] The trial is powered to detect a reduction in Chlamydia test positivity rates among young men in our intervention arms from 11% to 6% (a 45% reduction) at six months post randomisation.

Previous piloting suggests that the intervention is likely to be equally effective across all subgroups (deprivation, ethnicity, sexual orientation, age) [15,25].

In order to have 85% power to detect the projected difference in the analyses requires 476 participants in each of the arms (G*Power 3.1.9.2). To minimise risk to the trial and to reflect 36% attrition at follow-up (observed during our HIS-UK feasibility testing) [15], a total of 2231 participants will be randomised over a period of 30 months during three recruitment waves.

9.2 Planned Recruitment Rate

Participants will be randomised during three recruitment waves:

- Wave 1 (estimated months 1-3) 135 young men;
- Wave 2 (estimated months 4-15) 540 young men;
- Wave 3 (estimated months 16-30) 1556 young men.

We have based our recruitment time calculations on an estimated site recruitment rate of 15 young men randomised per calendar month.

Waves 1 and 2 of recruitment will take place within a minimum of three NHS Trust regions.

Additional sites (a minimum of three) will recruit during Wave 3; these will be selected in consultation with partnering NHS Trusts determined following a CRN-facilitated expression of interest call via the trial support service.

9.3 Statistical Analysis Plan

9.3.1 Data Analysis

Analysis and presentation of data will be in accordance with the revised CONSORT 2010 statement. [34] The statistical analysis will be performed on available cases following intention-to-treat principles (ITT) with due emphasis placed on confidence intervals for the between-arm comparisons. Baseline demographic (age, ethnicity, deprivation, sexual orientation, etc.) and self-reported outcome measure data (secondary process indicators) will be assessed for comparability between the arms using descriptive analyses.

The primary analysis will be undertaken using generalised linear modelling to compare the effectiveness of the active HIS-UK intervention delivered by proHIS and by eHIS to reduce the test positivity rate of Chlamydia at 6 months versus treatment as usual (control group). The analysis will be replicated for test positivity at twelve months to examine the longevity of any intervention effect. The models will include the baseline test result, the stratification factors and two dummy variables for the intervention arms.

The extent of missing data will be reported and baseline factors will be compared from completers and non-completers to assess the extent of any bias that may result. As our analysis is based on ITT principles, withdrawals and protocol violators will be analysed in their arms as randomised. Depending on the extent of any missing data and the potential of any bias, a further analysis may be undertaken on those participants who complete, as compared to the ITT results. Following multiple imputation sensitivity analysis with variable assumptions will be undertaken to investigate the potential effects of missing data.

Analyses will be extended to include the investigation of possible intervention moderators and mediators, the exploration of process measures (for example, number of condom tests completed and follow-up SS consultation method), and which young men benefit from proHIS and eHIS the most (age, sexual orientation, ethnicity, social deprivation).

Similar comparative analyses using the secondary process indicators (those through which the primary outcome is likely to be realised) collected at T0-T12 will be undertaken using generalised linear mixed modelling to allow for the analysis of repeated measurements over time and comparison between the trial arms.

A full statistical analysis plan will be agreed prior to commencing the final analysis.

9.4 Interim Analysis and Criteria for the Premature Termination of the Trial

The first wave of recruitment will be run as an internal pilot to assess trial acceptability, intervention fidelity, and the feasibility of randomisation and Chlamydia screening for trial continuation. Assessment of progression will be made based on a pilot cohort of 135 young men , followed up for a period of six months; the findings from in-depth process interviews conducted with all SS and a sub-sample of up to 20 young men; and the assessment of intervention fidelity recordings.

During this period we aim to answer the following questions:

- Can sites recruit eligible young men at a reasonable rate and to the numbers anticipated?
- Are young men willing to be randomised within the trial?
- Is Chlamydia screening at T0 and T6 sufficiently acceptable and feasible to implement?
- Do young men remain in the trial in sufficient numbers at six-month follow-up?
- Are the intervention and trial design sufficiently acceptable?
- Are SS able to deliver the intervention with reasonable fidelity?

9.4.1 Progression criteria

a) Min 75% target recruitment number during the pilot phase

b) Min 85% of eligible participants willing to be randomised

c) Min 90% uptake of STI screening in-clinic at T0

d) Min 70% postal STI screening kits returned at T0 and T6[2]

e) Maximum 36% attrition at 6 months

f) Intervention fidelity rated highly

g)Min of two additional recruitment sites enrolled to the trial during the pilot phase

Based on the outcomes of the criteria, the following scenarios are possible: No outcomes met (stop, main trial not feasible); some outcomes met and others amenable to improvement, such as enhanced recruitment strategies or alternative STI screening strategy (continue, main trial feasible with modifications); all criteria met (continue, main trial feasible with current design).

9.5 Economic Evaluation

The economic analysis will analyse the costs and outcomes associated with the three arms of the trial. This will involve evaluating the costs and benefits of the two delivery models for the HIS-UK intervention (pro-HIS and e-HIS), as compared with usual care. If pro-HIS and/or eHIS are effective in improving competency for consistent and correct condom use and reducing the incidence of STIs, there are likely to be important cost implications for the healthcare sector, for the wider public sector, and for society as a whole. The primary base case analysis will therefore adopt a public sector perspective, as far as this is possible, with healthcare and patient perspectives undertaken as secondary analyses.

9.5.1 Data Collection

Resource use data will be collected prospectively to estimate the costs associated with each of the trial arms (for the two delivery models for the intervention and for usual care). This will include: (1) the cost of the HIS-UK intervention delivery, for face-to-face (pro-HIS) and digital (eHIS) models, and the cost of usual care. For example: (1) The costs of the condom kits, consultation costs (face-to-face in-clinic and via video/telephone consultations), costs associated with digital delivery, and other resource use; (2) costs experienced after receiving the HIS-UK intervention (delivered by proHIS and eHIS) or usual care; for example, condom costs, GP/sexual health service visits, other public resource use; (3) costs associated with the treatment of any STIs and other conditions; (4) personal costs experienced by young people; for example, travel costs, internet and mobile data use, out-of-pocket expenses. Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost per participant to be calculated. E.g., [35]

Resource use data will be captured via a variety of mechanisms. Firstly, within the trial, the resource use and costs associated with delivering proHIS and eHIS and any follow-up care (for example, in relation to treatment of STIs in clinic) will be captured via trial reporting mechanisms. The main focus will be on the differences in resource use between the two different delivery models, and in relation to usual care. Wider NHS and public sector resource use will be captured via a questionnaire for young people; this will include the use of medication, Health Centre/GP visits, sexual health centre visits and other public sector resource use. We will also capture any patient costs associated with receiving the intervention (via the two models of delivery) and usual care.

Alongside the clinical outcomes collected in the trial and in line with recommendations from the National Institute of Health and Care Excellence (NICE), data will also be captured that will allow quality-adjusted life years (QALYs) to be used as outcome measures in the cost-effectiveness

[2] This reflects current return rate of kits requested via freetest.me run by Preventx Limited https://www.sciencedirect.com/science/article/pii/S0277953613006217

analysis. [36] It is recommended that QALYs are calculated so that cost-effectiveness can be compared across disease areas. This will require changes in health-related quality of life (HRQL) to be captured for all trial arms. While the EQ-5D-5L [37] is the questionnaire recommended by NICE to measure HRQL, NICE also recognises that this measure may not be suitable within economic evaluations of public health interventions. [38] This is particularly the case with sexual health interventions, which have an important psychosocial aspect. [39] For this trial, HRQL will therefore be collected using the SF-12 instrument, which has previously been successfully used in a related context [40] and the EQ5D-5L instrument. These questionnaires will be administered to compare changes in health-related quality of life for the three arms, at T0, T6 and T12 time periods.

9.5.2 Economic Analysis

In order to assess the costs and benefits of HIS-UK (delivered via proHIS and eHIS) compared with usual care, both a within trial analysis and a model-based economic analysis will be undertaken.

9.5.2.1 Within Trial Analysis

The within trial analysis will use the data collected within the trial, and so estimates of costs and benefits will relate to the initial period of 6 months and extended to 12 months, based on the primary outcome associated with the trial. The data used for this analysis will primarily be the trial-specific resource use data and costs. The main economic analysis will assess cost-effectiveness based on incremental cost per QALY gained at 6 months, with a secondary analysis of cost per case of Chlamydia avoided at 6 months, reflecting the primary outcome of the trial; this analysis will then be repeated to measure cost-effectiveness over a 12-month period. Initially, the base case analysis will be framed in terms of a cost-consequence analysis for the three trial arms, and data will be reported in a disaggregated manner on the incremental cost and important consequences assessed in the trial.

9.5.2.2 Model-based Analysis

If the trial shows that proHIS and/or eHIS are effective in reducing Chlamydia incidence and other condom use health behaviour outcomes, compared with usual condom distribution care, it will be necessary to assess the cost-effectiveness of the intervention delivery models in the longer term. Therefore, if deemed necessary, based on the results of the trial, a decision-analytic model will be used to extrapolate costs and outcomes beyond the end of the trial and synthesise data on costs and outcomes from a range of sources. [41] The evidence used in the model will be drawn from the trial and a comprehensive review of the literature. The literature review will include evidence on condom use and failure, prevalence of Chlamydia and other STIs, transmission rates and long term outcomes. If data availability permits (based on an assessment of the results of the RCT and the literature review), a public sector perspective will be adopted, as well as an NHS perspective, in line with recommendations [36, 42]. The review of the literature will evaluate existing economic evaluations and models, to inform the design and parameters of the model developed as part of the trial. There are a range of published economic models in this area, some focussing specifically on interventions to improve condom use, and these publications will be used to inform model construction e.g., [39, 43]. The final model will compare the incremental benefits gained and costs for the proHIS and eHIS interventions compared with usual care, over the lifetime of the patients where possible.

9.5.2.3 Presentation of Results and Sensitivity Analyses

The economic evaluation will be conducted and reported in accordance with relevant guidelines. [44. 45] Results will be presented using cost-effectiveness acceptability curves (CEACs) to show the uncertainty surrounding the cost-effectiveness of the proHIS and eHIS interventions, for a range of thresholds for cost-effectiveness. [46] We shall use both deterministic and probabilistic sensitivity analyses (PSA) to explore the inherent uncertainty around the estimates employed in the evaluation. [41] The choice of distributions for the PSA will be based upon current best practice in modelling. [47]. For the longer-term analyses, discounting will be undertaken to reflect recommendations by NICE and the Treasury.

10 DATA MANAGEMENT

10.1 Data Collection Tools and Source Document Identification

The investigator/institutions will keep records of all participants (excluding patient ID numbers). Trial sites will hold all participant case report forms (CRF – which contain sufficient information to link to patient records) unless instructed otherwise by the sponsor.

All participant source data will be collated within *Lifeguide* and stored on the *Lifeguide* server located within the University of Southampton iSolutions secure research data storage service. *Lifeguide* is an interactive web-based intervention software platform and secure validated data management system designed to collect participant information and deliver digital interventions (DI) to support health behaviour change. [26]

For the purposes of analysis the following software packages will be used:

- IBM SPSS Statistics
- Stata version 16 or above
- Excel
- MlwiN

10.1.1 Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

- Eligibility screening data
- Consent data
- Baseline questionnaire data (T0): standardised and non-standardised tools
- Consultation digital recordings
- Screening outcome data
- Condom/lubricant rating forms
- Follow-up questionnaire data (T1-T12)
- Follow-up screening outcome data
- Audio recordings and transcripts from interviews

10.1.2 Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Case report forms (CRF) and Non-eligibility response forms (NERF) are considered source documents. If instructed source documents are to be transmitted to the sponsor. NERF documents which do not contain participant data are to be transmitted via registered post, CRF documents will be transferred by courier. It is necessary for the trial sites to retain copies of all CRF and NERF to ensure that the PI has an independent account from the sponsor as to what has occurred during the trial at their site.

10.2 Data Handling and Record Keeping

All trial procedures will comply with the relevant General Data Protection Regulation (GDPR) and in accordance with the University of Southampton's Research Data Policy and that of the collaborating institutions.

The research team will ensure that all research data and records are:

- Accurate, complete, authentic and reliable;
- Identifiable, retrievable, and available when needed;
- Secure and safe;
- Kept in a manner that is compliant with our legal obligations (and the requirements of the funding body); and
- Able to be made available to others in line with appropriate ethical, data sharing and open access principles.

All data generated as part of the trial (electronic and hard copy) will be securely stored in line with procedures approved by the Faculty of Environmental and Life Sciences Ethics Committee at the University of Southampton.

All electronic data (including media files from digital recordings) will immediately be transferred and stored in the University of Southampton iSolutions secure research data storage service. The data stored within these facilities is regularly backed up and, a copy of the back-up in Southampton is regularly off-sited to a secure location for disaster recovery purposes. Only authorised users can access data stored within these facilities and it is managed under the governance of the University of Southampton's Research Data Management Policy. Anonymised transcripts (anonymised at the point of transcription) and any personalised data collected will also be stored on the University's managed storage in separate password protected folders. Transfer of pseudonymised electronic data between the research institutions will be via the University of Southampton's password secured Encrypted Electronic Safesend Service or courier. Transfer of participant data between the sites and the University of Southampton will be via the University of Southampton's password secured Electronic Safesend Service.

Hard-copy data will be securely stored in lockable filing cabinets. All personalised data will be independently stored (in separate filing cabinets) from hard-copy notes and transcripts.

Personal respondent information will not be released to, or viewed by, anyone other than that of the research team working on the project.

Data collected during the trial will be used only for research purposes, and results will be presented in a publically available final report. Results of the trial will also be submitted for publication in scientific journals, presented at scientific conferences, and disseminated to government departments, non-governmental organisations, health professionals, educators, academics and the general public as part of educational activities. No identifiable data (such as names or addresses) will be used in any publication or dissemination activity.

10.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor/host institution/CTU and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

10.4 Archiving, data documentation and preservation

Standard metadata procedures (e.g. Datacite) will be followed to ensure others are able to find, access and ultimately reuse data generated as part of this trial, with Digital Object Identifiers (DOIs) being issued for the dataset and data subsets as per the University of Southampton's DOI policy. Metadata records for the data (and published outputs) will also be maintained on the University of Southampton Institutional Research Repository. In accordance with the University's Data policy, the data will be

archived in an appropriate repository (UK Data Service, eprints and Dspace, for example) for a minimum of ten years after publication or last access, whichever is longer, to ensure long term access and safeguarding of the data and resulting outputs.

Future users of the data will be bound by data sharing agreements. Where suitable, a licence (currently Creative Commons) can be applied to data deposited in the repository.

All study essential documents making up the Trial Master File (TMF) will be held in an electronic repository stored in University of Southamptons secure online repository (SharePoint) and in an Investigator Site File (ISF) at each site.The ISF will either be in a paper format or electronic format, depending on the site's governance policy.

Following the closure of the study the essential documents stored in the ISF should be archived in accordance with local policy and procedures. The TMF will be archived according to the Sponsor's archiving policy.

Archiving will be 39ehavioura by the Sponsor following submission of the end of study report. All essential documents will be archived for a minimum of 5 years after completion of the study and can then be destroyed unless notified otherwise by the Sponsor. The research data will be stored for 10 years after the study has ended.

10.5 Data Destruction

To enable the secure disposal of locally held electronically data, the Sponsor retains an external company that specialises in destroying magnetic and solid state media and will provide a "Certificate of Assurance".

Print based materials will be destroyed carefully by shredding. Additionally, Southampton University Estates and Facilities provide a service for the specific removal of shredded confidential waste, defined as "material containing sensitive personal or business sensitive data which requires destruction to ensure that the contents remain private in order to comply with GDPR".

11 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment that may include on-site monitoring. This will be dependent on a documented risk assessment of the trial.

The processes reviewed will relate to participant enrolment, consent, eligibility, allocation to trial groups, adherence to trial interventions and policies to protect participants. Monitoring will be done by exploring the trial dataset, scrutiny of consultation digital recordings, telephone discussions with site Pis and, if necessary, by performing site visits.

Monitoring will be performed across all recruitment sites and will be undertaken by staff at Brighton and Sussex CTU in collaboration with the research team at University of Southampton.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee (REC) Review & Reports

Before the start of the trial, approval will be sought from the University of Southampton Research Integrity and Governance (RIG) Office for the trial protocol, informed online consent forms and other relevant documents as required. HRA approval will then be sought.

Substantial amendments that require review by REC will not be implemented until the REC and the University of Southampton RIG Office grants a favourable opinion for the trial.

All correspondence with the HRA will be retained in the Trial Master File (TMF) Management system.

An annual progress report (APR) 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.

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial.

If the trial is prematurely ended, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

12.2 Peer review

This protocol has been reviewed and agreed by NIHR Public Health Research Programme (funder).

12.3 Public and Patient Involvement

PPI will be actively involved in all of the following stages of the research:

- Design of the research
- Management of the research
- Contributing to developing ethics information and consent forms, trial advertisements
- Developing participant information resources
- Contributing to the reporting of the research
- Providing feedback on the final eHIS webpages
- Conducting interviews with participants
- Dissemination of project findings

The trial has a PPI representative who will sit on the Trial Steering Committee, Trial Management Group, Project Advisory Group and chair the Dissemination Working Group. There will be additional PPI representatives recruited to sit on the Project Advisory Group and the Dissemination Working Group.

All PPI representatives will be recruited from across the research sites with support from the other Co-Is. The role of the PPI representatives who sit on the Dissemination Working Group is to be actively involved in the development of the impact and dissemination strategy and all associated activities.

All PPI Advisory Group members will be offered a range of training activities, including learning sessions, quality materials and guidance, conference attendance opportunities (with opportunities to present if they wish), peer shared learning experiences and skills development courses (e.g., presentation skills). Project mentoring along with practical and emotional support will be provided through peer support mechanisms and team meetings.

The opportunity to train PPI representatives to conduct elements of the research (follow up in-depth interviews) will be explored. The involvement of young men in all of the above stages will ensure that the trial reflects their concerns/interests. All PPI activities and training have been costed appropriately using INVOLVE methodology.

12.4 Regulatory Compliance

Before any site can enrol participants into the trial, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the trial, the Chief Investigator or designee, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the trial delivery team) so they can put the necessary arrangements in place to implement the amendment to

confirm their support for the trial as amended.

12.5 Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g., it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can, however, happen at any time. They must be adequately documented on the relevant forms and reported to the BSCTU and Chief Investigator immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

12.6 Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a breach that is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

12.7 Financial and other Competing Interests for the Chief Investigator, Pis at each Site and Committee Members for the Overall Trial Management

We will identify and disclose in our final report any competing interests that might influence trial design, conduct, or reporting.

This will include:

- Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial.
- Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company.
- Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

12.8 Indemnity

Appropriate arrangements have been put in place for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management and/or design of the research.

Appropriate arrangements (NHS indemnity scheme) will be put in place for insurance and/ or indemnity to meet the potential legal liability of sites arising from harm to participants in the conduct of the research.

Appropriate arrangements have been put in place for insurance and/or indemnity to meet the potential legal liability of the sponsor arising in relations to the supply of tablet computers to sites.

12.9 Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC/HRA will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the

purposes of submission to the REC/HRA.

All amendments must be approved by the University of Southampton RIG Office. Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS capacity and capability for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to the HRA/NHS R&D (e.g. a change to the funding arrangements).

All amendments will be communicated to relevant stakeholders through the necessary communication channels.

Amendments history will be tracked by way of a version control table to identify the most recent protocol version.

12.10 Post-Trial Care

At the end of the trial all participants will be granted access to the eHIS website providing information and education regarding the effective and correct use of condoms and lubricants, along with a selection of condoms and lubricants.

12.11 Access to the Final Trial Dataset

Only the CI and all Co-Investigators will have access to the full trial dataset. The dataset shared with the Co-Investigators will be pseudo-anonymised.

13 DISSEMINATION POLICY

13.1 Dissemination Policy

It is a funder requirement that all project outputs must be notified to the funder at least 28 days before publication or presentation. An output is any item arising from NIHR-funded research that enters the public domain. Outputs can be written, audio/visual, electronic or verbally presented. The NIHR takes a broad definition of what constitutes an output and must be acknowledged as the funder of the research in both oral and written outputs. All published material must contain an acknowledgement of funding, and when mentioning research findings or opinions, an appropriate disclaimer.

On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared.

The full trial report will be made available on the project website, relevant institutional websites that of the funder, along with an executive lay summary. Participants will be informed of this.

The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals. The CI has final approval of all outputs.

Authorship will be based on the following four criteria plus any updates issued by the Sponsor throughout the study:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able

to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged.

As per the Sponsor Open Access Policy the following research outputs will be deposited and made publically available in the University of Southampton's institutional repository:

- The bibliographic metadata of all forms of published output, so there is a comprehensive record of research activity;
- The final, refereed, corrected, accepted manuscripts of all peer-reviewed journal articles and peer-reviewed conference articles at the point of acceptance for publication;
- Research data identified as significant under the University's Research Data Management Policy, including data underpinning publications;
- Outputs which the University issues with an ISSN, ISBN or DOI.

14 REFERENCES

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15 VERSION HISTORY

Protocol version number	Date	Summary of changes/ Notes
1.0	Aug 2019	N/A – Initial submission to REC
2.0	23 Oct 2019	Response to REC • Typographical corrections, administrative and formatting changes • Clarifications made in section 7.7.2 and 10.1 on data transfer • New section 8.6 added –Safeguarding of participants
3.0	02 Dec 2019	Non-substantial amendment • Section 7.6.3 updated to a minimum of eight different types of condoms will be used in the study
4.0	03 Apr 2020	Substantial amendment • Section 6.1 Inclusion criteria updated to include participants experiencing condom errors in the study • Section 7.5.2 and 7.7.2 Clarification on triple testing for chlamydia added • Section 7.5.2 and 7.7.2 Standard of care chlamydia tests result performed within 4 weeks of the time point may be used at baseline, 6 month and 12 month follow up, if deemed appropriate to do so by site staff. • Flowchart –summary of triple testing refusal processed moved from section 7.7.2 to 7.5.2 • Section 7.7.2 – Clarification on the postal kits process added and section re-ordered for simplification and clarity. • Section 7.7.2 updated to reflect that all participants will be given the option of a postal kit. Sites that do not or unable to provide a postal service will be substituted for provision supplied by the research team. • Section 7.8 – Clarification on the transfer of digital recordings added • Typographical corrections, administrative and formatting changes throughout the protocol. • Section 15 –Protocol version history added
5.0	16 Oct 2020	Substantial amendment • New sections added to reflect the impact of COVID-19 pandemic on the study. • Alternative options for online expression of interest, online self-registration and video consultations via an NHS approved video consultation system added to allow the study to continue in a safe manner,

		when required due to the pandemic status. • Two options for chlamydia screening – postal kits provided by the research team or in clinic by the site team. • Typographical corrections, administrative and formatting changes throughout the protocol.
6.0	24 Feb 2021	Non-substantial amendment: Section 7 updated to clarify: • The control arm is delivered as per standard of care • Site staff (SS) consultation to confirm participant self-registration can be performed via a telephone call for eHIS and Control arm participants. • At Baseline, sites can provide postal kits in clinic for Chlamydia screening to reduce to face to face contact, if required due to the pandemic.
7.0	20 Oct 2022	Non-substantial amendment: • Update to 10.4 to outline how the Trial Master File and Investigator Site Files are to be archived. • Section 12.10 updated to state all participants will receive condoms and lubricants at study completion.
8.0	05 Dec 2022	Non-substantial amendment: • Additional row on signature page to account for sponsor signature. • Section 15 Version History – Addition of protocol 7 and 8 .
9.0	25 Jan 2023	Non-substantial amendment: • Prof Cynthia Graham's telephone number updated and Dr Nicole Stone is responsible for the financial aspects of the study.