Trial Title: Screening with Tampons: Evaluating Diagnostic Accuracy for STIs, BV and HPV and Assessing Participant Views

Short title: STAMP

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Protocol Number: LH-DA-01

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Protocol signatures

Protocol Title: STAMP: Screening with Tampons: Evaluating Diagnostic Accuracy for STIs, BV and HPV and Assessing Participant Views

Protocol Date and Version No: V3.0 29 Nov 2023

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

Protocol Synopsis

Protocol Title	STAMP: Screening with Tampons: Evaluating Diagnostic Accuracy for STIs, BV and HPV and Assessing Participant Views
Protocol Version and Date	V3.0 29 Nov 2023
Protocol Number	LH-DA-01
Sponsor	Tampon Innovations LTD, which is a subsidiary of DAYE
CRO	Lindus Health
Trial Design	Diagnostic trial comparing the diagnostic accuracy of the DAYE Diagnostic Tampon (DDT) with a vaginal swab (self-collected and clinician taken).
Location	UK and Italy
Recruitment Strategy	Participants will be recruited centrally or via site visits. Participants will be identified via primary care, advertising on social media and to patient communities, or via clinic lists and clinic visits at a trial site.
Trial Aims	• To measure the diagnostic accuracy of the diagnostic tampon in a diverse population of people assigned female at birth. • To compare the performance of the diagnostic tampon with traditional diagnostic methods to identify potential advantages and challenges. • To assess the acceptability and usability of the diagnostic tampon among the target population and explore feasibility and clinician acceptability of the diagnostic tampon in clinical practice among key stakeholders. • To provide evidence-based recommendations for the integration and sustainability of the diagnostic tampon into current health practices.
Trial Objectives	**Primary Objective:** • Evaluate the diagnostic accuracy of the Daye

	diagnostic tampon for detecting Chlamydia, Gonorrhoea, BV and HPV, specifically demonstrating a sensitivity of more than 70% for DDT. **Secondary objectives:** ● Assess the usability of the DDT (via ASQ). ● Explore participants' views of the usability and acceptability of the DDT. ● Assess whether the DDT is a preferred sampling method for participants. ● Assess if the order of sample collection (self-swab vs DDT) impacts diagnostic accuracy. ● Understand the health economic consequences of using the DDT for STI, BV and HPV testing. ● Explore stakeholder attitudes to tampons as a means of sample collection for microbial testing. ● Assess the occurrence of AEs/SAEs as a result of tampon sampling. **Exploratory objective:** ● Explore the relationship between duration of wear and diagnostic accuracy.
Sample Size	350 participants Group 1: 50 participants with a recent confirmed HPV+ diagnosis (UK and Italy) Group 2: 300 participants from the general population (UK only)
Procedures	All participants will have 3 samples taken: the DAYE Diagnostic Tampon (DDT), a vaginal self-swab and a clinician taken vaginal swab that is validated for use for the downstream microbial test.
Randomisation	All participants will be randomised using block randomisation according to sample order for the DDT and self-swab: ● Group A: Approximately half the participants will perform the self-swab followed by the DDT. ● Group B: Approximately half the participants will perform the DDT followed by the self-swab
Daye Diagnostic	The DAYE Diagnostic Tampon is a class A in vitro diagnostic

Tampon	device. It has CE certification (self-certified via a declaration of conformity, following the IVDR (EU) 2017/746).
Eligibility	Inclusion Criteria 1. Individuals aged 25-65 years. 2. People assigned female at birth (AFAB). 3. Sexually active individuals. 4. **Group 1 only:** Confirmed HPV+ diagnosis within the past 4 weeks. a. *UK only*: Ability to upload evidence of this diagnosis to the trial ePRO system (e.g. via a screenshot of the NHS app, or similar to be reviewed by the trial team). 5. Willingness to give informed consent and adhere to trial procedures. Exclusion Criteria 1. Previous hysterectomy or total hysterectomy with removal of cervix 2. Known allergy or sensitivity to tampons 3. History of TSS (both tampon-associated and non-tampon associated) 4. Individuals who are pregnant or breastfeeding. 5. Participation in another interventional clinical trial or use of investigational drugs in the last 30 days. 6. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

To enquire about the trial, contact the STAMP Trial Team:

STAMP Trial

Lindus Health

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1. BACKGROUND AND RATIONALE

1.1 Background

Medical innovations routinely misunderstand and under-serve women's bodies and minds. This is unsurprising, as guidelines (EU/UK) and regulation (US) on inclusion of women as participants in modern medical research were only brought in during the 1990s. There is therefore a large gap in medical research available for a range of gynaecological conditions.[1]

Sexually Transmitted Infections (STIs), Human Papillomavirus (HPV) and vaginal infections are a serious threat to gynaecological health, with pelvic inflammatory disease, Cervical Cancer (CC), and infertility among the risk factors.[2,3] However 70% of gynaecological infections are asymptomatic and may remain undiagnosed.[4] Early detection of HPV, CC and STIs often leads to successful management and full recovery. Healthcare systems are struggling to increase testing uptake for HPV. Even before COVID disrupted screening programmes uptake was as low as 25% in many EU countries.[5] Clinician-taken swabs lead to higher healthcare costs and have a historically low uptake, limiting early STI and HPV detection. Challenges include emotional barriers and practical impediments such as embarrassment, discomfort, time constraints, and a labour-intensive collection process.[6]

Currently the process of screening and treatment of STIs, Bacterial Vaginosis (BV) and HPV through public healthcare services is very disjointed. While menstrual tampons are a novel method for sample collection, they are already widely used on a monthly basis by 85-90% of pre-menopausal women in western Europe, the UK, and the US.[7] They offer high absorbency and familiarity, making them a promising tool for sample collection.[8,9] Their utilisation could enhance screening accessibility, especially for women facing barriers such as cost, stigma, or inconvenience.

Developing a sensitive and user-friendly diagnostic tool using menstrual tampons could significantly improve women's health outcomes, reducing the incidence of HPV and STI-related cancers. Leveraging the convenience and familiarity of tampons may increase screening uptake and enhance early detection and treatment of STIs.

The Daye Diagnostic Tampon (DDT) is an at-home-based gynaecological test kit, using a menstrual tampon for sample collection. The DDT can be sent in a screening kit to the participants home and needs to be worn for a minimum of 20 minutes to collect a potent sample.

This trial aims to assess the feasibility and accuracy of using menstrual tampons as a specimen collection device for HPV, BV and STI testing, comparing it to self-collected and clinician-collected swabs. This method of testing offers an alternative to traditional methods like urine or blood samples that may not be accessible or convenient for everyone. By increasing testing rates and improving early detection, the use of menstrual tampons has the potential to enhance healthcare outcomes.

1.2 Rationale

Vaginal health screening often has very low uptake, meaning that most women are unaware of their HPV, BV and STI status. Knowledge of HPV status could encourage uptake of preventative treatments (such as HPV vaccine) and uptake of screening for cervical cancer. Cervical cancer is one of the most preventable and curable forms of cancer as long as it is detected early and managed effectively.[10] The Daye Diagnostic Tampon offers a preferred sampling method for screening which will help improve uptake of testing and enable timely diagnosis and treatment.

1.3 Clinical Studies

Preliminary research conducted by Daye has shown that self-collected tampons exhibit diagnostic accuracy on par with clinician-collected swabs for detecting HPV, BV and STIs. In this pilot work, Hologic Aptima swabs were the sample collection device selected as they are designed to optimise efficiency and accuracy of the PCR assays developed by Hologic.

Encouragingly, participants express a preference for tampon self-collection (90%) over clinician-collected swabs. However, future research involving larger and diverse participant groups is required to validate these outcomes and guide the implementation of tampon-based self-collection programs for cervical cancer screening and STI testing.

Daye's Pilot HPV Study (currently pending publication)

Daye conducted a comparative analysis of the DDT and traditional Health Care Worker (HCW)-collected cervical swabs. In a cohort of 60 participants, the study utilised real-time PCR technology to assess the detection efficiency for HPV and STIs.

Participants provided informed consent and underwent both clinician-collected and self-collected sample collection using the Daye Diagnostic Tampon. Acceptability was

assessed through a questionnaire with Likert-scale responses.

Study Design and Methods:

In the clinical stage, two arms were employed to compare different specimen collection methods. In the Reporting Arm, healthcare workers collected cervical and low vaginal specimens from the participants. In the Experimental Arm, participants used self-collected tampons to obtain their samples. These samples were then divided into two types of collection containers: the ThinPrep Vial (TP Vial) or the Aptima Multitest Swab Collection Kit (APTIMA). After collection, the samples were stored at room temperature for 4-6 weeks before RNA isolation. Each arm collected a total of 120 samples.

Results:
Among the 60 participants who completed the study, the self-collected tampons demonstrated sensitivity and specificity of 66.67% (95% CI: 22.3%-95.7%) and 90.74% (95% CI: 79.7%-96.9%) when using TP Vial and 83.33% (95% CI: 51.6%-97.9%) and 85.42% (95% CI: 72.2%-93.9%) when using APTIMA for HPV detection, respectively. For BV detection, the tampons exhibited sensitivity and specificity of 100.0% (95% CI: 51.8%-99.7%) and 96.43% (95% CI: 87.7%-99.6%) (TP Vial) and 88.89% (95% CI: 22.3%-95.7%) and 98.04% (95% CI: 89.06%-100.0%) (APTIMA), respectively. For APTIMA Combo 2 (AC2) detection (for chlamydia and gonorrhoea), sensitivity and specificity were 100.00% (95% CI: 2.5%-100.0%) and 100.0% (95% CI: 93.9%-100.0%) (TP Vial) and 100.00% (95% CI: 2.5%-100.0%) and 98.31% (95% CI: 90.9%-100.0%) (APTIMA), respectively. Notably, 90% of participants expressed a preference for tampon self-collection over clinician-collected swabs.

Conclusion:
Self-collected tampons demonstrated comparable diagnostic accuracy to clinician-collected swabs for HPV and STI detection. The tampon self-collection method was well-accepted and preferred by participants, suggesting its potential as an alternative screening tool, particularly in low-resource settings. Further research with larger and more diverse populations is recommended to validate these findings and inform tampon-based self-collection programs for cervical cancer screening.

2. OBJECTIVES AND OUTCOME MEASURES

Primary Objective

Objective	Outcome Measure	Timepoint(s) of evaluation
Evaluate the diagnostic accuracy of the Daye Diagnostic Tampon for detecting Chlamydia, Gonorrhea, BV and HPV, specifically demonstrating a sensitivity of more than 70% for DDT.	Accuracy of the STI, BV and HPV testing using menstrual tampons compared to other specimen collection methods (clinician taken and self-swab) using the following assays: - Hologic's APTIMA HPV (for HPV) - Hologic's APTIMA AC (for chlamydia and gonorrhoea) - Cepheid MPV assay (for BV)	Within 4 weeks of the samples being received at the lab.

Secondary Objectives

Objective	Outcome Measure	Timepoint(s) of evaluation
Assess the usability of the DDT (via ASQ)	After scenario questionnaire scores	Post-sampling (once all samples are collected)
Explore participants views of the usability and acceptability of the DDT	Quantitative and qualitative feedback from pre- and post-sampling questionnaires and focus groups	Pre-sampling (baseline) and Post-sampling (once all samples are collected)
Assess whether the DDT is a preferred sampling	User preferences (self-report)	Pre-sampling (baseline) and Post-sampling (once

method for participants		all samples are collected)
Assess if the order of sample collection (self-swab vs DDT) impacts diagnostic accuracy	Diagnostic accuracy	Post sample analysis
Understand the health economic consequences of using the DDT for STI, BV and HPV testing	Willingness to pay for the DDT, comparison of time taken for DDT vs clinician swab	Post-sampling (once all samples are collected)
Explore stakeholder attitudes to tampons as a means of sample collection for microbial testing.	Qualitative feedback from stakeholder questionnaires	Ongoing throughout the trial once stakeholders have engaged with the tampon
Assess the occurrence of AEs/SAEs as a result of tampon sampling.	AE/SAE occurrence.	None expected, but any events will be collected and recorded on an ongoing basis as outlined in section 7.

Exploratory Objective

Objective	Outcome Measure	Timepoint(s) of evaluation
Explore the relationship between duration of wear and diagnostic accuracy.	Duration of DDT wear and diagnostic accuracy	Post sample analysis

3. TRIAL DESIGN

A diagnostic trial comparing the diagnostic accuracy, usability and acceptability of the DAYE Diagnostic Tampon (DDT) compared to standard vaginal self-swabs and clinician administration of a vaginal swabs. Diagnostic accuracy will be compared for detection of Chlamydia, Gonorrhea, BV & HPV.

A total of 350 eligible participants will be enrolled into the trial in the UK and Italy. To adequately assess DDT performance on specificity and sensitivity, participants will be recruited from one of two groups:

- Group 1: 50 participants with a recent confirmed HPV diagnosis (UK and Italy)
- Group 2: 300 participants from the general population (UK only)

All participants will be randomised according to sample order for the DDT and self-swab using block randomisation:

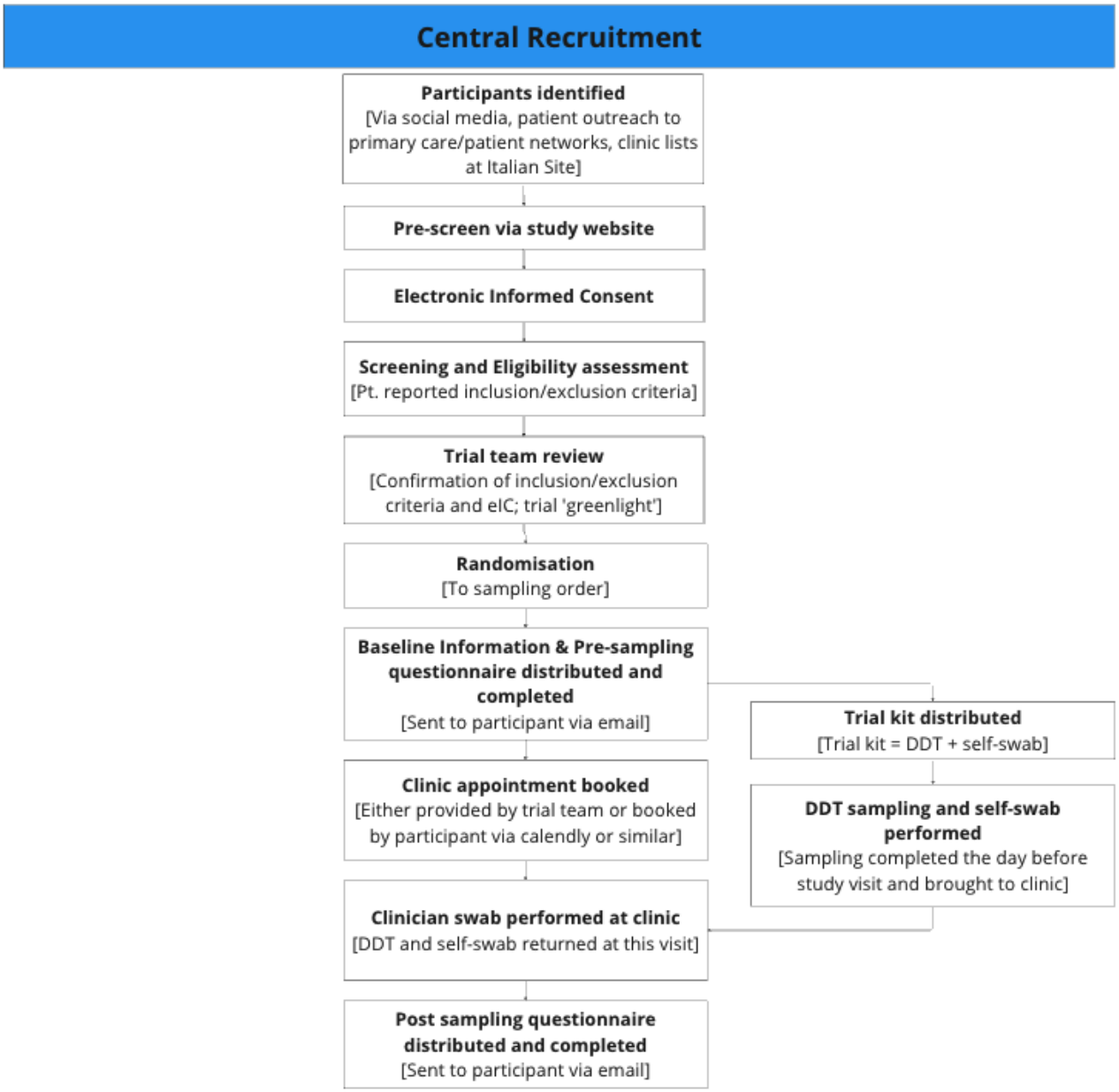
- Group A: Approximately half the participants will perform the self-swab followed by the DDT.
- Group B: Approximately half the participants will perform the DDT followed by the self-swab

Pre-screening, informed consent, screening and eligibility assessments may occur online or in person. Randomisation will be performed at the point of enrolment by a member of the trial team using a pre-generated list of treatment allocation blocks. Some demographic information and medical history will be collected at baseline. All eligible participants will be provided with a trial kit containing the DDT and self-swab and attend at least 1 clinic visit where they will have a clinician taken vaginal swab as part of their participation in the trial. Participants will also provide answers to questionnaires at baseline and after all sampling is complete. Participants will enter data directly into the EDC platform or via paper questionnaires completed in-person at the clinic visit and entered into the EDC platform by trained staff. Participation in the trial is expected to last approximately 2-4 weeks (dependent on timing of clinic appointment(s)). All samples collected during the trial will be sent to a central accredited laboratory for analysis, either in the UK or Italy i.e., samples will be analysed in the country they were collected.

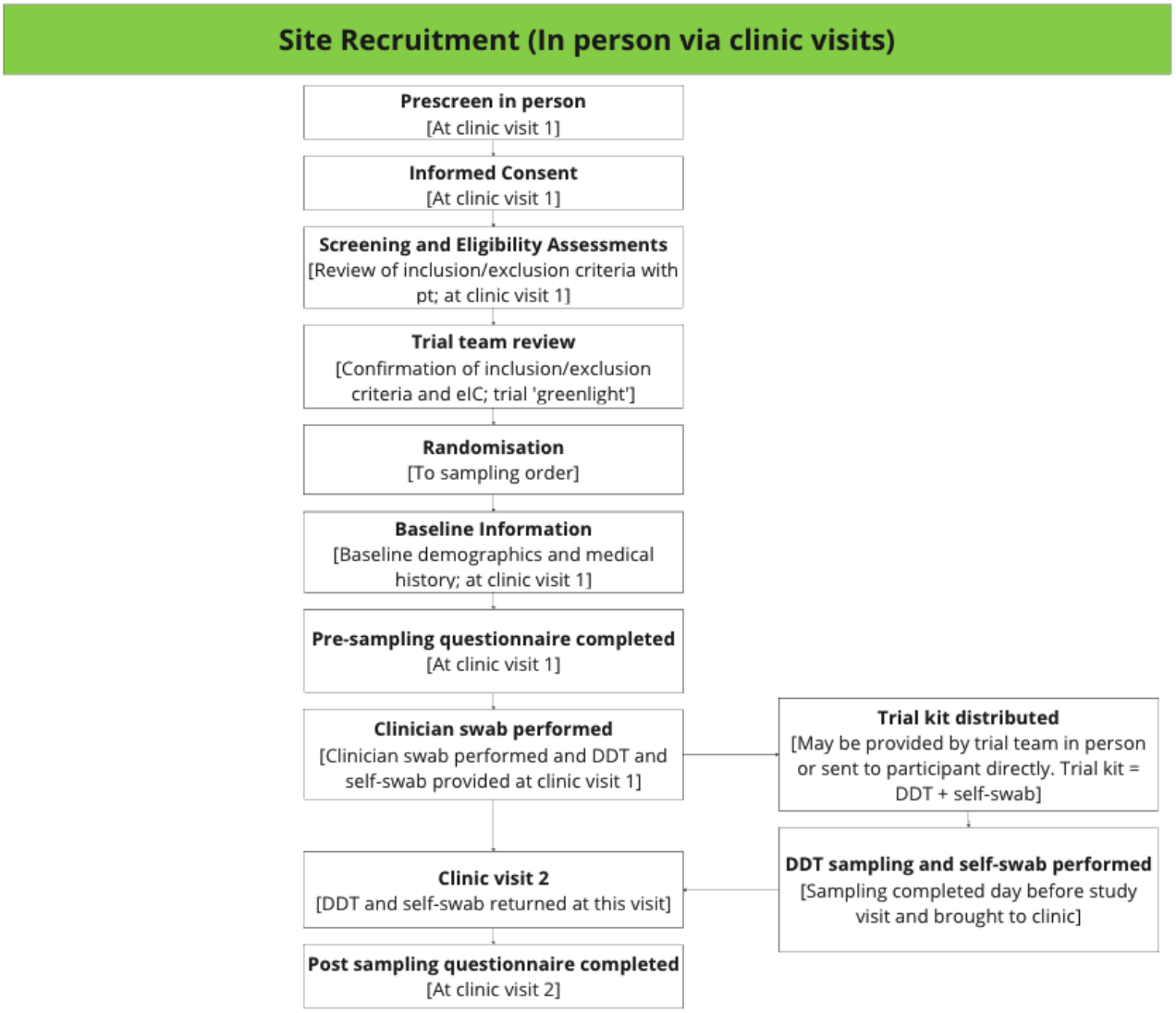
3.1. Participant Flowchart

Two participant flows are presented below. The central recruitment flow shows the participant flow from recruitment from patient outreach (e.g. social media, advertising to patient networks, clinic outreach to patient lists). The site recruitment flow shows the options for participant flow when participants are recruited in person via a site.

3.1.1 Central Recruitment



3.1.2 Site Recruitment



4. PARTICIPANT IDENTIFICATION

4.1. Trial Participants

Participants will be sexually active individuals assigned female at birth (AFAB) aged 25-65. A subset of participants (Group 1) will have had a recent HPV diagnosis. All inclusion and exclusion criteria refer to both Group 1 and Group 2 unless specifically stated.

4.2. Inclusion Criteria

Participants must meet all the following criteria:

1. Individuals aged 25-65 years.
2. People assigned female at birth (AFAB).
3. Sexually active individuals. In this case, "sexually active" is defined as having penetrative vaginal sex.
4. **Group 1 only:** Confirmed HPV+ diagnosis within the past 4 weeks.
    a. *UK only*: Ability to upload evidence of this diagnosis to the trial ePRO system (e.g. via a screenshot of the NHS app, or similar to be reviewed by the trial team).
5. Willingness to give informed consent and adhere to trial procedures.

4.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

1. Previous hysterectomy or total hysterectomy with removal of cervix
2. Known allergy or sensitivity to tampons
3. History of TSS (both tampon-associated and non-tampon associated)
4. Individuals who are pregnant or breastfeeding.
5. Participation in another interventional clinical trial or use of investigational drugs in the last 30 days.
6. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

5. TRIAL PROCEDURES

5.1. Schedule of Assessments

5.1.1 Schedule of Assessments – Central recruitment or site recruitment from clinic lists[a]

Contact Type	Pre-screening	Screening	Screening +1	Baseline	Pre Trial Visit	Trial Visit	Post Trial Visit
Contact time ***Assessments***	*Pre-screener accessed via participant outreach*	*Immediately following successful pre-screening*	*Normally within 1 working day of screening*	*Provided once enrolment confirmed*	*Approximately 24 hours before clinic visit*		*Immediately following trial visit once all sampling is complete*
Pre-screen via trial website	✔						
Written informed consent	✔						
Eligibility assessment[b]		✔					
Eligibility review, trial "greenlight" & enrolment[c]			✔				
Randomisation			✔				
Medical history[b]				✔			
Demographics[b]				✔			
Sampling							
DDT					✔		
Self-swab					✔		

Contact Type	Pre-screening	Screening	Screening +1	Baseline	Pre Trial Visit	Trial Visit	Post Trial Visit
Contact time ***Assessments***	*Pre-screener accessed via participant outreach*	*Immediately following successful pre-screening*	*Normally within 1 working day of screening*	*Provided once enrolment confirmed*	*Approximately 24 hours before clinic visit*		*Immediately following trial visit once all sampling is complete*
Clinician swab						✔	
Return of completed DDT/Self-Swab						✔	
Questionnaires[d]							
Pre-sampling questionnaire				✔			
Post-sampling questionnaire							✔
Safety							
AEs and SAEs[e]					✔	✔	✔

[a] This schedule also applies where a site has contacted participants from clinic lists in advance of visits and provided them with the pre-screening link.

[b] Key demographic and medical history data will be verified during the eligibility assessment to ensure suitability for inclusion. Detailed demographic and medical history data is collected following enrollment.

[c] Greenlight will be given once the trial team has reviewed eICF and participant reported eligibility.

[d] Questionnaires will be emailed directly to participants and completed via Citrus ePRO.

[e] Self-reported by participant as required.

5.1.2 Schedule of Assessments - Clinic recruitment (via in person clinic visits) - Italy Only

Contact Type	Screening	Baseline	Trial Visit 1	Pre Trial visit 2	Trial visit 2	Post Trial Visits
Contact time ***Assessments***	*At clinic visit*	*Provided once enrolment is confirmed*	*Continuation of screening visit*	*Approximately 24 hours before clinic visit*		*Immediately following trial visit once all sampling is complete*
Written informed consent	✔					
Eligibility assessment[a]	✔					
Trial "greenlight" & enrolment[b]	✔					
Randomisation	✔					
Medical history[a]		✔				
Demographics[a]		✔				
Sampling						
DDT				✔		
Self-swab				✔		
Clinician swab			✔			
Return of completed DDT/Self-Swab					✔	
Questionnaires[c]						
Pre-sampling questionnaire		✔				
Post-sampling questionnaire						✔
Safety						
AEs and SAEs[c]			✔	✔	✔	✔

[a] Key demographic and medical history data will be verified during the eligibility assessment to ensure suitability for inclusion. Detailed demographic and medical history data is collected following enrollment

[b] Greenlight will be given once screening is completed during the clinic visit.

[c] Questionnaires will be completed on paper and entered into the trial database by suitably qualified members of the trial team..

[d] Self-reported by participant as required.

5.2. Recruitment

5.2.1 Recruitment at sites

Participants will be recruited via clinic visits. The site team may review clinic lists for upcoming appointments to identify potentially eligible participants and contact these participants with an email link to the trial website where more information will be displayed and they will have the choice to sign up to receive the Patient Information Sheet (PIS) and commence pre-screening. Once enrolment is confirmed the participant will attend their clinic appointment as planned. Participants may also be approached at ongoing clinic visits and given the PIS. Flyers and posters will also advertise the trial in clinic waiting rooms. Participants who are recruited and consent in this way will be immediately enrolled and screened at their ongoing clinic visit.

5.2.2 Central recruitment

Participants will primarily be recruited via social media with central recruitment conducted by the Lindus Health team. Advertising on Facebook and other platforms will be used to highlight the trial to individuals who may be looking for screening. Adverts will make clear that the trial does not replace the need to seek medical advice. Adverts will direct potential participants to the trial website, where more information about the trial will be displayed and have the choice to sign up to receive the PIS. Once enrolled participants will book an in person clinic appointment to see a trial nurse at a clinic.

5.2.2 Participant Payments

All participants will receive £50 (UK) or €60 (Italy) for taking part in the trial on completion of all trial activities.

5.3. Pre-screening

Potential participants recruited centrally via social media, or sent information by the recruiting site in advance of a clinic visit, will be directed to the trial webpage, where they will be informed about the trial. If interested in taking part, they will complete an online pre-screening form to assess their eligibility for the trial.

If potentially eligible and once they submit the form, the PIS and Informed Consent Form (ICF) will be sent directly to the participant.

5.4. Informed Consent

Prior to consent, the potential participant will have received the PIS and ICF describing the trial. They will have had the opportunity to read through the details relating to the exact nature of the trial, the known side-effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. It will be confirmed that potential participants have reviewed the PIS.

Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. A trial team member experienced and trained in the informed consent process, will be available in person (in Italy) or via telephone (in Italy and the UK), prior to enrolment, if the participant has any questions regarding the trial. If the participant is willing, informed consent will be obtained.

The participant will provide their electronic signature at the end of the e-consent form and the central trial team member will verify the consent form. A copy of the ICF will be sent to the participant by email and an electronic copy retained by Lindus Health in a secure area with restricted access. In the case of paper consent signed in person, a copy of the completed consent form will be given to the participant and the signed consent form will be stored in a secure area with restricted access. In the UK, the participant's GP will be informed of their involvement in the trial.

Once the ICF has been signed the participant will complete the screening and eligibility assessment online or will complete screening and eligibility with the trial team at the clinic.

5.5. Screening and Eligibility Assessment

5.5.1. Screening and Eligibility Completed Centrally

Screening and eligibility will be self-reported via a survey on the trial website. Participants in group 1 will be asked to upload evidence of their recent HPV diagnosis (e.g. via a screenshot of their medical record in the NHS app). Eligibility data will be reviewed by the central trial team or site staff to confirm enrollment into the trial.

5.5.2. Screening and Eligibility at Sites

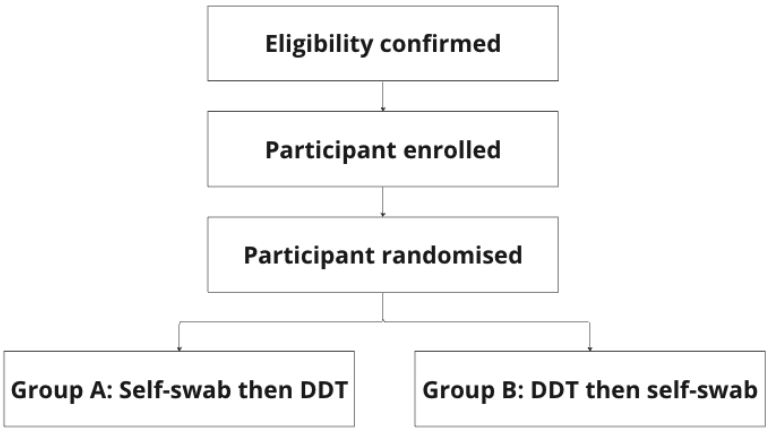
In cases where participants are identified via clinics lists in advance pre-screening and screening and eligibility will be completed online (see section 5.3 and 5.5.1). Where participants are recruited at clinic visits screening will be completed by a site staff member at that clinic visit. Eligibility will be reviewed and confirmed by the site team for enrolment into the trial.

5.5.3. Screen Failures

A screen failure is defined as a participant who consents to participate in the trial but is not subsequently assigned to the trial group. Minimal information, including Electronic Informed Consent Form (eIC) details, eligibility criteria, and demographics, will be collected. Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.

5.6. Registration / Enrolment & Randomisation

Once eligibility has been confirmed by the site team participants will be enrolled and randomised to a sampling order using a block randomisation method. Participants in group 1 will be stratified by country. Randomisation will be performed at the point of enrolment by a member of the trial team using a pre-generated list of treatment allocation blocks.



Participants will be assigned a trial number in the format STP-[UK/IT]-NUMBER.

5.7. Baseline Data

Participants will be asked to provide demographic data and information on their medical history following their enrollment into the trial. Participants recruited centrally

will be asked to book a clinic appointment. Participants recruited at sites will be provided with clinic appointment(s) by the site trial team.

5.8. Blinding and code-breaking

There will be no blinding in this trial.

5.9. Tampon Sampling & Self-Swab

Following enrolment and provision of baseline data participants will be provided with a trial kit (via post) containing the Daye Diagnostic Tampon (DDT) and the self-swab. An instruction booklet and sterile containers for each sample will also be provided. Participants will perform sampling in an order according to a randomisation which will place them in Group A (self-swab then DDT) or Group B (DDT then self-swab). The instructions provided to the participant in the trial kit will provide them with the sample order. A gap of at least 1 hour should be left between the samples in both groups.

5.10. Trial Clinic Visit

All participants will attend at least one clinic visit as part of their participation in the trial. During this visit the following assessments will be performed:

- Participants will meet with a trial nurse who will take a clinician administered vaginal swab. The same type of swab will be used for the at-home self-swab and the clinician administered swab to allow for direct comparison of samples.

Participants recruited at sites may have a second clinic visit scheduled to collect the DDT and self-swab from the participant.

5.11. Questionnaires

A pre-sampling questionnaire will be sent to the participant upon enrolment before any samples have been taken. This questionnaire will assess the participants initial views on the DDT in advance of sampling. This questionnaire must be completed prior to the participant having any samples taken.

A second questionnaire (post-sampling questionnaire) will be sent to the participant following their clinic appointment(s) once all samples have been taken. This

questionnaire should only be completed once all other trial procedures have been performed. This questionnaire will compare the participants' experiences with the DDT versus the standard self-swab and clinician swab methods.

5.12. Communication of Results

If the participant consents they will be informed of their test results directly via email. Participants will be advised that results are experimental and to contact their health provider if they are concerned.

UK

If the participant receives any positive results they will be offered the option of booking a call with a member of the trial team who will offer advice and support. The participant will be advised to contact their healthcare provider to request repeat testing via the standard pathways of care. Positive results for HPV do not replace the standard cervical screening service which all participants should continue to participate in. If the participant consents, their GP will also be informed of the results if any tests come back positive for a STI, BV or HPV.

Italy

In Italy the recruiting clinic will receive the results of the tests regardless of whether they are positive, negative or inconclusive and complete appropriate follow-up.

5.12.1. Process for discrepant results

In the event of discrepant results between sample types for the same participant the following process will be applied for communication of results to participants/GP/Dr:

1. Where possible the analysis on the discrepant sample will be repeated via re-extraction and re-running of the assay.
2. If, after repeat testing, 2 out of 3 samples are positive for an infection, the result will be reported as positive to the participant/GP/Dr.
3. If, after repeat testing, 1 out of the 3 samples are positive for an infection, the result will be reported as inconclusive to the participant/GP/Dr.

5.13. Qualitative Data Collection

5.13.1 Participant Focus Groups

Participants will have the option to take part in focus groups. This part of the trial will be optional. Participants will join a group discussion of 5-10 participants to explore in-depth their experiences with the DDT versus the other sampling methods.

15.3.1.1 Sampling

A list of participants who have consented for further contact for the focus group will be generated. Investigators will contact those in the sample list via email and/or phone until the required number of participants at each time point is reached. Inclusion will be given on a first come first served basis.

15.3.1.2 Focus Group Design

The focus groups will be semi-structured based on a topic guide. The focus groups will include 5-10 participants in each group and last up to 60 mins. Separate consent will be collected for participation in the focus group prior to the session starting. Focus groups will be conducted online using video conferencing software. All participants will be reminded before participation that they will be in an online group situation and accordingly, will be identifiable to the other participants. A trained facilitator who is part of the trial team will coordinate and guide the focus groups.

15.3.1.3 Focus Group Topics

A semi-structured topic guide will be used by the facilitator to initially engage participants in key topics and prompt focussed discussions. The guide will explore:

- Usability of the DDT
- Comfort using the DDT
- Acceptability and perceptions of using a tampon for sampling
- The DDT vs other common sampling methods

15.3.1.4 Focus Group Analysis

The transcript files will be downloaded from the video conferencing software and checked against the original recording for accuracy by a qualified member of the trial team who will generate an orthographic transcription for thematic analysis. The video will be deleted after checking is complete. Transcripts will be de-identified before coding to maintain confidentiality and privacy. The transcripts will be analysed using an inductive thematic analysis, an open coding approach in which themes and codes are generated from the data. This analysis follows a 6-step process outlined by Braun & Clarke, 2006[11] to include familiarising oneself with the data (step 1), generating codes (step 2), constructing themes (step 3), reviewing potential themes (step 4), defining and naming themes (step 5), and producing the report (step 6).

5.13.2 Stakeholder Questionnaire

Key stakeholders (healthcare workers including nurses, primary care providers and other relevant personnel) will be contacted via email with a questionnaire to explore attitudes to tampons as a means of sample collection for microbial testing. Individuals involved with the trial with experience working with the DDT will be contacted, as well as independent individuals who have signed up to existing mailing lists held at Lindus Health. The stakeholder questionnaire will collect an individual's job title and organisation only, and no further personal data will be collected. Completion of the questionnaire will be voluntary.

5.14. Sample Handling

Samples taken as part of the trial are research samples for analysis under this protocol and will be destroyed once analysis is completed. If explicit consent for use for future research is given, anonymised DNA and/or RNA will be kept for future ethically approved research projects.

5.14.1. Sample processing in the UK

All samples from participants in the UK will be sent to an accredited laboratory in the UK for analysis.

5.14.2. Sample processing in Italy

All samples from participants in Italy will be sent to an accredited laboratory in Italy for analysis.

5.14.3. Sample Analysis and storage

The accuracy of HPV and STI testing using menstrual tampons will be evaluated by comparing the results of the tampon self-sampling and self-swab sampling to the results of the clinician swab sampling. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) will be calculated to assess the performance of the tampon and swab sampling methods compared to the clinician swab as the gold standard.

There is no single assay test kit that is able to reliably test for all the organisms of interest in this trial, we have therefore chosen assays that have been proven to reliably detect the organisms of interest. All of the samples collected will be analysed using the following assays::

Infection	**HPV**	**Chlamydia/Gonorrhoea**	**Bacterial Vaginosis**
Assay	Hologic's APTIMA HPV	Hologic's APTIMA AC2	Cepheid MPV assay
Description and justification for use	Hologic APTIMA HPV assay is a well-established sensitive assay utilised by multiple centres involved in public healthcare and is included in the 2020 list of HPV assays suitable for primary cervical cancer screening[12]. This is a nucleic acid amplification test for qualitative detection of viral mRNA E6 and E7 genes of high-risk HPV genotypes are known oncogenes. This assay utilises transcription-mediated amplification (TMA) based (Aptima) amplification.	The APTIMA AC2 assay, is a nucleic acid amplification test utilised in various public healthcare settings. This assay is specifically designed for the qualitative detection of sexually transmitted infections (STIs), specifically Chlamydia and Gonorrhoea. It employs transcription-mediated amplification (TMA), a technology associated with the Aptima system. The test targets specific nucleic acid sequences related to STIs, providing sensitive and accurate results.[13] The APTIMA AC2 assay is recognized for its reliability and is widely used for STI screening and diagnosis in clinical settings.	The Cepheid MPV assay has been chosen as it has proven effectiveness for detecting organisms associated with bacterial vaginosis (Atopobium spp, BVAB2, Megasphaera) with high sensitivity and specificity[14]. It is a widely used test because of the short turnaround time of this assay (result within 60 minutes), In addition, because of this speed of turnaround it is appropriate for point of care testing (POCT) use.

Samples obtained from participants will be utilised solely for the explicit purpose of this project. In the event that a participant grants explicit consent, prior to destruction these samples will be processed and DNA or RNA extracted, undergo a de-identification process and the extracted DNA or RNA only will be securely stored for potential application in future ethically approved research endeavours. The remaining sample will be systematically and irreversibly destroyed to ensure confidentiality and compliance with ethical standards.

5.15. Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the trial at any time. Participants leaving the trial before randomisation will be considered screen failures; participants leaving the trial after randomisation will be considered withdrawals.

Following participant withdrawal, no further trial assessments will be performed. The participant will be contacted by a member of the central team and a reason for withdrawal will be requested and documented.

5.16. Definition of End of Trial

End of trial is defined as the last data capture of the last participant.

6 TRIAL PROCEDURES

All participants will receive all three of the trial procedures during their participation in the trial. Participants will be randomised according to sample order for the DDT and self-swab. A gap of at least 1 hour should be left between the at home samples. All materials and instructions for the trial procedures will be provided by the sponsor either directly to the participants or to the trial sites.

6.1. DAYE Diagnostic Tampon (DDT)

The DDT is constructed entirely from woven cotton and consists of an absorbent core wrapped in a protective sleeve. The DDT is loaded in an applicator to aid with insertion. The DDT needs to be worn for a minimum of 20 minutes (and no longer than 4 hours) for collection of the sample, and then once withdrawn should be placed immediately in the provided sterile container with a transport medium and then brought to the clinic visit. Participants should perform the sampling the day before their trial clinic appointment. Participants will receive detailed written and/or verbal instructions on the timing of their samples, the order to perform their samples in, and how to use the tampon. Clear instructions for packaging and sample handling will be provided to the participant.

6.2. Self Swab

Participants will be instructed to insert a swab into their vagina and rotate it three times to collect a sample. After removal, the swab will be placed in a sterile container with a transport medium and returned to the trial team. Participants should perform the self-swab the day before their trial clinic appointment. Participants will receive detailed written and/or verbal instructions on the timing of the samples, the order to perform their samples in and how to use the self-swab. Clear instructions for packaging and sample handling will be provided to the participant.

6.3. Clinician Swab

A clinician will perform a high vaginal swab for HPV and STI testing using a standard protocol that is validated for use for the downstream microbial test, as per local guidelines in each country. The swab will be collected by rotating the swab in the vaginal canal three times and then placing it in a sterile container.

7 SAFETY REPORTING

7.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: · results in death · is life-threatening · requires inpatient hospitalisation or prolongation of existing hospitalisation · results in persistent or significant disability/incapacity · consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

	*NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: · in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product · in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

7.2. Assessment of Causality

The relationship of each adverse event to the intervention must be determined by a medically qualified individual according to the following definitions:

- Not Related – where an event is not considered to be related to the intervention
- Possibly – although a relationship to the intervention cannot be completely ruled but the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible

- Probably – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Definitely – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the intervention.

7.3. Procedures for Reporting Adverse Events

We do not anticipate that the trial procedures (DDT or swabs) should result in any adverse events (AEs) but include this section in case such events are reported so that they can be considered for causal links to the trial procedures. Only AEs that are clinically judged by the research site PI as being caused by the trial procedures (related and unexpected) will be reported to the REC that gave favourable opinion.

Participants will be provided with contact information for the trial team and the clinic nurse in the event that they need to report a side effect or medical event from the DDT, self-swab or clinician swab.

Events related to the trial procedures will be collected from the collection of the first trial sample until the final questionnaire is submitted.

7.4. Reporting Procedures for Serious Adverse Events

Any AEs which fall under the definition of a SAE will be reported to the Chief Investigator or designated person within 24 hours, to be reviewed for relatedness and expectedness.

Reports of related and unexpected SAEs (in the opinion of the Chief Investigator or designated person) will be reported to the REC within 15 days of the CI and/or central trial team becoming aware of the event. The Chief Investigator will also notify the Sponsor of all trial SAEs.

Any pregnancy occurring during the trial will result in the immediate discontinuation of the participant if all samples have not yet been taken. Pregnancy in itself is not considered an SAE.

All SAEs will be recorded in the trial EDC platform and any concerns raised immediately with the CI.

There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

7.5. Expectedness

There are not anticipated to be any serious adverse events as a result of the DDT.

7.6. Measures to minimise the occurrence of AEs

Participants are advised not to wear the DDT for prolonged periods e.g. no longer than 4 hours, to minimise the risk of Toxic Shock Syndrome.

8 STATISTICS

8.1. Statistical Analysis Plan (SAP)

The plan for the statistical analyses of the trial are outlined below. There is not a separate SAP document in use for the trial.

8.2. Description of Statistical Methods

Descriptive statistics are used to describe the participants in each group. Continuous demographic variables collected at screening will be summarised using arithmetic mean, standard deviation, minimum and maximum values, 25% and 75% quartiles and median. For categorical variables, absolute and relative frequencies are reported.

8.2.1 Primary Endpoints

For the primary endpoints, assessing the diagnostic accuracy of Daye diagnostic tampons for detecting Chlamydia, Gonorrhea, and BV, and HPV, respectively, the outcome of the tampon sample and the clinician collected sample are compared, with the clinician collected sample serving as the reference. This yields the following contingency table with A, B, C and D referring to the number of participants with the respective outcome on the tampon an clinician collected swabs:

		Daye diagnostic tampon	
		+	**-**
Clinician collected sample	**+**	A	B
	-	C	D

The following parameters are calculated:

Sensitivity = $\frac{A}{A+B}$

Specificity = $\frac{D}{C+D}$

Positive Predictive Value (PPV) = $\frac{A}{A+C}$

Negative Predictive Value (NPV) = $\frac{D}{B+D}$

Accuracy = $\frac{A+D}{A+B+C+D}$

The accuracy parameters are indicated per condition, including the number of participants used to calculate the parameter and the corresponding 95% confidence intervals using the Wilson score method. As samples are analysed for RNA/DNA using PCR, a positive result in either collection method very likely indicates the presence of the condition. Samples tested positive from DDT but negative from clinician-collected swabs would be classified as false-positive (C) in this assessment, although they actually are true-positive. This results in an underestimation of PPV, specificity, and accuracy.

Additionally, one-proportion z-tests are conducted to test if the sensitivity for Daye diagnostic tampons is higher than 70% for each condition.

Data from both groups will be pooled for analysis of the primary and secondary endpoints. Additionally, all analyses will be carried out for each subgroup separately.

8.2.2 Secondary Endpoints

The secondary endpoints will be assessed by analysing the items of the questionnaires descriptively at each assessment point in time (pre-sampling and post-sampling). A change score will be calculated for continuous items assessed both pre-sampling and post-sampling, and appropriate statistical methods are used to compare pre- to post-sampling values (e.g., t-test for repeated measurements, Wilcoxon signed-rank test). For categorical items, the absolute and relative frequency of each answer option will be reported, as well as the change between categories pre- and post-sampling where feasible.

The *Occurrence of AEs/SAEs* will be analysed descriptively by indicating the absolute and relative frequency of each AE/SAE over the course of the trial duration.

To assess whether the order of sampling influences the diagnostic accuracy, sensitivity and specificity of self-swabs and DDT are compared using McNemar tests for clinician-swab-positive and -negative samples, respectively. Additionally, Cohen's kappa will be calculated to assess the concordance of results from self-swabs and DDT.

8.2.3 Exploratory Endpoint

In an exploratory analysis, the duration of the DDT sampling is analysed descriptively using arithmetic mean, standard deviation, median, minimum and maximum values, as well as quantiles, as well as appropriate graphical procedures (e.g., probability density plots, box plots, histograms). To assess the relation between sampling duration and diagnostic accuracy, the duration between positive and negative DDT swabs is compared using a t-test or Mann-Whitney-U test, depending on the distribution of sampling duration, for clinician-positive and -negative swabs, respectively. Additionally, appropriate graphical procedures are used to visualise the relationship between sampling duration and diagnostic accuracy.

8.2.4 Subgroup Analyses

As data from group 1 (participants with a recent diagnosis of HPV) will be collected in the UK and Italy, the sensitivity and specificity for each diagnostic target will be calculated for participants in each country separately and compared between countries using Fisher's exact tests. If the results show no significant differences, the data will be pooled for analysis.

8.3. Sample Size Determination

The sample size for this trial was determined to reach an adequate power to show that Daye diagnostic tampons possess adequate diagnostic accuracy for each condition. Since the majority of the sample participants are expected to not have the respective condition, determining the sensitivity will be more challenging than determining the specificity. Hence, we focus on determining an appropriate sample size to establish adequate sensitivity. The prevalence of the conditions varies in the population, with HPV infections occurring least common. For group 1, we assume that women who have recently had a HPV diagnosis will still have an acute HPV infection in 70% of cases at the time of sample collection. This group is therefore used to calculate the sample size needed for HPV. Group 2 will be used to assess the sensitivity for detecting Chlamydia and Gonorrhea (grouped as sexually transmitted infections, STI), as well as BV. For each of the groups, a sample size for disease-positive patients is determined based on the parameters of a binomial test of proportions, testing if the sensitivity is higher than 70%, when the assumed sensitivity is 95% and assuming a power of 90% and a significance level of 5%. This number is then weighted by the assumed prevalence of each condition in the respective group to obtain the number of participants needed to include.

The calculation yields the following sample sizes:

Group	Condition	α	Power (1-β)	Assumed sensitivity	Reference sensitivity	N (with condition)	Prevalence	N (total)
1	HPV	5%	90%	95%	70%	21	70%	31
2	STI	5%	90%	95%	70%	21	10%	210
2	BV	5%	90%	95%	70%	21	30%	70

The total sample size is then determined by the smallest number for each group, which is 31 for group 1 and 210 for group 2. To account for uncertainties in the prevalence in each group and potential missing, lost, or inconclusive samples, the sample size numbers were adjusted by adding 40% to group 1 and 60% to group 2. The final sample sizes are:

Group	N (total)
1	50
2	300

In total, 350 participants are included in the trial.

8.4. Analysis Populations

The primary and secondary endpoints will be evaluated using all complete pairs of samples from the Daye diagnostic tampon and clinician collected samples.

8.5. Subgroup Analyses

The primary and secondary endpoints will be assessed for each group separately as exploratory subgroup analyses.

8.6. Decision Points

One interim analysis on the primary endpoints may be performed once 35 participants of group 1 and 215 participants of group 2 have been evaluated. The interim analysis is conducted to assess the prevalence of each condition within the respective group and

the sample size will be adjusted to meet the determined number of participants with the respective condition if needed.

8.7. The Level of Statistical Significance

Effects are considered statistically significant if the associated two-tailed *p*-value is less than 5%.

8.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

As per section 8.4 data will only be used for analysis if none of the required values for the respective analysis is missing. Swabs not yielding a conclusive result will also be excluded. Participants who provide swab results, but have missing pre- or post-sampling questionnaires will not be excluded from the analysis population. The number of missing values and inconclusive results will be reported for each sample (Daye diagnostic tampon swabs, self-swabs, and clinician collected samples). Missing data will not be replaced for analysis.

8.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the statistical procedures laid out in this document and their reasons will be recorded in an amendment to this document.

9 DATA MANAGEMENT

The data management aspects of the trial are summarised here with details fully described in the Data Management Plan.

9.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history may be summarised into the CRF), participant questionnaires and correspondence.

EDC entries will be considered source data if the EDC is the site of the original recording. All documents will be stored securely and safely in confidential conditions.

9.2. Access to Data

Data will be entered into a validated EDC platform. Direct access to the EDC platform will be granted to delegated site users. Access will also be granted to authorised representatives from the Sponsor and Lindus Health to allow trial-related monitoring and/or audits to ensure compliance with regulations. Access to this system will be strictly on a need to know basis and the system will be on a secure server. In Italy some data may be entered onto paper CRFs before being transcribed into the EDC platform. Access to the paper documents will be strictly on a need to know basis and these documents will be stored in an access controlled room. To ensure data transparency, the trial will be registered on a publicly available database for clinical studies.

9.3. Data Recording and Record Keeping

The data management will be run in accordance with Lindus Health SOPs, which are fully compliant with Good Clinical Practice (GCP), GDPR and the Data Protection Act 2018.

Research data will be de-identified upon collection. Identifiable information will be stored separately from the research data.

A unique trial specific number and/or code in the database will be used to identify the participants. Where necessary for trial conduct the participants name, date of birth and address will be shared with third parties and vendors who require these details for the logistics of trial conduct.

An online secure data entry system (Citrus) designed to collect sensitive data, such as participant contact details, will be used. All identifiable participant data is encrypted using the Advanced Encryption Standard. Citrus will also manage online ePRO.

Informed consent (e-consent) will be completed using worksheet templates, online or in person, which will be retained in a secure area with restricted access. The remaining data, including reconfirmation of consent and records of eligibility confirmation will be collected directly onto the EDC platform, therefore no further source will be available. In Italy some data may be entered onto paper CRFs before being transcribed into the EDC platform.

Identifiable participant data will be kept for 12 months beyond the end of the trial. Non-identifiable participant data will be maintained for a minimum of ten years unless otherwise required to comply with legislation or regulation and reviewed on an annual basis.

10 QUALITY ASSURANCE PROCEDURES

10.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

Risk Mitigation:

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and Standard Operating Procedures. All site staff will receive training in trial procedures according to GCP where required.

10.2. Monitoring

Regular monitoring will be performed according to GCP using a risk-based approach. In the UK, Lindus Health will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to, and that appropriate action is taken to safeguard participants and the quality of the trial itself. In Italy, the sponsor will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to, and that

appropriate action is taken to safeguard participants and the quality of the trial itself. The level of monitoring required will be informed by the risk assessment.

Please refer to the trial Monitoring Plan(s) for further details.

10.3. Trial Operations Group

There will be a central trial team, composed of representatives from DAYE (Tampon Innovations Ltd), Lindus Health and the Italian site who will meet regularly to monitor trial progress. There will be no other trial committees.

11 PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented and filed in the trial master file.

A Lindus Health SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

12 SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect 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".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, in the UK the CRO (Lindus Health) will report it to the REC committee, Regulatory authority and the relevant host organisations according to local regulatory timelines. In Italy the serious breach will be reported to the ethics committee and regulatory authority by the sponsor.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheets and any proposed informing material will be submitted to an appropriate Research Ethics Committee (REC) in both participating countries, and host institution(s) for written approval. The PI and recruiting sites will ensure and confirm correct regulatory approvals are gained prior to recruitment.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Other Ethical Considerations

Data collected will be of a sensitive nature, and steps will be taken to ensure data is protected. All data will be collected and reported with the trial ID only and access to the trial database will be restricted.

Test results will be shared directly with the participants via text message or email by the trial teams and consent for this is collected at trial entry. Contact details for this will be stored in an access controlled area of the trial database.

13.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where

required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

13.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on the ISRCTN Database. Results will be uploaded to this register within 12 months of the end of trial date as given on the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of trial date as given on the end of the trial declaration.

13.7. Participant Confidentiality

The trial will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, and the General Data Protection Regulation (EU GDPR) which require data to be anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant trial number only on all trial documents and any electronic database(s). All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

13.8. Expenses and Benefits

Reasonable travel expenses up to a maximum of £50 for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. Additional reasonable and justifiable expenses may be available in cases where a participant is unable to use public transport (e.g. for medical reasons).

Participants will be paid £50 for their participation in the trial on completion of all trial activities.

14 FINANCE AND INSURANCE

14.1. Funding

The trial will be funded by Tampon Innovations LTD.

14.2. Insurance

The Sponsor, Tampon Innovations Ltd, has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research.

14.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

15 PUBLICATION POLICY

15.1. Authorship and Acknowledgements

15.1.1. Authorship Criteria:

Authorship for scientific publications resulting from the trial will follow established guidelines set forth by the appropriate journal, ICMJE and any relevant industry standards. Those who meet the criteria for authorship should be listed as authors on the publication.

15.1.2. Authorship Contributions:

Individuals who have made substantial intellectual contributions to the conception, design, execution, or interpretation of the trial may qualify for authorship. These contributions may include, but are not limited to, designing the trial, collecting and analysing data, drafting or revising the manuscript, and providing critical intellectual input.

15.1.3. Acknowledgments:

Contributors who do not meet the criteria for authorship but have provided significant contributions to the trial or publication, such as data collection, analysis, or critical review, will be acknowledged appropriately in the publication.

15.2. Review Procedures

15.2.1. Internal Review:

Before submission, all publications will undergo an internal review process led by the principal investigator (PI) and other relevant stakeholders. This review will ensure the accuracy, validity, and ethical considerations of the findings and conclusions.

15.2.2. Peer Review:

Where applicable, submissions will be subjected to peer review by independent experts in the relevant field. Reviewer feedback will be taken into account for revisions to enhance the quality and credibility of the publication.

15.3. Compliance with Department/Institution Policy and Contracts

15.3.1. Adherence to Policies:

This publication policy aligns with existing departmental and institutional policies, agreements, and any relevant legal frameworks. Authors are expected to adhere to these policies and agreements throughout the publication process.

15.3.2. Contractual Obligations:

Authors and contributors must ensure that the publication policy outlined here is consistent with any contractual agreements pertaining to the trial. Legal and contractual obligations will be considered during the publication process to avoid conflicts or breaches of agreements.

15.4. Trial Results Dissemination to Participants

15.4.1. Transparency and Timeliness:

Trial participants have a right to access accurate trial results. Trial results will be disseminated to participants in a transparent and timely manner, reflecting the importance of their contribution to the trial's success.

15.4.2. Method of Dissemination

Trial results will be shared with participants through appropriate channels, which may include written reports or electronic communications via the trial website.

15.4.3. Clear Language:

The dissemination of trial results to participants will be conducted in clear and understandable language, avoiding technical jargon as much as possible, to ensure participants can comprehend the outcomes of the trial.

15.5. Amendments and Updates

15.5.1. Policy Updates:

This publication policy is subject to updates and revisions as necessary. Any changes will be communicated to all relevant parties involved in the trial and publication process.

15.5.2. Retroactive application:

In case of policy updates or revisions, ongoing publications and trials will be assessed to determine the applicability of the new policy provisions. Authors will be guided on the steps to ensure compliance.

By adhering to this Publication Policy and Trial Results Dissemination Protocol, we aim to maintain the highest standards of scientific integrity, ethical conduct, and transparency throughout the trial and publication processes.

16 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

In accordance with clause 7 of the Master Services Agreement dated 18 June 2023 entered into between the parties, any new IP relating to DAYE products will be the sole property of Tampon Innovations Ltd, and any new IP relating to trial management and/or Lindus Health tools will be the sole property of Lindus Health.

17 ARCHIVING

Trial materials will be archived according to Linds Health SOPs for a minimum of ten years, personal data will be retained for a minimum of 12 months after trial end, compliant with applicable legislation and trial regulations.

18 REFERENCES

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19 APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	3.0	29 Nov 2023	Tessa Griffiths	General minor clarifications and administrative changes throughout

				Section 2.0: Clarification to the primary objective and outcome. 5.12: Clarification on communication of results to participants and process for discrepant results. Section 5.13.1.2: Clarification around focus group consent. Section 5.13.2: Additional details around individuals completing the stakeholder questionnaire Section 5.14.3: Changes to the assays being used and addition of description and justification for each one. Section 8: Statistical clarifications around sample size, significance and missing questionnaires. Section 9.3: Clarification around sharing of personal data with vendors for trial processes. Section 13.8 Clarification to travel expenses.

N/A	2.0	06 Oct 2023	Amy Moore	Section 4.2: Amendment to the definition of sexually active in inclusion 3.
N/A	1.0	28 Sept 2023	Tessa Griffiths	First version.

20 APPENDIX B: SUPPLEMENTARY MATERIAL

A. Abbreviations

AE	Adverse event
AR	Adverse reaction
BV	Bacterial Vaginosis
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation

CTRG	Clinical Trials and Research Governance
DDT	Daye Diagnostic Tampon
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HPV	Human Papillomavirus
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency

NHS	National Health Service
RES	Research Ethics Service
PCR	Polymerase chain reaction
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

TSS	Toxic Shock Syndrome

B. Key trial contacts

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