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Rationale and design of The Self-TI Study: an HPV self-testing pilot study among transgender adults

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (hrHPV) is the causal agent of several cancers including cervical, anal, and oropharyngeal cancer. Transgender men and transmasculine non-binary (TMNB) people with a cervix are much less likely to undergo cervical cancer screening than cisgender women. Transgender women and transfeminine non-binary (TWNB) people assigned male at birth may be at increased risk of HPV. Both TMNB and TWNB people face many barriers to HPV testing including medical mistrust due to stigma and discrimination.

Methods and analysis: The Self-TI Study (Self-TI) is a pilot study designed to measure acceptability and feasibility of HPV self-testing among transgender and non-binary people in England. TMNB people aged 25–65, with at least one year of testosterone and TWNB people, aged 18 and over are eligible to participate. Participants self-collect up to four samples: an oral rinse, a first void urine sample, a vaginal swab (if applicable), and an anal swab. TMNB participants are asked to have an additional clinician-collected cervical swab taken following their routine Cervical Screening Programme sample. TWNB are asked to take a self-collection kit to perform additional self-collection at home and mail the samples back to the clinic. Acceptability is assessed by a self-administered online survey and feasibility is measured as the proportion of samples returned in the clinic and from home.

Ethics and dissemination: Self-TI received ethical approval from the Regulatory Ethics Committee of Wales 4 (Wales REC 4) and Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute. Self-TI was co-produced by members of the transgender and non-binary community, who

served as authors, collaborators, and members of the patient and public involvement (PPI) group. Results of this study will be shared with the community prior to being published in peer-reviewed journals and the PPI group will help to design the results dissemination strategy. The evidence generated from this pilot study could be used to inform a larger, international study of HPV self-testing in the transgender and non-binary community.

Trial registration number: NCT05883111

Strengths and Limitations

- The study addresses the lack of evidence around acceptability of human papillomavirus (HPV) self-sampling in transgender and non-binary people.
- This study collects samples from four body sites including an oral rinse, a urine sample, a vaginal swab, and an anal swab to assess correlation between samples.
- This pilot study examines the concordance between self-collected and clinician-collected samples.
- This pilot study offers participants an at-home collection kit to assess the feasibility of HPV testing at home.
- Findings from this study will be used to inform a larger, international study.

INTRODUCTION

Persistent infection with one of 12 high-risk human papillomavirus (hrHPV) genotypes is the causative agent of several cancers including cervical, anogenital, and oropharyngeal.[1] The widespread implementation of cervical cancer screening with Pap cytology or HPV testing, combined with HPV vaccination, has greatly reduced cervical cancer incidence and mortality.[2] Consensus guidelines for anal cancer screening now include transgender women.[3 4]

Transgender men and transmasculine non-binary (TMNB) adults (those who were registered female at birth and have a masculine or non-binary gender identity) are less likely to have ever undergone cervical cancer screening than cisgender women.[5 6] As many as one third of TMNB adults are not up-to-date with recommended screening guidelines.[7 8] Among those screened, TMNB patients are eight times more likely than cisgender women to have an inadequate Pap where the test cannot be evaluated for a variety of reasons such as lack of sufficient cellularity or bleeding resulting from testosterone induced cervical and vaginal atrophy.[9] TMNB adults face many additional barriers to cervical cancer screening than cisgender people, including an increased likelihood of discrimination in medical settings.[10-12] During gynecologic exams, TMNB patients may experience gender dysphoria (distress associated with the incongruence between gender identity and sex registered at birth) due to the focus on genitalia and the gendered nature of cervical cancer screening, such as feminine waiting rooms and expectations of gender conformity.[13-15] Clinicians may also erroneously believe that TMNB are not a risk for HPV due to incorrect assumptions about TMNB anatomy and

sexual practices, and are less likely to recommend screening.[14] Further, TMNB patients may be less likely to be vaccinated against HPV than cisgender women.[16]

Transgender women and transfeminine non-binary (TWNB) adults (those who were registered male at birth and have a female or non-binary gender identity) may be at increased risk of HPV infection compared to cisgender individuals. England began a national HPV immunisation programme for adolescent girls with the bivadults,HPV vaccine in 2008 and switched to the quadrivalent in 2012.[17] The UK implemented a gender-neutral vaccination program in 2019 with a catch-up programme for people up to the age of 45 years who are considered high risk for HPV (e.g., men who have sex with men).[18] Though transgender and non-binary people may be eligible for vaccination through the catch-up programme, barriers to healthcare and lack of perceived risk means that many TWNB adults may still be unvaccinated.[19] Additionally, co-infection with HIV, which may be elevated among TWNB adults compared to the general population,[20] increases the risk of persistent HPV infection[21-23] and HPV associated cancers.[24 25] One small US study reported a study HPV prevalence of 89% in anal and 9% in oral specimens from TWNB adults.[26] A Brazilian study of 268 transgender women reported a study prevalence to be 77% in anal, 34% in genital, and 11% oral specimens.[27] Studies from both The Netherlands and Thailand estimate a 20% prevalence of neovaginal hrHPV, though these two studies had a high proportion of invalid HPV results, suggesting the true prevalence may be higher.[28 29] The oncogenic potential of persistent hrHPV infection in the vagina of TWNB is poorly understood and current guidelines do not recommend screening for this population.[30] Both low- and

high-grade squamous intraepithelial lesions have been reported in the vagina of TWNB adults but incidence data is lacking.[31 32]

Prior research conducted in cisgender women has shown that self-sampling for hrHPV with PCR-based assays has comparable performance to clinician-collected samples for the detection of cervical hrHPV.[33 34] Limited research suggests that most TMNB patients may prefer HPV testing by self-collection,[35 36] though patients have expressed concern about the lack of evidence-based guidelines specific to TMNB to inform their preference.[35 37] Indeed, only one small study[38] has compared the performance of clinician- and self-collected samples in TMNB, showing good concordance; however more research is needed to assess whether this is an acceptable approach for cervical screening in TMNB. Reisner *et al.*[39] found a study HPV prevalence of 16% among 130 TM participants and that HPV testing by self-sample showed good concordance with clinician-collected samples. Similarly, one US study that included TWNB adults found that people were more likely to engage in anal cancer screening with an at-home self-collection kit than attend a clinician-collected screening appointment.[40]

The objective of this pilot study is to assess the feasibility and acceptability of HPV self-testing at four body sites among TMNB and TWNB adults.

METHODS AND ANALYSIS

Study design and setting

The Self-TI Study (Self-TI) is a pilot study examining the acceptability and feasibility of HPV self-testing among transgender and non-binary people conducted in England (IRAS# 319364 and clincialtrials.gov NCT05883111). The study received

ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4, #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to the protocol and study materials are approved by the REC and the protocol was last revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all participants provide informed written consent to participate to the study staff. Participants are asked if they consent to future use of their research specimens; otherwise specimens will be destroyed after the aims of the study protocol are met.

Study setting and participant recruitment

Enrolment began in February 2024 and will continue for one year. Self-TI seeks to enroll 50 participants who identify as TMNB with a cervix and 50 participants who identify as TWNB assigned male at birth. Participants are recruited at one of three clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or Clinic-T in Brighton. These sites were chosen as they are in areas with large transgender and non-binary populations, their providers are specialists in transgender and non-binary sexual health, and the clinic staff have experience conducting research studies. Participants can be recruited and pre-screened for study eligibility when they book an appointment for a cervical cancer screening (TMNB study group only) or a sexual health screening (TWNB study group only). Recruitment occurs through advertisement posters and banners placed in the clinics, and flyers placed in gender identity clinics and general practitioners' offices known to have transgender and non-binary patients. Self-TI has created a website (www.self-ti.com), which contains information on the study, HPV and cancer education, and links to contact the study sites

to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to record a 45 second advertisement video. This video is posted the activist's social media sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and the Self-TI's website and social media sites. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is available as an online supplemental file.[41]

Participants

Individuals who identify as TMNB with a cervix, aged 25–65, with at least one year of self-reported testosterone therapy, are eligible to participate in the TMNB study group. Testosterone exposure is a requirement of study participation because it may affect the accuracy and acceptability of clinician- and self-collected HPV testing. Individuals who identify as TWNB, aged 18 and over, are eligible to participate in the TWNB study group. TWNB participants with a vagina are preferentially selected into the study, with the first three months of enrolment restricted to individuals who had undergone vaginoplasty. After three months, the study team will evaluate whether it is feasible to reach the targeted sample size with this restriction and if not, the eligibility criterion will be removed. Individuals with a vagina must have undergone vaginoplasty greater than one year prior to entering the study due to safety concerns over self-sampling on recently healed epithelium. All participants are given a participant information sheet, which is discussed with study staff as part of informed consent procedures.

Data collection

Study activities and timeline are presented in Table 1 and Figure 1. After giving consent, participants fill out demographics and medical history questionnaires. The demographics form asks for sexual orientation, race and ethnicity, and height and weight. The medical history form asks about previous cancer screening, previous cancer diagnoses, HPV vaccination, hormone therapy, and HIV status. Study staff review these questionnaires with the participants to make sure they are complete and to answer any questions the participants have.

Table 1. Study activities and timeline

	Prior to Day 1	In Clinic Day 1		At Home ≦ 4 weeks (TWNB only)
Study procedure	**Screening**	**Clinician**	**Self-Sampling**	**Self-Sampling**
Eligibility assessment	X			
Informed consent			X	
Demographics			X	
Medical history			X	
Vaginal swab			X*	X*
Anal swab			X	X
Oral rinse			X	X
Urine			X	
Cervical swab		X (TMNB only)		
Survey			X (TMNB only)	X
Adverse event assessment		X	X	X

*All TMNB and only TWNB who have undergone vaginoplasty.

Abbreviations: TMNB = transmasculine and non-binary people with a cervix; TWNB= trans women and non-binary people assigned male at birth

Sampling

All participants are asked to self-collect samples in the clinic in the following order: oral rinse, urine, vagina, and anus (collection materials are provided in Table 2). Each participant will receive a self-sampling kit with written instructions for self-collection that includes a QR code linked to an instructional video. Study staff will also explain the self-collection procedures to the participants.

Table 2. Collection materials of study specimens

Specimen Type	Collection Method
Vaginal/neo-vaginal	Evalyn® Brush (Rovers® Medical, Belgium) or Dacron swab (DuPont, US)
Anal	FLOQSwab (COPAN Diagnostics Inc., US)
Oral rinse	Scope (Proctor and Gamble, US)
Urine	Colli-Pee (Novosanis, Belgium)
Cervical	Endocervical broom (Hologic, US)

The participants use Scope mouthwash (Proctor and Gamble, US) to collect buccal cells and a Colli-pee® collection device (Novosanis, Belgium) to collect first void urine (Table 2). The Colli-pee® device was selected as it has been used successfully by sexual and gender minority participants in other studies and can accommodate a variety of genital anatomies.

For the vaginal sample, participants have a choice to use either an Evalyn Brush® (Rovers Medical, Belgium) or a Dacron swab (DuPont, US) (Table 2), if applicable. The Evalyn Brush® was chosen for several features which make it easier to use for populations unfamiliar with self-sampling. It has wings to guide the participant as to how far they should insert the device, a plunger which releases the bristle brush to the cervix and clicks to aid in the counting of the rotations. Participants who prefer a slimmer vaginal swab are provided with a Dacron swab upon request (Table 2).

Participants use a FLOQSwab® (COPAN Diagnostics Inc., US) to collect the anal sample (Table 2).

After the self-administered samples are collected, TMNB participants have a pelvic exam as part of the standard cervical cancer screening. In England, individuals with a cervix are invited to participate in the National Cervical Screening Programme (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those between the ages of 50-65. Screening is conducted with a primary HPV test and if positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI, the clinician will take two cervical swabs; the first for the (CSP) sent to the National Health Service (NHS) laboratories, and the second for the clinician-collected sample for Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so that if the participant declines further samples the standard of care is met.

After TWNB participants collect their self-administered samples, they will be given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at home. Once collected, the participant places the dry brushes and samples in the pre-addressed, postage paid mailer provided before dropping it in the post within one month of their first study visit. The kit includes written instructions with a QR code linked to an instructional video. Study staff follow up with TWNB study participants on a weekly basis for up to four weeks to ensure the return of their study samples.

Self-administered online survey

After self-collection, participants take a self-administered online survey, which takes approximately 20–25 minutes to complete. The survey includes questions on

sensitive demographic characteristics, acceptability of self-sampling, comparing self-collected to clinician-collected sampling (TMNB study group only), comparing self-collected sampling in the clinic to at-home collection (TWNB study group only), history of HPV vaccination, knowledge of HPV, medical mistrust, and sexual history. Participants receive a £20 gift card to a large online retailer, as renumeration for their participation in Self-TI.

Outcomes

The primary study outcomes are the acceptability and feasibility of self-sampling among participants that will inform a larger study. Acceptability is measured by the physical and emotional responses to self-sampling for each collection method using a 7-point Likert scale. Feasibility is measured by the proportion of specimens returned from self-collection in the clinic and those mailed from home.

This pilot study will also estimate the study prevalence of HPV (positivity and genotype) and the correlation of HPV detection between the four self-collected samples. The concordance between the vaginal self-collected sample and clinician-collected cervical sample will be estimated among TMNB. Among TWNB, we will estimate the correlation between the samples collected by participants in the clinic with the samples collected at home. Finally, Self-TI will collect exploratory data on risk factors associated with HPV prevalence, which can be fully assessed in a larger trial.

HPV testing

The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are

shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will be tested using a next-generation sequencing based-assay (TypeSeq) developed by CGR, which generates a positive/negative result for 51 HPV genotypes.[42]

Data management

Data management and project coordination is done at the Division of Cancer Epidemiology and Genetics at NCI. Study oversight and data management are led by the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-identified participant data into an electronic data capture system. All participant information (including laboratory data) is confidential and stored in a secure location. Only the personnel listed on the delegation log will have access to participant data; the statistician and laboratory personnel have access to deidentified data only. Participant data are checked at regular intervals for quality assurance. The number of AEs is expected to be very small and thus an independent Data Monitoring Committee was not appointed. However, all adverse events will be collected, and severe adverse events deemed by the chief investigator to be related to study procedures and unexpected, will be reported to the sponsor within 24 hours and to the REC within 15 days of learning of the event.

Statistical analysis

Acceptability of self-sampling procedures will be measured on the self-administered online survey, which uses a 7-point Likert scale with 1 indicating strong disagreement and 7 indicating strong agreement. Summary measures of these questions will be reported (average score for each question) separately for each group. For all participants, feasibility will be measured by the proportion of participants who are

able to complete the self-collection procedures in the clinic. For TWNB participants, at-home feasibility will be measured by the proportion of TWNB participants who are able to complete and return all self-collection procedures at home.

For our secondary objectives, we will estimate the prevalence of HPV, overall, and by genotype in each of the self-collected samples from the two groups, separately. The phi-coefficient and associated *P*-values will be estimated to assess HPV positivity correlation between the four anatomic sites. Further, we will calculate the Cohen's kappa statistic as a measure of percent positive agreement of HPV positivity in self-collected vaginal samples versus the clinician-collected cervical samples among TMNB and in self-collected in clinic samples versus self-collected at home samples among TWNB, respectively.

Patient and public involvement

A patient and public involvement (PPI) group was formed prior to the submission of the Self-TI protocol to regulatory bodies. PPI played an important role in the design and conduct of the study, and participant recruitment. Six group meetings were held between May 2022–August 2023 with six members. PPI members represented the target population of Self-TI, including transfeminine, transmasculine, and non-binary individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by SOC or EW who are members of the transgender and non-binary community, and SOC is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and queer individuals. PPI members reviewed the study protocol, data collection forms, online self-administered survey, advertisement and recruitment plan, instructional video, and results dissemination plan. Meetings were conducted over Zoom in the evenings to

accommodate members' schedules and followed up via email to provide additional opportunities for written feedback on materials. Online meetings included short presentations on HPV-related cancer topics given by experts in the field to provide information exchange. PPI members were compensated for their time with multi-retailer gift cards to an amount in line with National Institute for Health Research guidelines.

Several important suggestions were made by the PPI group and adopted into the study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which was suggested could be off putting to our participants, so we worked with the manufacturers to provide Self-TI with devices in a more neutral blue color. Though the Evalyn® brush has several features that make it ideal for individuals who are not familiar with self-sampling, one drawback is that it is slightly thicker than other swabs used for vaginal sampling. Therefore, it was suggested by the PPI group that participants be provided with a slimmer swab upon request. Additionally, though it is preferred that TMNB participants complete the survey in the clinic after their exam, the PPI group felt that participants should be given the option to complete the survey at home. This change was implemented and TMNB participants can scan or be emailed a QR code to the survey link after leaving the clinic if desired. The group felt that some participants would want to leave the clinic immediately after their speculum exam as it may result in increased feelings of dysphoria and can be uncomfortable or painful for some participants.

ETHICS AND DISSEMINATION

People with a male gender marker in their medical record are not invited to participate in the CSP and the laboratory may reject cervical samples from male

patients. The chief investigator worked with the laboratories processing CSP samples for Self-TI participants to ensure samples would not be discarded prior to testing. Senior staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group about returning study results to the participants. Because the assay under study in Self-TI is a research test and not approved for clinical use in the UK, participants will not have their study results returned to them. Instead, TMNB participants should defer to the HPV result provided by the CSP, as applicable. Further, in cases where the HPV result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in the case of TWNB samples), senior study staff felt that providing participants with a result that could not be followed up with clinically could cause distress and would be unethical. Only HPV positive results taken from samples as part of the CSP will warrant follow up under the NHS.

Information gained from this study will be published in peer-reviewed journals and presented at national and international conferences. Prior to scientific dissemination, we will engage with the PPI group in writing the lay results, results dissemination strategy and final publication. The lay summary of the results will be posted to the Self-TI website, participating clinic websites, and the websites of charities and organisations supporting trans and non-binary people so that study participants and community members may be notified of the results first at the PPI group's request. Several online webinars are planned to disseminate the results and allow community members to engage in a discussion with the researchers. These webinars will be recorded and posted on the Self-TI website. Finally, data from this pilot study will inform a larger, multi-center, international study.

DISCUSSION

The overarching goal of this pilot study is to provide important insight into the acceptability and feasibility of HPV self-sampling among transgender and gender diverse individuals for a larger study. The pilot study will provide essential data that will inform recruitment, study procedures, and sample size calculations for this larger study.

Authors' contributions: AMB and SSJ conceived, designed, and supervised the study. AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC supervised the HPV methylation assay and provided several methodological contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating the study survey. All authors revised the manuscript and approved the final draft.

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Competing interest statement: AMB is a trustee of OUTpatients, of which SOC is CEO. None of the other authors have any conflicts to declare.

Patient and public involvement: Patients and the community were involved in the design, conduct, and dissemination plans of this research. Refer to the Methods section for further details.

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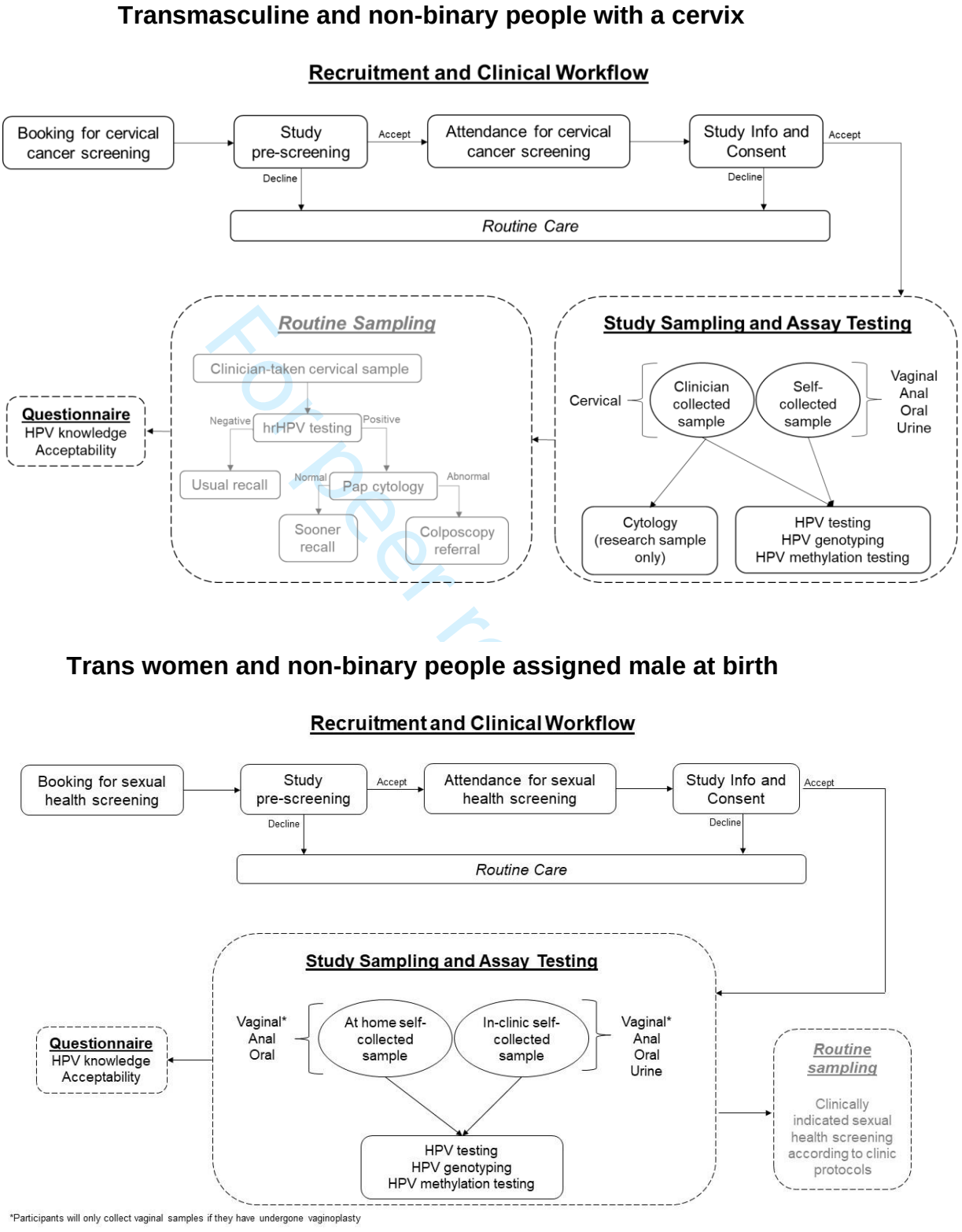
Figure 1. Study Flow



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3 and 6
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-12, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8, and 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12-13 and Table 2

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Rationale and design of The Self-TI Study protocol: a cross-sectional human papillomavirus self-testing pilot study among transgender adults in England

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Rationale and design of The Self-TI Study protocol: a cross-sectional human papillomavirus self-testing pilot study among transgender adults in England

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Key words: human papillomavirus, HPV, transgender and non-binary, cancer screening, cervical cancer, anal cancer

Abstract

Introduction: Persistent infection with high-risk human papillomavirus (HPV) is the causal agent of several cancers including cervical, anal, and oropharyngeal cancer. Transgender men and transmasculine non-binary (TMNB) people with a cervix are much less likely to undergo cervical cancer screening than cisgender women. Transgender women and transfeminine non-binary (TWNB) people assigned male at birth may be at increased risk of HPV. Both TMNB and TWNB people face many barriers to HPV testing including medical mistrust due to stigma and discrimination.

Methods and analysis: The Self-TI Study (Self-TI) is a pilot study designed to measure acceptability and feasibility of HPV self-testing among transgender and non-binary people in England. TMNB people aged 25–65, with at least one year of testosterone and TWNB people, aged 18 and over are eligible to participate. Participants self-collect up to four samples: an oral rinse, a first void urine sample, a vaginal swab (if applicable), and an anal swab. TMNB participants are asked to have an additional clinician-collected cervical swab taken following their routine Cervical Screening Programme sample. TWNB are asked to take a self-collection kit to perform additional self-collection at home and mail the samples back to the clinic. Acceptability is assessed by a self-administered online survey and feasibility is measured as the proportion of samples returned in the clinic and from home.

Ethics and dissemination: Self-TI received ethical approval from the Regulatory Ethics Committee of Wales 4 (Wales REC 4) and Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute. Self-TI was co-produced by members of the transgender and non-binary community, who

served as authors, collaborators, and members of the patient and public involvement (PPI) group. Results of this study will be shared with the community prior to being published in peer-reviewed journals and the PPI group will help to design the results dissemination strategy. The evidence generated from this pilot study could be used to inform a larger, international study of HPV self-testing in the transgender and non-binary community.

Trial registration number: NCT05883111

Strengths and Limitations

- The pilot study addresses the lack of evidence around acceptability of human papillomavirus (HPV) self-sampling in transgender and non-binary people and was co-designed with community members.
- This pilot study collects samples from four body sites including an oral rinse, a urine sample, a vaginal swab, and an anal swab to assess correlation between samples.
- This pilot study examines the concordance between self-collected and clinician-collected samples.
- This pilot study offers participants an at-home collection kit to assess the feasibility of HPV testing at home.
- The generalizability of study findings is limited due the convenience sampling of participants.

INTRODUCTION

Persistent infection with one of 12 high-risk human papillomavirus (HPV) genotypes is the causative agent of several cancers including cervical, anogenital, and oropharyngeal.[1] The widespread implementation of cervical cancer screening with Pap cytology or HPV testing, combined with HPV vaccination, has greatly reduced cervical cancer incidence and mortality.[2] Consensus guidelines for anal cancer screening now include transgender women.[3 4]

Transgender men and transmasculine non-binary (TMNB) adults (those who were registered female at birth and have a masculine or non-binary gender identity) are less likely to have ever undergone cervical cancer screening than cisgender women.[5 6] As many as one third of TMNB adults are not up-to-date with recommended screening guidelines.[7 8] Among those screened, TMNB patients are eight times more likely than cisgender women to have an inadequate Pap where the test cannot be evaluated for a variety of reasons such as lack of sufficient cellularity or bleeding resulting from testosterone induced cervical and vaginal atrophy.[9] TMNB adults face many additional barriers to cervical cancer screening than cisgender people, including an increased likelihood of discrimination in medical settings.[10-12] During gynecologic exams, TMNB patients may experience gender dysphoria (distress associated with the incongruence between gender identity and sex registered at birth) due to the focus on genitalia and the gendered nature of cervical cancer screening, such as feminine waiting rooms and expectations of gender conformity.[13-15] Clinicians may also erroneously believe that TMNB are not a risk for HPV due to incorrect assumptions about TMNB anatomy and

sexual practices, and are less likely to recommend screening.[14] Further, TMNB patients may be less likely to be vaccinated against HPV than cisgender women.[16]

Transgender women and transfeminine non-binary (TWNB) adults (those who were registered male at birth and have a female or non-binary gender identity) may be at increased risk of HPV infection compared to cisgender individuals. England began a national HPV immunisation programme for adolescent girls with the bivalent HPV vaccine in 2008, switching to the quadrivalent in 2012 and the nonavalent in 2021.[17 18] The UK implemented a gender-neutral vaccination program in 2019 with a catch-up programme for people up to the age of 45 years who are considered high risk for HPV (e.g., men who have sex with men).[19] Though transgender and non-binary people may be eligible for vaccination through the catch-up programme, barriers to healthcare and lack of perceived risk means that many TWNB adults may still be unvaccinated.[20] Additionally, co-infection with HIV, which may be elevated among TWNB adults compared to the general population,[21] increases the risk of persistent HPV infection[22-24] and HPV associated cancers.[25 26] One small US study reported a study HPV prevalence of 89% in anal and 9% in oral specimens from TWNB adults.[27] A Brazilian study of 268 transgender women reported a study prevalence to be 77% in anal, 34% in genital, and 11% oral specimens.[28] Studies from both The Netherlands and Thailand estimate a 20% prevalence of neovaginal high-risk HPV, though these two studies had a high proportion of invalid HPV results, suggesting the true prevalence may be higher.[29 30] The oncogenic potential of persistent high-risk HPV infection in the vagina of TWNB is poorly understood and current guidelines do not recommend screening for this

population.[31] Both low- and high-grade squamous intraepithelial lesions have been reported in the vagina of TWNB adults but incidence data is lacking.[32 33]

Prior research conducted in cisgender women (largely from high-income countries) has shown that self-sampling for HPV with PCR-based assays has comparable performance to clinician-collected samples for the detection of cervical HPV.[34 35] Limited research suggests that most TMNB patients may prefer HPV testing by self-collection,[36 37] though patients have expressed concern about the lack of evidence-based guidelines specific to TMNB to inform their preference.[36 38] Indeed, only one small study[39] has compared the performance of clinician- and self-collected samples in TMNB, showing good concordance; however more research is needed to assess whether this is an acceptable approach for cervical screening in TMNB. Reisner *et al.*[40] found a study HPV prevalence of 16% among 130 TM participants and that HPV testing by self-sample showed good concordance with clinician-collected samples. Similarly, one US study that included TWNB adults found that people were more likely to engage in anal cancer screening with an at-home self-collection kit than attend a clinician-collected screening appointment.[41]

We present the protocol for Self-TI, a pilot study whose objective is to assess the feasibility and acceptability of HPV self-testing at four body sites among TMNB and TWNB adults.

METHODS AND ANALYSIS

Study design and setting

The Self-TI Study (Self-TI) is a pilot study examining the acceptability and feasibility of HPV self-testing among transgender and non-binary people conducted in

England (IRAS# 319364 and clincialtrials.gov NCT05883111). The study received ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4, #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to the protocol and study materials are approved by the REC and the protocol was last revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all participants provide informed written consent to participate to the study staff. Participants are asked if they consent to future use of their research specimens; otherwise specimens will be destroyed after the aims of the study protocol are met.

Study setting and participant recruitment

Enrolment began in February 2024 and will continue for one year. Self-TI seeks to enroll 50 participants who identify as TMNB with a cervix and 50 participants who identify as TWNB assigned male at birth. Participants are recruited at one of three clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or Clinic-T in Brighton. These sites were chosen as they are in areas with large transgender and non-binary populations, their providers are specialists in transgender and non-binary sexual health, and the clinic staff have experience conducting research studies. Participants can be recruited and pre-screened for study eligibility when they book an appointment for a cervical cancer screening (TMNB study group only) or a sexual health screening (TWNB study group only). Recruitment occurs through advertisement posters and banners placed in the clinics, and flyers placed in gender identity clinics and general practitioners' offices known to have transgender and non-binary patients. Self-TI has created a website (www.self-ti.com), which contains

information on the study, HPV and cancer education, and links to contact the study sites to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to record a 45 second advertisement video. This video is posted the activist's social media sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and the Self-TI's website and social media sites. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is available as an online supplemental file.[42]

Participants

Individuals who identify as TMNB with a cervix, aged 25–65, with at least one year of self-reported testosterone therapy, are eligible to participate in the TMNB study group. Testosterone exposure is a requirement of study participation as it is associated with vaginal atrophy such that speculum and swab insertion to the recommended depth could be painful, unpleasant, or necessitate additional lubricant affecting the accuracy and acceptability of clinician- and self-collected HPV testing.[9 40] Individuals who identify as TWNB, aged 18 and over, are eligible to participate in the TWNB study group. TWNB participants with a vagina are preferentially selected into the study, with the first three months of enrolment restricted to individuals who had undergone vaginoplasty. After three months, the study team will evaluate whether it is feasible to reach the targeted sample size with this restriction and if not, the eligibility criterion will be removed. Individuals with a vagina must have undergone vaginoplasty greater than one year prior to entering the study due to safety concerns over self-sampling on recently healed epithelium. All participants are given a participant information sheet, which is discussed with study staff as part of informed consent procedures.

Data collection

Study activities and timeline are presented in Table 1 and Figure 1. After giving consent, participants fill out demographics and medical history questionnaires. The demographics form asks for sexual orientation, race and ethnicity, and height and weight. The medical history form asks about previous cancer screening, previous cancer diagnoses, HPV vaccination, hormone therapy, and HIV status. Study staff review these questionnaires with the participants to make sure they are complete and to answer any questions the participants have.

Table 1. Study activities and timeline

	Prior to Day 1	In Clinic Day 1		At Home ≦ 4 weeks (TWNB only)
Study procedure	**Screening**	**Clinician**	**Self-Sampling**	**Self-Sampling**
Eligibility assessment	X			
Informed consent			X	
Demographics			X	
Medical history			X	
Vaginal swab			X*	X*
Anal swab			X	X
Oral rinse			X	X
Urine			X	
Cervical swab		X (TMNB only)		
Survey			X (TMNB only)	X
Adverse event assessment		X	X	X

*All TMNB and only TWNB who have undergone vaginoplasty.

Abbreviations: TMNB = transmasculine and non-binary people with a cervix; TWNB= trans women and non-binary people assigned male at birth

Sampling

All participants are asked to self-collect samples in the clinic in the following order: oral rinse, urine, vagina, and anus (collection materials are provided in Table 2). Each participant will receive a self-sampling kit with written instructions for self-collection that includes a QR code linked to an instructional video. Study staff will also explain the self-collection procedures to the participants.

Table 2. Collection materials of study specimens

Specimen Type	Collection Method
Vaginal/neo-vaginal	Evalyn® Brush (Rovers® Medical, Belgium) or Dacron swab (DuPont, US)
Anal	FLOQSwab (COPAN Diagnostics Inc., US)
Oral rinse	Scope (Proctor and Gamble, US)
Urine	Colli-Pee (Novosanis, Belgium)
Cervical	Endocervical broom (Hologic, US)

The participants use Scope mouthwash (Proctor and Gamble, US) to collect buccal cells and a Colli-pee® collection device (Novosanis, Belgium) to collect first void urine (Table 2). The Colli-pee® device was selected as it has been used successfully by sexual and gender minority participants in other studies and can accommodate a variety of genital anatomies.

For the vaginal sample, participants have a choice to use either an Evalyn Brush® (Rovers Medical, Belgium) or a Dacron swab (DuPont, US) (Table 2), if applicable. The Evalyn Brush® was chosen for several features which make it easier to use for populations unfamiliar with self-sampling. It has wings to guide the participant as to how far they should insert the device, a plunger which releases the bristle brush to the cervix and clicks to aid in the counting of the rotations. Participants who prefer a slimmer vaginal swab are provided with a Dacron swab upon request (Table 2). Participants use a FLOQSwab® (COPAN Diagnostics Inc., US) to collect the anal

sample (Table 2). The choice of sampling methods was based on a review of previous studies that examined the same body sites and concordance between in-clinic and at-home sampling methods.[43 44]

After the self-administered samples are collected, TMNB participants have a pelvic exam as part of the standard cervical cancer screening. In England, individuals with a cervix are invited to participate in the National Cervical Screening Programme (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those between the ages of 50-65. Screening is conducted with a primary HPV test and if positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI, the clinician will take two cervical swabs; the first for the (CSP) sent to the National Health Service (NHS) laboratories, and the second for the clinician-collected sample for Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so that if the participant declines further samples the standard of care is met.

After TWNB participants collect their self-administered samples, they will be given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at home. Once collected, the participant places the dry brushes and samples in the pre-addressed, postage paid mailer provided before dropping it in the post within one month of their first study visit. The kit includes written instructions with a QR code linked to an instructional video. Study staff follow up with TWNB study participants on a weekly basis for up to four weeks to ensure the return of their study samples.

Self-administered online survey

After self-collection, participants take a self-administered online survey, which takes approximately 20–25 minutes to complete. The survey includes questions on based on previously validated surveys that capture sensitive demographic characteristics, acceptability of self-sampling (e.g., physical and emotional comfort, confidence in collection), comparing self-collected to clinician-collected sampling (TMNB study group only),[39] comparing self-collected sampling in the clinic to at-home collection (TWNB study group only), history of HPV vaccination, knowledge of HPV,[39] comparing self-collected to clinician-collected sampling (TMNB study group only), medical mistrust,[45] and sexual history.[39 46] comparing self-collected sampling in the clinic to at-home collection (TWNB study group only), history of HPV vaccination, knowledge of HPV,[15] medical mistrust,[45] and sexual history.[46] Participants receive a £20 gift card to a large online retailer, as renumeration for their participation in Self-TI.

Outcomes

The primary study outcomes are the acceptability and feasibility of self-sampling among participants that will inform a larger study. Acceptability is measured by the physical and emotional responses to self-sampling for each collection method using a 7-point Likert scale. Feasibility is measured by the proportion of specimens returned from self-collection in the clinic and those mailed from home.

This pilot study will also estimate the study prevalence of HPV (positivity and genotype) and the correlation of HPV detection between the four self-collected samples. The concordance between the vaginal self-collected sample and clinician-collected cervical sample will be estimated among TMNB. Among TWNB, we will estimate the correlation between the samples collected by participants in the clinic with the samples

collected at home. Finally, Self-TI will collect exploratory data on risk factors associated with HPV prevalence, which can be fully assessed in a larger trial.

HPV testing

The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will be tested using a next-generation sequencing based-assay (TypeSeq) developed by CGR, which generates a positive/negative result for 51 HPV genotypes.[47]

Data management

Data management and project coordination is done at the Division of Cancer Epidemiology and Genetics at NCI. Study oversight and data management are led by the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-identified participant data into an electronic data capture system. All participant information (including laboratory data) is confidential and stored in a secure location. Only the personnel listed on the delegation log will have access to participant data; the statistician and laboratory personnel have access to deidentified data only. Participant data are checked at regular intervals for quality assurance. The number of AEs is expected to be very small and thus an independent Data Monitoring Committee was not appointed. However, all adverse events will be collected, and severe adverse events deemed by the chief investigator to be related to study procedures and unexpected, will be reported to the sponsor within 24 hours and to the REC within 15 days of learning of the event.

Statistical analysis

Acceptability of self-sampling procedures will be measured on the self-administered online survey, which uses a 7-point Likert scale with 1 indicating strong disagreement and 7 indicating strong agreement. Summary measures of these questions will be reported (average score for each question) separately for each group. For all participants, feasibility will be measured by the proportion of participants who are able to complete the self-collection procedures in the clinic. For TWNB participants, at-home feasibility will be measured by the proportion of TWNB participants who are able to complete and return all self-collection procedures at home.

For our secondary objectives, we will estimate the prevalence of HPV, overall, and by genotype in each of the self-collected samples from the two groups, separately. The phi-coefficient and associated *P*-values will be estimated to assess HPV positivity correlation between the four anatomic sites. Further, we will calculate the Cohen's kappa statistic as a measure of percent positive agreement of HPV positivity in self-collected vaginal samples versus the clinician-collected cervical samples among TMNB and in self-collected in clinic samples versus self-collected at home samples among TWNB, respectively.

Patient and public involvement

A patient and public involvement (PPI) group was formed prior to the submission of the Self-TI protocol to regulatory bodies. PPI played an important role in the design and conduct of the study, and participant recruitment. Six group meetings were held between May 2022–August 2023 with six members. PPI members represented the target population of Self-TI, including transfeminine, transmasculine, and non-binary

individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by SOC or EW who are members of the transgender and non-binary community, and SOC is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and queer individuals. PPI members reviewed the study protocol, data collection forms, online self-administered survey, advertisement and recruitment plan, instructional video, and results dissemination plan. Meetings were conducted over Zoom in the evenings to accommodate members' schedules and followed up via email to provide additional opportunities for written feedback on materials. Online meetings included short presentations on HPV-related cancer topics given by experts in the field to provide information exchange. PPI members were compensated for their time with multi-retailer gift cards to an amount in line with National Institute for Health Research guidelines.

Several important suggestions were made by the PPI group and adopted into the study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which was suggested could be off putting to our participants, so we worked with the manufacturers to provide Self-TI with devices in a more neutral blue color. Though the Evalyn® brush has several features that make it ideal for individuals who are not familiar with self-sampling, one drawback is that it is slightly thicker than other swabs used for vaginal sampling. Therefore, it was suggested by the PPI group that participants be provided with a slimmer swab upon request. Additionally, though it is preferred that TMNB participants complete the survey in the clinic after their exam, the PPI group felt that participants should be given the option to complete the survey at home. This change was implemented and TMNB participants can scan or be emailed a QR code to the survey link after leaving the clinic if desired. The group felt that some

participants would want to leave the clinic immediately after their speculum exam as it may result in increased feelings of dysphoria and can be uncomfortable or painful for some participants.

ETHICS AND DISSEMINATION

People with a male gender marker in their medical record are not invited to participate in the CSP and the laboratory may reject cervical samples from male patients. The chief investigator worked with the laboratories processing CSP samples for Self-TI participants to ensure samples would not be discarded prior to testing. Senior staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group about returning study results to the participants. Because the assay under study in Self-TI is a research test and not approved for clinical use in the UK, participants will not have their study results returned to them. Instead, TMNB participants should defer to the HPV result provided by the CSP, as applicable. Further, in cases where the HPV result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in the case of TWNB samples), senior study staff felt that providing participants with a result that could not be followed up with clinically could cause distress and would be unethical. Only HPV positive results taken from samples as part of the CSP will warrant follow up under the NHS.

Information gained from this study will be published in peer-reviewed journals and presented at national and international conferences. Prior to scientific dissemination, we will engage with the PPI group in writing the lay results, results dissemination strategy and final publication. The lay summary of the results will be posted to the Self-TI website, participating clinic websites, and the websites of charities

and organisations supporting trans and non-binary people so that study participants and community members may be notified of the results first at the PPI group's request. Several online webinars are planned to disseminate the results and allow community members to engage in a discussion with the researchers. These webinars will be recorded and posted on the Self-TI website. Finally, data from this pilot study will inform a larger, multi-center, international study.

DISCUSSION

The overarching goal of this pilot study is to provide important insight into the acceptability and feasibility of HPV self-sampling among transgender and gender diverse individuals for a larger study. The pilot study will provide essential data that will inform recruitment, study procedures, and sample size calculations for this larger study.

A major strength of our study is community involvement from conception to implementation. We included community voices at every stage of protocol development and have had a dedicated PPI group in addition to transgender and non-binary senior study staff advising our study throughout. This strategy has led to improved advertisements, study materials, and outreach efforts. Continued work with community members will help us disseminate study results to a wider audience.

Potential study limitations include the inability to generalize our results to the wider transgender population in England as we used sexual health clinics in two major cities to recruit our participants. Compared to the general population of transgender individuals, our study participants may be more engaged in care, have greater access to care, and have higher health seeking behaviors. This recruitment strategy was chosen to maximize the proportion of positive HPV tests, to enable recruitment of a reasonable

sample size in a short amount of time. Finally, the implementation of HPV self-sampling methods and strategies may reduce barriers for transgender and non-binary people in high-resourced areas, but barriers will remain for individuals who live in areas where there is widespread discrimination resulting in a lack of access to culturally appropriate screening.

Authors' contributions: AMB and SSJ conceived, designed, and supervised the study. AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC supervised the HPV methylation assay and provided several methodological contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating the study survey. All authors revised the manuscript and approved the final draft.

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Collaborators: Self-TI Study group: Affiliated with The Caldecot Centre and CliniQ at King's College Hospital NHS Trust: Ellen Adams, Kate Flanagan, Lucy Campbell, and Birgit Barbini; Brighton and Howe Sexual Health Clinic: Sophie Ross and Lisa Barbour; and Ambrose Kings Centre: Chloe Orkin, Kyle Ring and James Hand; Center for Genomic Research at the National Cancer Institute: Amy Hutchinson and Casey Dagnell. Special thanks to the members of our PPI group, Fox Fisher, and Emrah Onal.

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Sponsorship information: Queen Mary University of London, Dr Mays Jawad, Research Governance Operations Manager, Joint Research Management Office, research.governance@qmul.ac.uk

Sponsors references: IRAS Number: 319364; Edge Number: 155220

Competing interest statement: AMB is a trustee of OUTpatients, of which SOC is CEO. None of the other authors have any conflicts to declare.

Patient and public involvement: Patients and the community were involved in the design, conduct, and dissemination plans of this research. Refer to the Methods section for further details.

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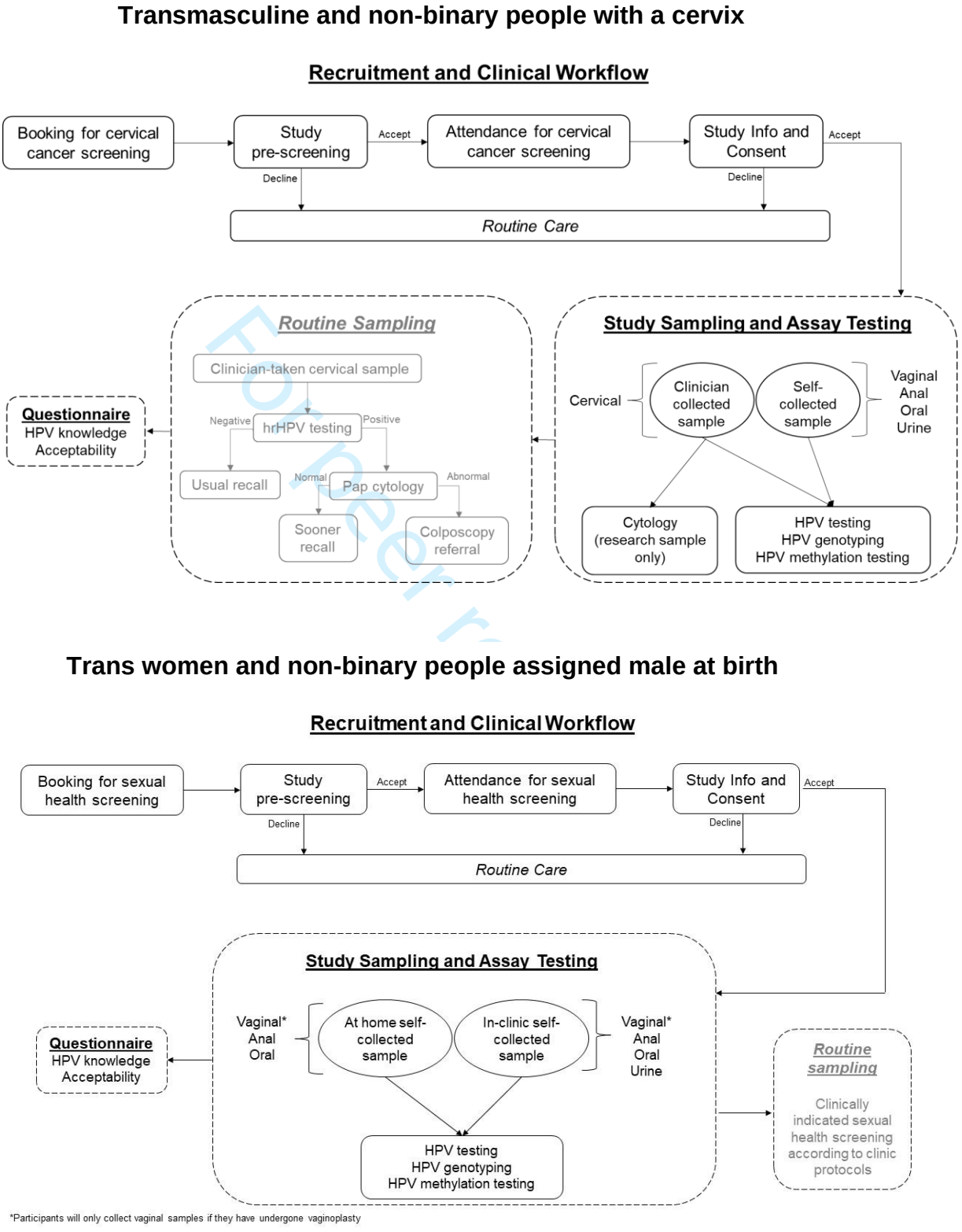
Figure 1. Study Flow



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3 and 6
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-12, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8, and 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12-13 and Table 2

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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Rationale and design of The Self-TI Study protocol: a cross-sectional human papillomavirus self-testing pilot study among transgender adults in England

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Rationale and design of The Self-TI Study protocol: a cross-sectional human papillomavirus self-testing pilot study among transgender adults in England

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (HPV) is the causal agent of several cancers including cervical, anal, and oropharyngeal cancer. Transgender men and transmasculine non-binary (TMNB) people with a cervix are much less likely to undergo cervical cancer screening than cisgender women. Transgender women and transfeminine non-binary (TWNB) people assigned male at birth may be at increased risk of HPV. Both TMNB and TWNB people face many barriers to HPV testing including medical mistrust due to stigma and discrimination.

Methods and analysis: The Self-TI Study (Self-TI) is a pilot study designed to measure acceptability and feasibility of HPV self-testing among transgender and non-binary people in England. TMNB people aged 25–65, with at least one year of testosterone and TWNB people, aged 18 and over are eligible to participate. Participants self-collect up to four samples: an oral rinse, a first void urine sample, a vaginal swab (if applicable), and an anal swab. TMNB participants are asked to have an additional clinician-collected cervical swab taken following their routine Cervical Screening Programme sample. TWNB are asked to take a self-collection kit to perform additional self-collection at home and mail the samples back to the clinic. Acceptability is assessed by a self-administered online survey and feasibility is measured as the proportion of samples returned in the clinic and from home.

Ethics and dissemination: Self-TI received ethical approval from the Regulatory Ethics Committee of Wales 4 (Wales REC 4) and Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute. Self-TI was co-produced by members of the transgender and non-binary community, who

served as authors, collaborators, and members of the patient and public involvement (PPI) group. Results of this study will be shared with the community prior to being published in peer-reviewed journals and the PPI group will help to design the results dissemination strategy. The evidence generated from this pilot study could be used to inform a larger, international study of HPV self-testing in the transgender and non-binary community.

Trial registration number: NCT05883111

Strengths and Limitations

- The pilot study addresses the lack of evidence around acceptability of human papillomavirus (HPV) self-sampling in transgender and non-binary people and was co-designed with community members.
- This pilot study collects samples from four body sites including an oral rinse, a urine sample, a vaginal swab, and an anal swab to assess correlation between samples.
- This pilot study examines the concordance between self-collected and clinician-collected samples.
- This pilot study offers participants an at-home collection kit to assess the feasibility of HPV testing at home.
- The generalizability of study findings is limited due to the convenience sampling of participants.

INTRODUCTION

Persistent infection with one of 12 high-risk human papillomavirus (HPV) genotypes is the causative agent of several cancers including cervical, anogenital, and oropharyngeal.[1] The widespread implementation of cervical cancer screening with Pap cytology or HPV testing, combined with HPV vaccination, has greatly reduced cervical cancer incidence and mortality.[2] Consensus guidelines for anal cancer screening now include transgender women.[3 4]

Transgender men and transmasculine non-binary (TMNB) adults (those who were registered female at birth and have a masculine or non-binary gender identity) are less likely to have ever undergone cervical cancer screening than cisgender women.[5 6] As many as one third of TMNB adults are not up-to-date with recommended screening guidelines.[7 8] Among those screened, TMNB patients are eight times more likely than cisgender women to have an inadequate Pap where the test cannot be evaluated for a variety of reasons such as lack of sufficient cellularity or bleeding resulting from testosterone induced cervical and vaginal atrophy.[9] TMNB adults face many additional barriers to cervical cancer screening than cisgender people, including an increased likelihood of discrimination in medical settings.[10-12] During gynecologic exams, TMNB patients may experience gender dysphoria (distress associated with the incongruence between gender identity and sex registered at birth) due to the focus on genitalia and the gendered nature of cervical cancer screening, such as feminine waiting rooms and expectations of gender conformity.[13-15] Clinicians may also erroneously believe that TMNB are not a risk for HPV due to incorrect assumptions about TMNB anatomy and

sexual practices, and are less likely to recommend screening.[14] Further, TMNB patients may be less likely to be vaccinated against HPV than cisgender women.[16]

Transgender women and transfeminine non-binary (TWNB) adults (those who were registered male at birth and have a female or non-binary gender identity) may be at increased risk of HPV infection compared to cisgender individuals. England began a national HPV immunisation programme for adolescent girls with the bivalent HPV vaccine in 2008, switching to the quadrivalent in 2012 and the nonavalent in 2021.[17 18] The UK implemented a gender-neutral vaccination program in 2019 with a catch-up programme for people up to the age of 45 years who are considered high risk for HPV (e.g., men who have sex with men).[19] Though transgender and non-binary people may be eligible for vaccination through the catch-up programme, barriers to healthcare and lack of perceived risk means that many TWNB adults may still be unvaccinated.[20] Additionally, co-infection with HIV, which may be elevated among TWNB adults compared to the general population,[21] increases the risk of persistent HPV infection[22-24] and HPV associated cancers.[25 26] One small US study reported a study HPV prevalence of 89% in anal and 9% in oral specimens from TWNB adults.[27] A Brazilian study of 268 transgender women reported a study prevalence to be 77% in anal, 34% in genital, and 11% oral specimens.[28] Studies from both The Netherlands and Thailand estimate a 20% prevalence of neovaginal high-risk HPV, though these two studies had a high proportion of invalid HPV results, suggesting the true prevalence may be higher.[29 30] The oncogenic potential of persistent high-risk HPV infection in the vagina of TWNB is poorly understood and current guidelines do not recommend screening for this

population.[31] Both low- and high-grade squamous intraepithelial lesions have been reported in the vagina of TWNB adults but incidence data is lacking.[32 33]

Prior research conducted in cisgender women (largely from high-income countries) has shown that self-sampling for HPV with PCR-based assays has comparable performance to clinician-collected samples for the detection of cervical HPV.[34 35] Limited research suggests that most TMNB patients may prefer HPV testing by self-collection,[36 37] though patients have expressed concern about the lack of evidence-based guidelines specific to TMNB to inform their preference.[36 38] Indeed, only one small study[39] has compared the performance of clinician- and self-collected samples in TMNB, showing good concordance; however more research is needed to assess whether this is an acceptable approach for cervical screening in TMNB. Reisner *et al.*[40] found a study HPV prevalence of 16% among 130 TM participants and that HPV testing by self-sample showed good concordance with clinician-collected samples. Similarly, one US study that included TWNB adults found that people were more likely to engage in anal cancer screening with an at-home self-collection kit than attend a clinician-collected screening appointment.[41]

We present the protocol for Self-TI, a pilot study whose objective is to assess the feasibility and acceptability of HPV self-testing at four body sites among TMNB and TWNB adults.

METHODS AND ANALYSIS

Study design and setting

The Self-TI Study (Self-TI) is a pilot study examining the acceptability and feasibility of HPV self-testing among transgender and non-binary people conducted in

England (IRAS# 319364 and clincialtrials.gov NCT05883111). The study received ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4, #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to the protocol and study materials are approved by the REC and the protocol was last revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all participants provide informed written consent to participate to the study staff. Participants are asked if they consent to future use of their research specimens; otherwise specimens will be destroyed after the aims of the study protocol are met.

Study setting and participant recruitment

Enrolment began in February 2024 and will continue for one year. Self-TI seeks to enroll 50 participants who identify as TMNB with a cervix and 50 participants who identify as TWNB assigned male at birth. Participants are recruited at one of three clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or Clinic-T in Brighton. These sites were chosen as they are in areas with large transgender and non-binary populations, their providers are specialists in transgender and non-binary sexual health, and the clinic staff have experience conducting research studies. Participants can be recruited and pre-screened for study eligibility when they book an appointment for a cervical cancer screening (TMNB study group only) or a sexual health screening (TWNB study group only). Recruitment occurs through advertisement posters and banners placed in the clinics, and flyers placed in gender identity clinics and general practitioners' offices known to have transgender and non-binary patients. Self-TI has created a website (www.self-ti.com), which contains

information on the study, HPV and cancer education, and links to contact the study sites to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to record a 45 second advertisement video. This video is posted the activist's social media sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and the Self-TI's website and social media sites. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is available as an online supplemental file.[42]

Participants

Individuals who identify as TMNB with a cervix, aged 25–65, with at least one year of self-reported testosterone therapy, are eligible to participate in the TMNB study group. Testosterone exposure is a requirement of study participation as it is associated with vaginal atrophy such that speculum and swab insertion to the recommended depth could be painful, unpleasant, or necessitate additional lubricant affecting the accuracy and acceptability of clinician- and self-collected HPV testing.[9 40] Individuals who identify as TWNB, aged 18 and over, are eligible to participate in the TWNB study group. TWNB participants with a vagina are preferentially selected into the study, with the first three months of enrolment restricted to individuals who had undergone vaginoplasty. After three months, the study team will evaluate whether it is feasible to reach the targeted sample size with this restriction and if not, the eligibility criterion will be removed. Individuals with a vagina must have undergone vaginoplasty greater than one year prior to entering the study due to safety concerns over self-sampling on recently healed epithelium. All participants are given a participant information sheet, which is discussed with study staff as part of informed consent procedures.

Data collection

Study activities and timeline are presented in Table 1 and Figure 1. After giving consent, participants fill out demographics and medical history questionnaires. The demographics form asks for sexual orientation, race and ethnicity, and height and weight. The medical history form asks about previous cancer screening, previous cancer diagnoses, HPV vaccination, hormone therapy, and HIV status. Study staff review these questionnaires with the participants to make sure they are complete and to answer any questions the participants have.

Table 1. Study activities and timeline

	Prior to Day 1	In Clinic Day 1		At Home ≦ 4 weeks (TWNB only)
Study procedure	**Screening**	**Clinician**	**Self-Sampling**	**Self-Sampling**
Eligibility assessment	X			
Informed consent			X	
Demographics			X	
Medical history			X	
Vaginal swab			X*	X*
Anal swab			X	X
Oral rinse			X	X
Urine			X	
Cervical swab		X (TMNB only)		
Survey			X (TMNB only)	X
Adverse event assessment		X	X	X

*All TMNB and only TWNB who have undergone vaginoplasty.

Abbreviations: TMNB = transmasculine and non-binary people with a cervix; TWNB= trans women and non-binary people assigned male at birth

Sampling

All participants are asked to self-collect samples in the clinic in the following order: oral rinse, urine, vagina, and anus (collection materials are provided in Table 2). Each participant will receive a self-sampling kit with written instructions for self-collection that includes a QR code linked to an instructional video. Study staff will also explain the self-collection procedures to the participants.

Table 2. Collection materials of study specimens

Specimen Type	Collection Method
Vaginal/neo-vaginal	Evalyn® Brush (Rovers® Medical, Belgium) or Dacron swab (DuPont, US)
Anal	FLOQSwab (COPAN Diagnostics Inc., US)
Oral rinse	Scope (Proctor and Gamble, US)
Urine	Colli-Pee (Novosanis, Belgium)
Cervical	Endocervical broom (Hologic, US)

The participants use Scope mouthwash (Proctor and Gamble, US) to collect buccal cells and a Colli-pee® collection device (Novosanis, Belgium) to collect first void urine (Table 2). The Colli-pee® device was selected as it has been used successfully by sexual and gender minority participants in other studies and can accommodate a variety of genital anatomies.

For the vaginal sample, participants have a choice to use either an Evalyn Brush® (Rovers Medical, Belgium) or a Dacron swab (DuPont, US) (Table 2), if applicable. The Evalyn Brush® was chosen for several features which make it easier to use for populations unfamiliar with self-sampling. It has wings to guide the participant as to how far they should insert the device, a plunger which releases the bristle brush to the cervix and clicks to aid in the counting of the rotations. Participants who prefer a slimmer vaginal swab are provided with a Dacron swab upon request (Table 2). Participants use a FLOQSwab® (COPAN Diagnostics Inc., US) to collect the anal

sample (Table 2). The choice of sampling methods was based on a review of previous studies that examined the same body sites and concordance between in-clinic and at-home sampling methods[43 44], though the mailing of dry swabs without transport media may affect anal specimen adequacy, especially if fecal matter is present.[45]

After the self-administered samples are collected, TMNB participants have a pelvic exam as part of the standard cervical cancer screening. In England, individuals with a cervix are invited to participate in the National Cervical Screening Programme (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those between the ages of 50-65. Screening is conducted with a primary HPV test and if positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI, the clinician will take two cervical swabs; the first for the (CSP) sent to the National Health Service (NHS) laboratories, and the second for the clinician-collected sample for Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so that if the participant declines further samples the standard of care is met.

After TWNB participants collect their self-administered samples, they will be given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at home. Once collected, the participant places the dry brushes and samples in the pre-addressed, postage paid mailer provided before dropping it in the post within one month of their first study visit. The kit includes written instructions with a QR code linked to an instructional video. Study staff follow up with TWNB study participants on a weekly basis for up to four weeks to ensure the return of their study samples.

Self-administered online survey

After self-collection, participants take a self-administered online survey, which takes approximately 20–25 minutes to complete. The survey includes questions on based on previously validated surveys that capture sensitive demographic characteristics, acceptability of self-sampling (e.g., physical and emotional comfort, confidence in collection), comparing self-collected to clinician-collected sampling (TMNB study group only),[39] comparing self-collected sampling in the clinic to at-home collection (TWNB study group only), history of HPV vaccination, knowledge of HPV,[39] comparing self-collected to clinician-collected sampling (TMNB study group only), medical mistrust,[46] and sexual history.[39 47] comparing self-collected sampling in the clinic to at-home collection (TWNB study group only), history of HPV vaccination, knowledge of HPV,[15] medical mistrust,[46] and sexual history.[47] Participants receive a £20 gift card to a large online retailer, as renumeration for their participation in Self-TI.

Outcomes

The primary study outcomes are the acceptability and feasibility of self-sampling among participants that will inform a larger study. Acceptability is measured by the physical and emotional responses to self-sampling for each collection method using a 7-point Likert scale. Feasibility is measured by the proportion of specimens returned from self-collection in the clinic and those mailed from home.

This pilot study will also estimate the study prevalence of HPV (positivity and genotype) and the correlation of HPV detection between the four self-collected samples. The concordance between the vaginal self-collected sample and clinician-collected cervical sample will be estimated among TMNB. Among TWNB, we will estimate the correlation between the samples collected by participants in the clinic with the samples

collected at home. Finally, Self-TI will collect exploratory data on risk factors associated with HPV prevalence, which can be fully assessed in a larger trial.

HPV testing

The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will be tested using a next-generation sequencing based-assay (TypeSeq) developed by CGR, which generates a positive/negative result for 51 HPV genotypes.[48]

Data management

Data management and project coordination is done at the Division of Cancer Epidemiology and Genetics at NCI. Study oversight and data management are led by the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-identified participant data into an electronic data capture system. All participant information (including laboratory data) is confidential and stored in a secure location. Only the personnel listed on the delegation log will have access to participant data; the statistician and laboratory personnel have access to deidentified data only. Participant data are checked at regular intervals for quality assurance. The number of AEs is expected to be very small and thus an independent Data Monitoring Committee was not appointed. However, all adverse events will be collected, and severe adverse events deemed by the chief investigator to be related to study procedures and unexpected, will be reported to the sponsor within 24 hours and to the REC within 15 days of learning of the event.

Statistical analysis

Acceptability of self-sampling procedures will be measured on the self-administered online survey, which uses a 7-point Likert scale with 1 indicating strong disagreement and 7 indicating strong agreement. Summary measures of these questions will be reported (average score for each question) separately for each group. For all participants, feasibility will be measured by the proportion of participants who are able to complete the self-collection procedures in the clinic. For TWNB participants, at-home feasibility will be measured by the proportion of TWNB participants who are able to complete and return all self-collection procedures at home.

For our secondary objectives, we will estimate the prevalence of HPV, overall, and by genotype in each of the self-collected samples from the two groups, separately. The phi-coefficient and associated *P*-values will be estimated to assess HPV positivity correlation between the four anatomic sites. Further, we will calculate the Cohen's kappa statistic as a measure of percent positive agreement of HPV positivity in self-collected vaginal samples versus the clinician-collected cervical samples among TMNB and in self-collected in clinic samples versus self-collected at home samples among TWNB, respectively.

Patient and public involvement

A patient and public involvement (PPI) group was formed prior to the submission of the Self-TI protocol to regulatory bodies. PPI played an important role in the design and conduct of the study, and participant recruitment. Six group meetings were held between May 2022–August 2023 with six members. PPI members represented the target population of Self-TI, including transfeminine, transmasculine, and non-binary

individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by SOC or EW who are members of the transgender and non-binary community, and SOC is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and queer individuals. PPI members reviewed the study protocol, data collection forms, online self-administered survey, advertisement and recruitment plan, instructional video, and results dissemination plan. Meetings were conducted over Zoom in the evenings to accommodate members' schedules and followed up via email to provide additional opportunities for written feedback on materials. Online meetings included short presentations on HPV-related cancer topics given by experts in the field to provide information exchange. PPI members were compensated for their time with multi-retailer gift cards to an amount in line with National Institute for Health Research guidelines.

Several important suggestions were made by the PPI group and adopted into the study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which was suggested could be off putting to our participants, so we worked with the manufacturers to provide Self-TI with devices in a more neutral blue color. Though the Evalyn® brush has several features that make it ideal for individuals who are not familiar with self-sampling, one drawback is that it is slightly thicker than other swabs used for vaginal sampling. Therefore, it was suggested by the PPI group that participants be provided with a slimmer swab upon request. Additionally, though it is preferred that TMNB participants complete the survey in the clinic after their exam, the PPI group felt that participants should be given the option to complete the survey at home. This change was implemented and TMNB participants can scan or be emailed a QR code to the survey link after leaving the clinic if desired. The group felt that some

participants would want to leave the clinic immediately after their speculum exam as it may result in increased feelings of dysphoria and can be uncomfortable or painful for some participants.

ETHICS AND DISSEMINATION

People with a male gender marker in their medical record are not invited to participate in the CSP and the laboratory may reject cervical samples from male patients. The chief investigator worked with the laboratories processing CSP samples for Self-TI participants to ensure samples would not be discarded prior to testing. Senior staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group about returning study results to the participants. Because the assay under study in Self-TI is a research test and not approved for clinical use in the UK, participants will not have their study results returned to them. Instead, TMNB participants should defer to the HPV result provided by the CSP, as applicable. Further, in cases where the HPV result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in the case of TWNB samples), senior study staff felt that providing participants with a result that could not be followed up with clinically could cause distress and would be unethical. Only HPV positive results taken from samples as part of the CSP will warrant follow up under the NHS.

Information gained from this study will be published in peer-reviewed journals and presented at national and international conferences. Prior to scientific dissemination, we will engage with the PPI group in writing the lay results, results dissemination strategy and final publication. The lay summary of the results will be posted to the Self-TI website, participating clinic websites, and the websites of charities

and organisations supporting trans and non-binary people so that study participants and community members may be notified of the results first at the PPI group's request. Several online webinars are planned to disseminate the results and allow community members to engage in a discussion with the researchers. These webinars will be recorded and posted on the Self-TI website. Finally, data from this pilot study will inform a larger, multi-center, international study.

DISCUSSION

The overarching goal of this pilot study is to provide important insight into the acceptability and feasibility of HPV self-sampling among transgender and gender diverse individuals for a larger study. The pilot study will provide essential data that will inform recruitment, study procedures, and sample size calculations for this larger study.

A major strength of our study is community involvement from conception to implementation. We included community voices at every stage of protocol development and have had a dedicated PPI group in addition to transgender and non-binary senior study staff advising our study throughout. This strategy has led to improved advertisements, study materials, and outreach efforts. Continued work with community members will help us disseminate study results to a wider audience.

Potential study limitations include the inability to generalize our results to the wider transgender population in England as we used sexual health clinics in two major cities to recruit our participants. Compared to the general population of transgender individuals, our study participants may be more engaged in care, have greater access to care, and have higher health seeking behaviors. This recruitment strategy was chosen to maximize the proportion of positive HPV tests, to enable recruitment of a reasonable

sample size in a short amount of time. Our decision to use dry swabs for anal sampling may affect acceptability as dry swabs were reported to cause pain in 19% of users[49] as well as adequacy as the presence of feces was shown to inhibit HPV assays.[45] Finally, the implementation of HPV self-sampling methods and strategies may reduce barriers for transgender and non-binary people in high-resourced areas, but barriers will remain for individuals who live in areas where there is widespread discrimination resulting in a lack of access to culturally appropriate screening.

Authors' contributions: AMB and SSJ conceived, designed, and supervised the study. SSJ, CO, and AMB were responsible for costings, ethics approval, and study set-up. AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC supervised the HPV methylation assay and provided several methodological contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating the study survey. All authors revised the manuscript and approved the final draft.

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Competing interest statement: AMB is a trustee of OUTpatients, of which SOC is CEO. None of the other authors have any conflicts to declare.

Patient and public involvement: Patients and the community were involved in the design, conduct, and dissemination plans of this research. Refer to the Methods section for further details.

Figure 1. Study flow diagram

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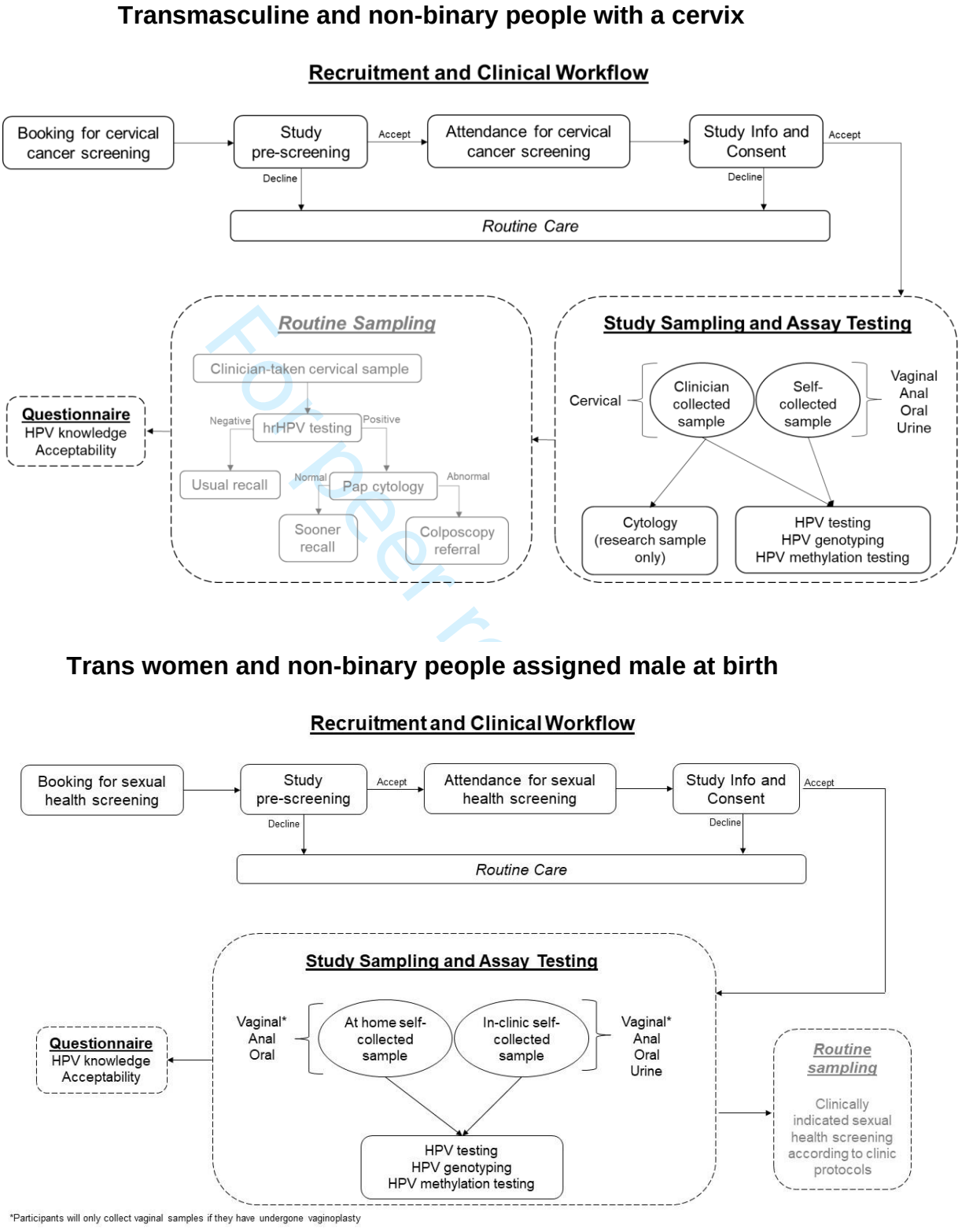
Figure 1. Study Flow



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3 and 6
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-12, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8, and 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12-13 and Table 2

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.