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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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Manuscripts

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3 **Rationale and design of The Self-TI Study: an HPV self-testing pilot study among**
4 **transgender adults**
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52 screening, cervical cancer, anal cancer
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58

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

1
2
3 served as authors, collaborators, and members of the patient and public involvement
4 (PPI) group. Results of this study will be shared with the community prior to being
5
6 published in peer-reviewed journals and the PPI group will help to design the results
7
8 dissemination strategy. The evidence generated from this pilot study could be used to
9
10 inform a larger, international study of HPV self-testing in the transgender and non-binary
11
12 community.
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18 **Trial registration number:** NCT05883111
19

20 21 **Strengths and Limitations**

- 22
23 • The study addresses the lack of evidence around acceptability of human
24 papillomavirus (HPV) self-sampling in transgender and non-binary people.
25
26
- 27 • This study collects samples from four body sites including an oral rinse, a urine
28 sample, a vaginal swab, and an anal swab to assess correlation between
29 samples.
30
31
- 32 • This pilot study examines the concordance between self-collected and clinician-
33 collected samples.
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35
- 36 • This pilot study offers participants an at-home collection kit to assess the
37 feasibility of HPV testing at home.
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- 40 • Findings from this study will be used to inform a larger, international study.
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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

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2
3 sexual practices, and are less likely to recommend screening.¹⁴ Further, TMNB patients
4
5 may be less likely to be vaccinated against HPV than cisgender women.¹⁶
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8 Transgender women and transfeminine non-binary (TWNB) adults (those who
9
10 were registered male at birth and have a female or non-binary gender identity) may be
11
12 at increased risk of HPV infection compared to cisgender individuals. England began a
13
14 national HPV immunisation programme for adolescent girls with the bivalent HPV
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16 vaccine in 2008 and switched to the quadrivalent in 2012.¹⁷ The UK implemented a
17
18 gender-neutral vaccination program in 2019 with a catch-up programme for people up to
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20 the age of 45 years who are considered high risk for HPV (e.g., men who have sex with
21
22 men).¹⁸ Though transgender and non-binary people may be eligible for vaccination
23
24 through the catch-up programme, barriers to healthcare and lack of perceived risk
25
26 means that many TWNB adults may still be unvaccinated.¹⁹ Additionally, co-infection
27
28 with HIV, which may be elevated among TWNB adults compared to the general
29
30 population,²⁰ increases the risk of persistent HPV infection²¹⁻²³ and HPV associated
31
32 cancers.^{24 25} One small US study reported a study HPV prevalence of 89% in anal and
33
34 9% in oral specimens from TWNB adults.²⁶ A Brazilian study of 268 transgender women
35
36 reported a study prevalence to be 77% in anal, 34% in genital, and 11% oral
37
38 specimens.²⁷ Studies from both The Netherlands and Thailand estimate a 20%
39
40 prevalence of neovaginal hrHPV, though these two studies had a high proportion of
41
42 invalid HPV results, suggesting the true prevalence may be higher.^{28 29} The oncogenic
43
44 potential of persistent hrHPV infection in the vagina of TWNB is poorly understood and
45
46 current guidelines do not recommend screening for this population.³⁰ Both low- and
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3 high-grade squamous intraepithelial lesions have been reported in the vagina of TWNB
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5 adults but incidence data is lacking.^{31 32}
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8 Prior research conducted in cisgender women has shown that self-sampling for
9
10 hrHPV with PCR-based assays has comparable performance to clinician-collected
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12 samples for the detection of cervical hrHPV.^{33 34} Limited research suggests that most
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14 TMNB patients may prefer HPV testing by self-collection,^{35 36} though patients have
15
16 expressed concern about the lack of evidence-based guidelines specific to TMNB to
17
18 inform their preference.^{35 37} Indeed, only one small study³⁸ has compared the
19
20 performance of clinician- and self-collected samples in TMNB, showing good
21
22 concordance; however more research is needed to assess whether this is an
23
24 acceptable approach for cervical screening in TMNB. Reisner *et al.*³⁹ found a study HPV
25
26 prevalence of 16% among 130 TM participants and that HPV testing by self-sample
27
28 showed good concordance with clinician-collected samples. Similarly, one US study that
29
30 included TWNB adults found that people were more likely to engage in anal cancer
31
32 screening with an at-home self-collection kit than attend a clinician-collected screening
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34 appointment.⁴⁰
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40 The objective of this pilot study is to assess the feasibility and acceptability of
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42 HPV self-testing at four body sites among TMNB and TWNB adults.
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44 **METHODS AND ANALYSIS**

45 **Study design and setting**

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48 The Self-TI Study (Self-TI) is a pilot study examining the acceptability and
49
50 feasibility of HPV self-testing among transgender and non-binary people conducted in
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52 England (IRAS# 319364 and clincialtrials.gov NCT05883111). The study received
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3 ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4,
4 #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology
5 and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to
6 the protocol and study materials are approved by the REC and the protocol was last
7 revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all
8 participants provide informed written consent to participate to the study staff.
9
10 Participants are asked if they consent to future use of their research specimens;
11 otherwise specimens will be destroyed after the aims of the study protocol are met.
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22 **Study setting and participant recruitment**

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24 Enrolment began in February 2024 and will continue for one year. Self-TI seeks
25 to enroll 50 participants who identify as TMNB with a cervix and 50 participants who
26 identify as TWNB assigned male at birth. Participants are recruited at one of three
27 clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or
28 Clinic-T in Brighton. These sites were chosen as they are in areas with large
29 transgender and non-binary populations, their providers are specialists in transgender
30 and non-binary sexual health, and the clinic staff have experience conducting research
31 studies. Participants can be recruited and pre-screened for study eligibility when they
32 book an appointment for a cervical cancer screening (TMNB study group only) or a
33 sexual health screening (TWNB study group only). Recruitment occurs through
34 advertisement posters and banners placed in the clinics, and flyers placed in gender
35 identity clinics and general practitioners' offices known to have transgender and non-
36 binary patients. Self-TI has created a website (www.self-ti.com), which contains
37 information on the study, HPV and cancer education, and links to contact the study sites
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3 to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to
4 record a 45 second advertisement video. This video is posted the activist's social media
5 sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and
6 the Self-TI's website and social media sites. The Standard Protocol Items:
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12 Recommendations for Interventional Trials (SPIRIT) checklist is available as an online
13 supplemental file.⁴¹
14

15 16 17 **Participants**

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19 Individuals who identify as TMNB with a cervix, aged 25–65, with at least one
20 year of self-reported testosterone therapy, are eligible to participate in the TMNB study
21 group. Testosterone exposure is a requirement of study participation because it may
22 affect the accuracy and acceptability of clinician- and self-collected HPV testing.
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26
27 Individuals who identify as TWNB, aged 18 and over, are eligible to participate in the
28 TWNB study group. TWNB participants with a vagina are preferentially selected into the
29 study, with the first three months of enrolment restricted to individuals who had
30 undergone vaginoplasty. After three months, the study team will evaluate whether it is
31 feasible to reach the targeted sample size with this restriction and if not, the eligibility
32 criterion will be removed. Individuals with a vagina must have undergone vaginoplasty
33 greater than one year prior to entering the study due to safety concerns over self-
34 sampling on recently healed epithelium. All participants are given a participant
35 information sheet, which is discussed with study staff as part of informed consent
36 procedures.
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51 **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

Study procedure	Prior to Day 1		In Clinic Day 1		At Home ≤ 4 weeks (TWNB only)
	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).

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3 Participants use a FLOQSwab® (COPAN Diagnostics Inc., US) to collect the anal
4
5 sample (Table 2).
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8 After the self-administered samples are collected, TMNB participants have a
9
10 pelvic exam as part of the standard cervical cancer screening. In England, individuals
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12 with a cervix are invited to participate in the National Cervical Screening Programme
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14 (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those
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16 between the ages of 50-65. Screening is conducted with a primary HPV test and if
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18 positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so
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20 that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI,
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22 the clinician will take two cervical swabs; the first for the (CSP) sent to the National
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24 Health Service (NHS) laboratories, and the second for the clinician-collected sample for
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26 Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so
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28 that if the participant declines further samples the standard of care is met.
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33 After TWNB participants collect their self-administered samples, they will be
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35 given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at
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37 home. Once collected, the participant places the dry brushes and samples in the pre-
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39 addressed, postage paid mailer provided before dropping it in the post within one month
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41 of their first study visit. The kit includes written instructions with a QR code linked to an
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43 instructional video. Study staff follow up with TWNB study participants on a weekly
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45 basis for up to four weeks to ensure the return of their study samples.
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49 **Self-administered online survey**

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51 After self-collection, participants take a self-administered online survey, which
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53 takes approximately 20–25 minutes to complete. The survey includes questions on
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3 sensitive demographic characteristics, acceptability of self-sampling, comparing self-
4 collected to clinician-collected sampling (TMNB study group only), comparing self-
5 collected sampling in the clinic to at-home collection (TWNB study group only), history
6 of HPV vaccination, knowledge of HPV, medical mistrust, and sexual history.
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8 Participants receive a £20 gift card to a large online retailer, as remuneration for their
9 participation in Self-TI.
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16 **Outcomes**

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19 The primary study outcomes are the acceptability and feasibility of self-sampling
20 among participants that will inform a larger study. Acceptability is measured by the
21 physical and emotional responses to self-sampling for each collection method using a 7-
22 point Likert scale. Feasibility is measured by the proportion of specimens returned from
23 self-collection in the clinic and those mailed from home.
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31 This pilot study will also estimate the study prevalence of HPV (positivity and
32 genotype) and the correlation of HPV detection between the four self-collected samples.
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34 The concordance between the vaginal self-collected sample and clinician-collected
35 cervical sample will be estimated among TMNB. Among TWNB, we will estimate the
36 correlation between the samples collected by participants in the clinic with the samples
37 collected at home. Finally, Self-TI will collect exploratory data on risk factors associated
38 with HPV prevalence, which can be fully assessed in a larger trial.
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46 **HPV testing**

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49 The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with
50 PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before
51 freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are
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3 shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will
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5 be tested using a next-generation sequencing based-assay (TypeSeq) developed by
6
7 CGR, which generates a positive/negative result for 51 HPV genotypes.⁴²
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10 **Data management**

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12 Data management and project coordination is done at the Division of Cancer
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14 Epidemiology and Genetics at NCI. Study oversight and data management are led by
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16 the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-
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18 identified participant data into an electronic data capture system. All participant
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20 information (including laboratory data) is confidential and stored in a secure location.
21
22 Only the personnel listed on the delegation log will have access to participant data; the
23
24 statistician and laboratory personnel have access to deidentified data only. Participant
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26 data are checked at regular intervals for quality assurance. The number of AEs is
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28 expected to be very small and thus an independent Data Monitoring Committee was not
29
30 appointed. However, all adverse events will be collected, and severe adverse events
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32 deemed by the chief investigator to be related to study procedures and unexpected, will
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34 be reported to the sponsor within 24 hours and to the REC within 15 days of learning of
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36 the event.
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42 **Statistical analysis**

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44 Acceptability of self-sampling procedures will be measured on the self-
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46 administered online survey, which uses a 7-point Likert scale with 1 indicating strong
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48 disagreement and 7 indicating strong agreement. Summary measures of these
49
50 questions will be reported (average score for each question) separately for each group.
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52 For all participants, feasibility will be measured by the proportion of participants who are
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3 able to complete the self-collection procedures in the clinic. For TWNB participants, at-
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5 home feasibility will be measured by the proportion of TWNB participants who are able
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7 to complete and return all self-collection procedures at home.
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10 For our secondary objectives, we will estimate the prevalence of HPV, overall,
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12 and by genotype in each of the self-collected samples from the two groups, separately.
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14 The phi-coefficient and associated P -values will be estimated to assess HPV positivity
15
16 correlation between the four anatomic sites. Further, we will calculate the Cohen's
17
18 kappa statistic as a measure of percent positive agreement of HPV positivity in self-
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20 collected vaginal samples versus the clinician-collected cervical samples among TMNB
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22 and in self-collected in clinic samples versus self-collected at home samples among
23
24 TWNB, respectively.
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28 **Patient and public involvement**

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30 A patient and public involvement (PPI) group was formed prior to the submission
31
32 of the Self-TI protocol to regulatory bodies. PPI played an important role in the design
33
34 and conduct of the study, and participant recruitment. Six group meetings were held
35
36 between May 2022–August 2023 with six members. PPI members represented the target
37
38 population of Self-TI, including transfeminine, transmasculine, and non-binary
39
40 individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by
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42 SOC or EW who are members of the transgender and non-binary community, and SOC
43
44 is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and
45
46 queer individuals. PPI members reviewed the study protocol, data collection forms,
47
48 online self-administered survey, advertisement and recruitment plan, instructional video,
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50 and results dissemination plan. Meetings were conducted over Zoom in the evenings to
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3 accommodate members' schedules and followed up via email to provide additional
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5 opportunities for written feedback on materials. Online meetings included short
6
7 presentations on HPV-related cancer topics given by experts in the field to provide
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9 information exchange. PPI members were compensated for their time with multi-retailer
10
11 gift cards to an amount in line with National Institute for Health Research guidelines.
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14
15 Several important suggestions were made by the PPI group and adopted into the
16
17 study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which
18
19 was suggested could be off putting to our participants, so we worked with the
20
21 manufacturers to provide Self-TI with devices in a more neutral blue color. Though the
22
23 Evalyn® brush has several features that make it ideal for individuals who are not
24
25 familiar with self-sampling, one drawback is that it is slightly thicker than other swabs
26
27 used for vaginal sampling. Therefore, it was suggested by the PPI group that
28
29 participants be provided with a slimmer swab upon request. Additionally, though it is
30
31 preferred that TMNB participants complete the survey in the clinic after their exam, the
32
33 PPI group felt that participants should be given the option to complete the survey at
34
35 home. This change was implemented and TMNB participants can scan or be emailed a
36
37 QR code to the survey link after leaving the clinic if desired. The group felt that some
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39 participants would want to leave the clinic immediately after their speculum exam as it
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41 may result in increased feelings of dysphoria and can be uncomfortable or painful for
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43 some participants.
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49 **ETHICS AND DISSEMINATION**

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51 People with a male gender marker in their medical record are not invited to
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53 participate in the CSP and the laboratory may reject cervical samples from male
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3 patients. The chief investigator worked with the laboratories processing CSP samples
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5 for Self-TI participants to ensure samples would not be discarded prior to testing. Senior
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7 staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group
8
9 about returning study results to the participants. Because the assay under study in Self-
10
11 TI is a research test and not approved for clinical use in the UK, participants will not
12
13 have their study results returned to them. Instead, TMNB participants should defer to
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15 the HPV result provided by the CSP, as applicable. Further, in cases where the HPV
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17 result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in
18
19 the case of TWNB samples), senior study staff felt that providing participants with a
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21 result that could not be followed up with clinically could cause distress and would be
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23 unethical. Only HPV positive results taken from samples as part of the CSP will warrant
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25 follow up under the NHS.
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31 Information gained from this study will be published in peer-reviewed journals
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33 and presented at national and international conferences. Prior to scientific
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35 dissemination, we will engage with the PPI group in writing the lay results, results
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37 dissemination strategy and final publication. The lay summary of the results will be
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39 posted to the Self-TI website, participating clinic websites, and the websites of charities
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41 and organisations supporting trans and non-binary people so that study participants and
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43 community members may be notified of the results first at the PPI group's request.
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45 Several online webinars are planned to disseminate the results and allow community
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47 members to engage in a discussion with the researchers. These webinars will be
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49 recorded and posted on the Self-TI website. Finally, data from this pilot study will inform
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51 a larger, multi-center, international study.
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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.

For peer review only

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2
3 **Authors' contributions:** AMB and SSJ conceived, designed, and supervised the study.

4
5 AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC
6
7 supervised the HPV methylation assay and provided several methodological
8
9 contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the
10
11 coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating
12
13 the study survey. All authors revised the manuscript and approved the final draft.
14
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41
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45 **Sponsorship information:** Queen Mary University of London, Dr Mays Jawad,
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3 **Competing interest statement:** AMB is a trustee of OUTpatients, of which SOC is
4
5 CEO. None of the other authors have any conflicts to declare.
6

7
8 **Patient and public involvement:** Patients and the community were involved in the
9
10 design, conduct, and dissemination plans of this research. Refer to the Methods section
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12 for further details.
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For peer review only

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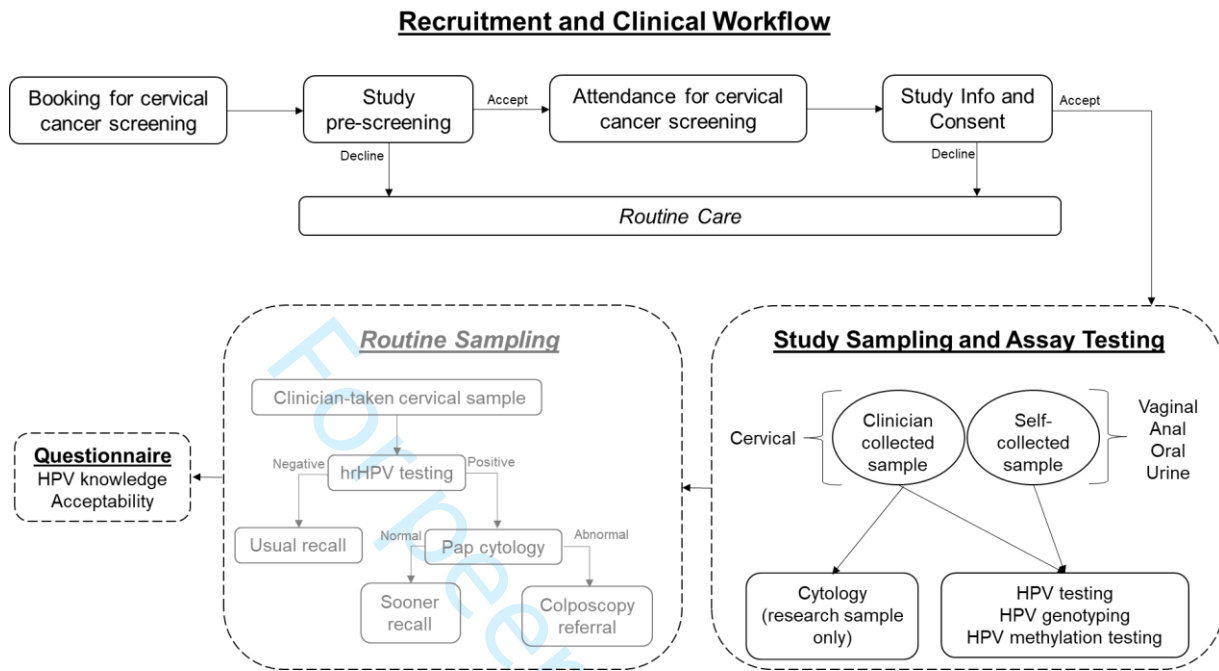
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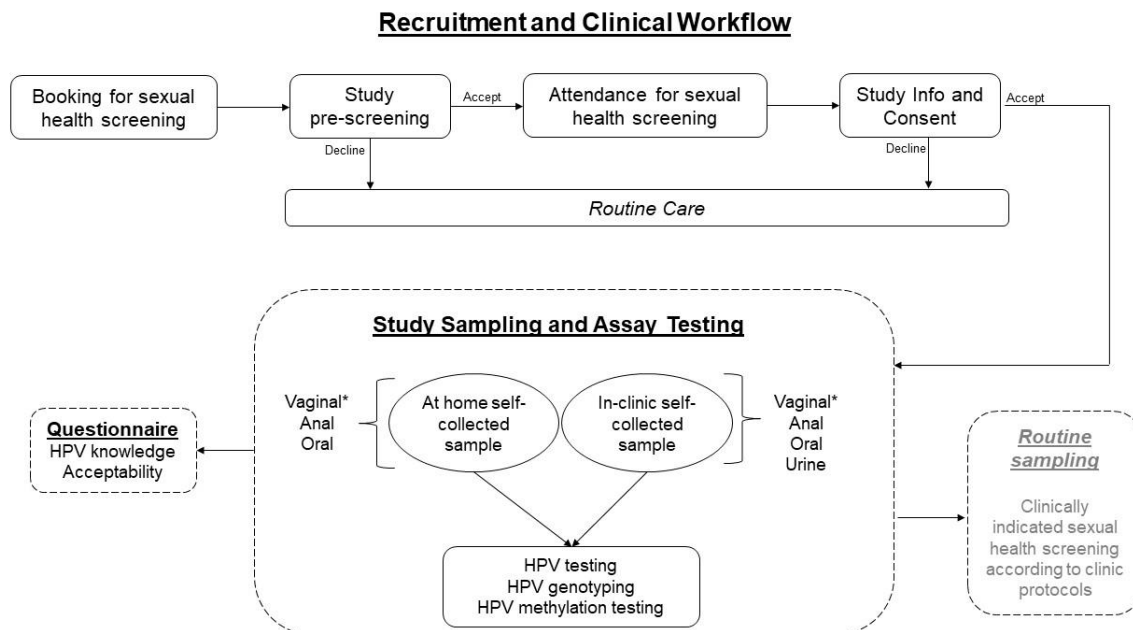
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Figure 1. Study Flow

Transmasculine and non-binary people with a cervix



Trans women and non-binary people assigned male at birth



*Participants will only collect vaginal samples if they have undergone vaginoplasty



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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

1 **Introduction**

2

3 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

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6 6b Explanation for choice of comparators N/A

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8 Objectives 7 Specific objectives or hypotheses 6

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10 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

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14 **Methods: Participants, interventions, and outcomes**

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16 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

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19 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

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23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8-12

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26 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

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29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 12

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32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A

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34 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

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40 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

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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	<u>7</u>
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>7, 8, and 12</u>
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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	<u>N/A</u>
11				
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16	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	<u>N/A</u>
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
28				
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31	Methods: Data collection, management, and analysis			
32				
33	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	<u>9-12</u>
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39		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	<u>11</u>
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1	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	<u>13</u>
2				
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5	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	<u>13-14</u>
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>N/A</u>
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10		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)	<u>N/A</u>
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14	Methods: Monitoring			
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16	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	<u>13</u>
17				
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22		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	<u>N/A</u>
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24				
25	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	<u>13</u>
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>13</u>
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>7</u>
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36				
37	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)	<u>7</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>7</u>
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>7</u>
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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	<u>12</u>
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>17</u>
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13	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	<u>13</u>
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17	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	<u>N/A</u>
18				
19				
20	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	<u>15-16</u>
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
32				
33				
34	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	<u>12-13 and Table 2</u>
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*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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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Manuscript ID	bmjopen-2024-086099.R1
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Primary Subject Heading:	Sexual health
Secondary Subject Heading:	Infectious diseases, Oncology, Obstetrics and gynaecology, Public health
Keywords:	Human Papillomavirus Viruses, Transgender Persons, Uterine Cervical Neoplasms, Health Equity

SCHOLARONE™
Manuscripts

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3 **Rationale and design of The Self-TI Study protocol: a cross-sectional human**
4 **papillomavirus self-testing pilot study among transgender adults in England**
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54 screening, cervical cancer, anal cancer
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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

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2
3 served as authors, collaborators, and members of the patient and public involvement
4 (PPI) group. Results of this study will be shared with the community prior to being
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6 published in peer-reviewed journals and the PPI group will help to design the results
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8 dissemination strategy. The evidence generated from this pilot study could be used to
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10 inform a larger, international study of HPV self-testing in the transgender and non-binary
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12 community.
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18 **Trial registration number:** NCT05883111
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20 21 **Strengths and Limitations**

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

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

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

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3 23 sexual practices, and are less likely to recommend screening.¹⁴ Further, TMNB patients
4
5 24 may be less likely to be vaccinated against HPV than cisgender women.¹⁶
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8 25 Transgender women and transfeminine non-binary (TWNB) adults (those who
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10 26 were registered male at birth and have a female or non-binary gender identity) may be
11
12 27 at increased risk of HPV infection compared to cisgender individuals. England began a
13
14 28 national HPV immunisation programme for adolescent girls with the bivalent HPV
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16 29 vaccine in 2008, switching to the quadrivalent in 2012 and the nonavalent in 2021.^{17 18}
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18
19 30 The UK implemented a gender-neutral vaccination program in 2019 with a catch-up
20
21 31 programme for people up to the age of 45 years who are considered high risk for HPV
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23 32 (e.g., men who have sex with men).¹⁹ Though transgender and non-binary people may
24
25 33 be eligible for vaccination through the catch-up programme, barriers to healthcare and
26
27 34 lack of perceived risk means that many TWNB adults may still be unvaccinated.²⁰
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29 35 Additionally, co-infection with HIV, which may be elevated among TWNB adults
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31 36 compared to the general population,²¹ increases the risk of persistent HPV infection²²⁻²⁴
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33 37 and HPV associated cancers.^{25 26} One small US study reported a study HPV prevalence
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35 38 of 89% in anal and 9% in oral specimens from TWNB adults.²⁷ A Brazilian study of 268
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37 39 transgender women reported a study prevalence to be 77% in anal, 34% in genital, and
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39 40 11% oral specimens.²⁸ Studies from both The Netherlands and Thailand estimate a
40
41 41 20% prevalence of neovaginal high-risk HPV, though these two studies had a high
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43 42 proportion of invalid HPV results, suggesting the true prevalence may be higher.^{29 30}
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45 43 The oncogenic potential of persistent high-risk HPV infection in the vagina of TWNB is
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47 44 poorly understood and current guidelines do not recommend screening for this
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3 45 population.³¹ Both low- and high-grade squamous intraepithelial lesions have been
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5 46 reported in the vagina of TWNB adults but incidence data is lacking.^{32 33}
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8 47 Prior research conducted in cisgender women (largely from high-income
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10 48 countries) has shown that self-sampling for HPV with PCR-based assays has
11
12 49 comparable performance to clinician-collected samples for the detection of cervical
13
14 50 HPV.^{34 35} Limited research suggests that most TMNB patients may prefer HPV testing
15
16 51 by self-collection,^{36 37} though patients have expressed concern about the lack of
17
18 52 evidence-based guidelines specific to TMNB to inform their preference.^{36 38} Indeed, only
19
20 53 one small study³⁹ has compared the performance of clinician- and self-collected
21
22 54 samples in TMNB, showing good concordance; however more research is needed to
23
24 55 assess whether this is an acceptable approach for cervical screening in TMNB. Reisner
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26 56 *et al.*⁴⁰ found a study HPV prevalence of 16% among 130 TM participants and that HPV
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28 57 testing by self-sample showed good concordance with clinician-collected samples.
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31 58 Similarly, one US study that included TWNB adults found that people were more likely
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33 59 to engage in anal cancer screening with an at-home self-collection kit than attend a
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35 60 clinician-collected screening appointment.⁴¹
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40 61 We present the protocol for Self-TI, a pilot study whose objective is to assess
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42 62 the feasibility and acceptability of HPV self-testing at four body sites among TMNB and
43
44 63 TWNB adults.
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46 64 **METHODS AND ANALYSIS**

47 65 **Study design and setting**

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49 66 The Self-TI Study (Self-TI) is a pilot study examining the acceptability and
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51 67 feasibility of HPV self-testing among transgender and non-binary people conducted in
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3 68 England (IRAS# 319364 and clinicaltrials.gov NCT05883111). The study received
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5 69 ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4,
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7 70 #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology
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9 71 and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to
10
11 72 the protocol and study materials are approved by the REC and the protocol was last
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13 73 revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all
14
15 74 participants provide informed written consent to participate to the study staff.
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17 75 Participants are asked if they consent to future use of their research specimens;
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19 76 otherwise specimens will be destroyed after the aims of the study protocol are met.
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24 77 **Study setting and participant recruitment**

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26 78 Enrolment began in February 2024 and will continue for one year. Self-TI seeks
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28 79 to enroll 50 participants who identify as TMNB with a cervix and 50 participants who
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30 80 identify as TWNB assigned male at birth. Participants are recruited at one of three
31
32 81 clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or
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34 82 Clinic-T in Brighton. These sites were chosen as they are in areas with large
35
36 83 transgender and non-binary populations, their providers are specialists in transgender
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38 84 and non-binary sexual health, and the clinic staff have experience conducting research
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40 85 studies. Participants can be recruited and pre-screened for study eligibility when they
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42 86 book an appointment for a cervical cancer screening (TMNB study group only) or a
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44 87 sexual health screening (TWNB study group only). Recruitment occurs through
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46 88 advertisement posters and banners placed in the clinics, and flyers placed in gender
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48 89 identity clinics and general practitioners' offices known to have transgender and non-
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50 90 binary patients. Self-TI has created a website (www.self-ti.com), which contains
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3 91 information on the study, HPV and cancer education, and links to contact the study sites
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5 92 to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to
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7 93 record a 45 second advertisement video. This video is posted the activist's social media
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9 94 sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and
10
11 95 the Self-TI's website and social media sites. The Standard Protocol Items:
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14 96 Recommendations for Interventional Trials (SPIRIT) checklist is available as an online
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16 97 supplemental file.⁴²
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19 98 **Participants**

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21 99 Individuals who identify as TMNB with a cervix, aged 25–65, with at least one
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23 100 year of self-reported testosterone therapy, are eligible to participate in the TMNB study
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25 101 group. Testosterone exposure is a requirement of study participation as it is associated
26
27 102 with vaginal atrophy such that speculum and swab insertion to the recommended depth
28
29 103 could be painful, unpleasant, or necessitate additional lubricant affecting the accuracy
30
31 104 and acceptability of clinician- and self-collected HPV testing.^{9 40} Individuals who identify
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33 105 as TWNB, aged 18 and over, are eligible to participate in the TWNB study group. TWNB
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35 106 participants with a vagina are preferentially selected into the study, with the first three
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37 107 months of enrolment restricted to individuals who had undergone vaginoplasty. After
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39 108 three months, the study team will evaluate whether it is feasible to reach the targeted
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41 109 sample size with this restriction and if not, the eligibility criterion will be removed.
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43 110 Individuals with a vagina must have undergone vaginoplasty greater than one year prior
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45 111 to entering the study due to safety concerns over self-sampling on recently healed
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47 112 epithelium. All participants are given a participant information sheet, which is discussed
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49 113 with study staff as part of informed consent procedures.
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114 Data collection

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

Table 1. Study activities and timeline

Study procedure	Prior to Day 1		In Clinic Day 1		At Home ≤ 4 weeks (TWNB only)
	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

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123 Sampling

124 All participants are asked to self-collect samples in the clinic in the following
 125 order: oral rinse, urine, vagina, and anus (collection materials are provided in Table 2).
 126 Each participant will receive a self-sampling kit with written instructions for self-
 127 collection that includes a QR code linked to an instructional video. Study staff will also
 128 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)

129
 130 The participants use Scope mouthwash (Proctor and Gamble, US) to collect
 131 buccal cells and a Colli-pee® collection device (Novosanis, Belgium) to collect first void
 132 urine (Table 2). The Colli-pee® device was selected as it has been used successfully by
 133 sexual and gender minority participants in other studies and can accommodate a variety
 134 of genital anatomies.

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

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3 143 sample (Table 2). The choice of sampling methods was based on a review of previous
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5 144 studies that examined the same body sites and concordance between in-clinic and at-
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8 145 home sampling methods.^{43 44}
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10 146 After the self-administered samples are collected, TMNB participants have a
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12 147 pelvic exam as part of the standard cervical cancer screening. In England, individuals
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14 148 with a cervix are invited to participate in the National Cervical Screening Programme
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17 149 (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those
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19 150 between the ages of 50-65. Screening is conducted with a primary HPV test and if
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22 151 positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so
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24 152 that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI,
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26 153 the clinician will take two cervical swabs; the first for the (CSP) sent to the National
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28 154 Health Service (NHS) laboratories, and the second for the clinician-collected sample for
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31 155 Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so
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33 156 that if the participant declines further samples the standard of care is met.
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35 157 After TWNB participants collect their self-administered samples, they will be
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37 158 given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at
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40 159 home. Once collected, the participant places the dry brushes and samples in the pre-
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42 160 addressed, postage paid mailer provided before dropping it in the post within one month
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45 161 of their first study visit. The kit includes written instructions with a QR code linked to an
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47 162 instructional video. Study staff follow up with TWNB study participants on a weekly
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49 163 basis for up to four weeks to ensure the return of their study samples.
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51 164 **Self-administered online survey**

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3 165 After self-collection, participants take a self-administered online survey, which
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5 166 takes approximately 20–25 minutes to complete. The survey includes questions on
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7 167 based on previously validated surveys that capture sensitive demographic
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9 168 characteristics, acceptability of self-sampling (e.g., physical and emotional comfort,
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11 169 confidence in collection), comparing self-collected to clinician-collected sampling (TMNB
12
13 170 study group only),³⁹ comparing self-collected sampling in the clinic to at-home collection
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15 171 (TWNB study group only), history of HPV vaccination, knowledge of HPV,³⁹ comparing
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17 172 self-collected to clinician-collected sampling (TMNB study group only), medical
18
19 173 mistrust,⁴⁵ and sexual history.^{39 46} comparing self-collected sampling in the clinic to at-
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21 174 home collection (TWNB study group only), history of HPV vaccination, knowledge of
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23 175 HPV,¹⁵ medical mistrust,⁴⁵ and sexual history.⁴⁶ Participants receive a £20 gift card to a
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25 176 large online retailer, as remuneration for their participation in Self-TI.

177 **Outcomes**

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

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

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3 188 collected at home. Finally, Self-TI will collect exploratory data on risk factors associated
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5 189 with HPV prevalence, which can be fully assessed in a larger trial.
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7 190 **HPV testing**

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10 191 The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with
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12 192 PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before
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14 193 freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are
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16 194 shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will
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18 195 be tested using a next-generation sequencing based-assay (TypeSeq) developed by
19
20 196 CGR, which generates a positive/negative result for 51 HPV genotypes.⁴⁷
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23 197 **Data management**

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26 198 Data management and project coordination is done at the Division of Cancer
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28 199 Epidemiology and Genetics at NCI. Study oversight and data management are led by
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30 200 the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-
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32 201 identified participant data into an electronic data capture system. All participant
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34 202 information (including laboratory data) is confidential and stored in a secure location.
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36 203 Only the personnel listed on the delegation log will have access to participant data; the
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38 204 statistician and laboratory personnel have access to deidentified data only. Participant
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40 205 data are checked at regular intervals for quality assurance. The number of AEs is
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42 206 expected to be very small and thus an independent Data Monitoring Committee was not
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44 207 appointed. However, all adverse events will be collected, and severe adverse events
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46 208 deemed by the chief investigator to be related to study procedures and unexpected, will
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48 209 be reported to the sponsor within 24 hours and to the REC within 15 days of learning of
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50 210 the event.
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211 **Statistical analysis**

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

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

228 **Patient and public involvement**

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

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3 234 individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by
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5 235 SOC or EW who are members of the transgender and non-binary community, and SOC
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7 236 is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and
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10 237 queer individuals. PPI members reviewed the study protocol, data collection forms,
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12 238 online self-administered survey, advertisement and recruitment plan, instructional video,
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14 239 and results dissemination plan. Meetings were conducted over Zoom in the evenings to
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17 240 accommodate members' schedules and followed up via email to provide additional
18
19 241 opportunities for written feedback on materials. Online meetings included short
20
21 242 presentations on HPV-related cancer topics given by experts in the field to provide
22
23 243 information exchange. PPI members were compensated for their time with multi-retailer
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25
26 244 gift cards to an amount in line with National Institute for Health Research guidelines.

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28 245 Several important suggestions were made by the PPI group and adopted into the
29
30 246 study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which
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32 247 was suggested could be off putting to our participants, so we worked with the
33
34 248 manufacturers to provide Self-TI with devices in a more neutral blue color. Though the
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36
37 249 Evalyn® brush has several features that make it ideal for individuals who are not
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39 250 familiar with self-sampling, one drawback is that it is slightly thicker than other swabs
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41 251 used for vaginal sampling. Therefore, it was suggested by the PPI group that
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43 252 participants be provided with a slimmer swab upon request. Additionally, though it is
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45 253 preferred that TMNB participants complete the survey in the clinic after their exam, the
46
47 254 PPI group felt that participants should be given the option to complete the survey at
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49 255 home. This change was implemented and TMNB participants can scan or be emailed a
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51 256 QR code to the survey link after leaving the clinic if desired. The group felt that some
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3 257 participants would want to leave the clinic immediately after their speculum exam as it
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5 258 may result in increased feelings of dysphoria and can be uncomfortable or painful for
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8 259 some participants.
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10 260 **ETHICS AND DISSEMINATION**

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12 261 People with a male gender marker in their medical record are not invited to
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14 262 participate in the CSP and the laboratory may reject cervical samples from male
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17 263 patients. The chief investigator worked with the laboratories processing CSP samples
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19 264 for Self-TI participants to ensure samples would not be discarded prior to testing. Senior
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21 265 staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group
22
23 266 about returning study results to the participants. Because the assay under study in Self-
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25
26 267 TI is a research test and not approved for clinical use in the UK, participants will not
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28 268 have their study results returned to them. Instead, TMNB participants should defer to
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30
31 269 the HPV result provided by the CSP, as applicable. Further, in cases where the HPV
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33 270 result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in
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35 271 the case of TWNB samples), senior study staff felt that providing participants with a
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37 272 result that could not be followed up with clinically could cause distress and would be
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40 273 unethical. Only HPV positive results taken from samples as part of the CSP will warrant
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42 274 follow up under the NHS.
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44 275 Information gained from this study will be published in peer-reviewed journals
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46 276 and presented at national and international conferences. Prior to scientific
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49 277 dissemination, we will engage with the PPI group in writing the lay results, results
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51 278 dissemination strategy and final publication. The lay summary of the results will be
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54 279 posted to the Self-TI website, participating clinic websites, and the websites of charities
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3 280 and organisations supporting trans and non-binary people so that study participants and
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5 281 community members may be notified of the results first at the PPI group's request.
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8 282 Several online webinars are planned to disseminate the results and allow community
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10 283 members to engage in a discussion with the researchers. These webinars will be
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12 284 recorded and posted on the Self-TI website. Finally, data from this pilot study will inform
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14
15 285 a larger, multi-center, international study.

16 17 286 **DISCUSSION**

18
19 287 The overarching goal of this pilot study is to provide important insight into the
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21 288 acceptability and feasibility of HPV self-sampling among transgender and gender
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23 289 diverse individuals for a larger study. The pilot study will provide essential data that will
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25
26 290 inform recruitment, study procedures, and sample size calculations for this larger study.

27
28 291 A major strength of our study is community involvement from conception to
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30 292 implementation. We included community voices at every stage of protocol development
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32 293 and have had a dedicated PPI group in addition to transgender and non-binary senior
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34 294 study staff advising our study throughout. This strategy has led to improved
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37 295 advertisements, study materials, and outreach efforts. Continued work with community
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39 296 members will help us disseminate study results to a wider audience.

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42 297 Potential study limitations include the inability to generalize our results to the
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44 298 wider transgender population in England as we used sexual health clinics in two major
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47 299 cities to recruit our participants. Compared to the general population of transgender
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49 300 individuals, our study participants may be more engaged in care, have greater access to
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51 301 care, and have higher health seeking behaviors. This recruitment strategy was chosen
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54 302 to maximize the proportion of positive HPV tests, to enable recruitment of a reasonable

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3 303 sample size in a short amount of time. Finally, the implementation of HPV self-sampling
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5 304 methods and strategies may reduce barriers for transgender and non-binary people in
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7 305 high-resourced areas, but barriers will remain for individuals who live in areas where
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9 306 there is widespread discrimination resulting in a lack of access to culturally appropriate
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11 307 screening.
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3 **Authors' contributions:** AMB and SSJ conceived, designed, and supervised the study.

4
5 AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC
6
7 supervised the HPV methylation assay and provided several methodological
8
9 contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the
10
11 coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating
12
13 the study survey. All authors revised the manuscript and approved the final draft.
14
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43

44
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46
47 Research Governance Operations Manager, Joint Research Management Office,
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49 research.governance@qmul.ac.uk
50

51
52 **Sponsors references:** IRAS Number: 319364; Edge Number: 155220
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3 **Competing interest statement:** AMB is a trustee of OUTpatients, of which SOC is
4
5 CEO. None of the other authors have any conflicts to declare.
6

7
8 **Patient and public involvement:** Patients and the community were involved in the
9
10 design, conduct, and dissemination plans of this research. Refer to the Methods section
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12 for further details.
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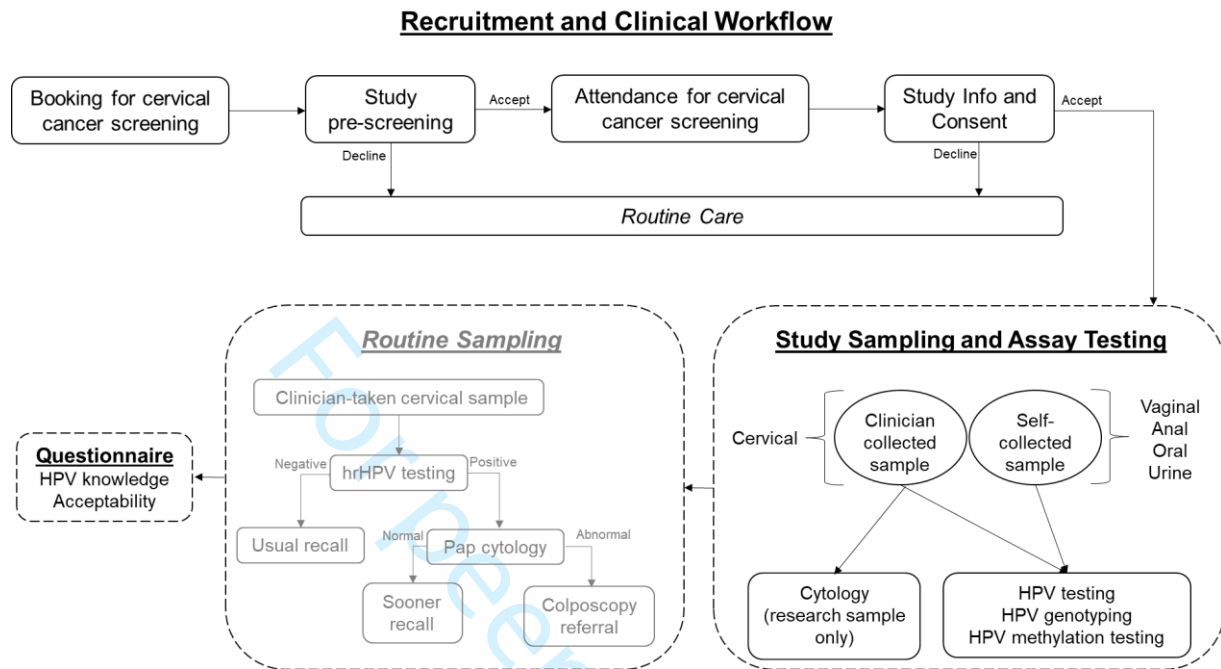
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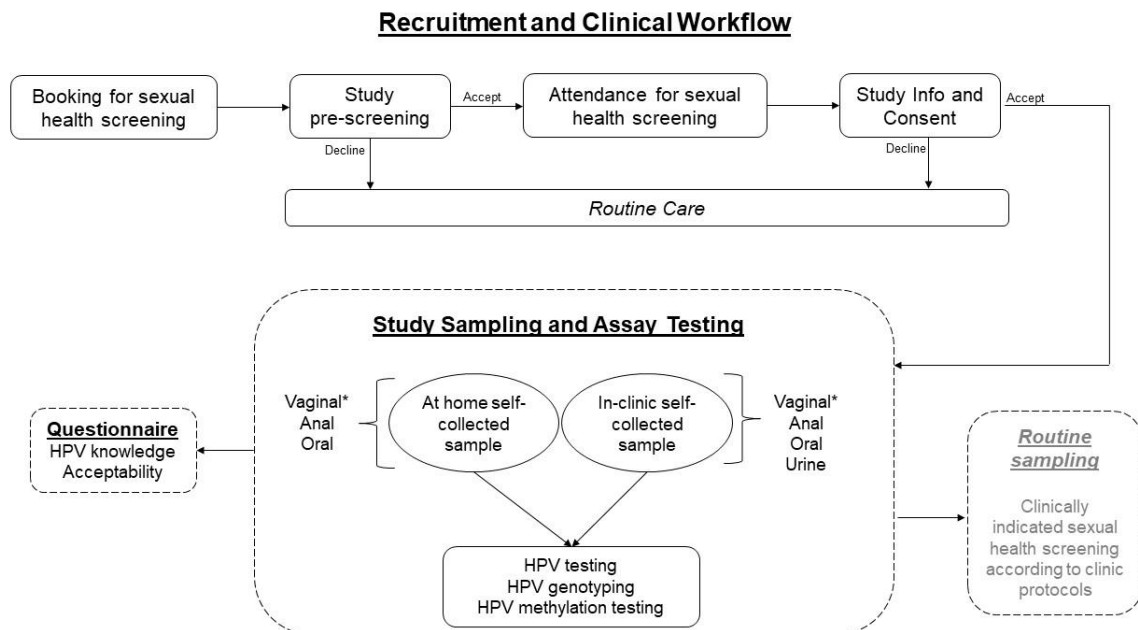
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Figure 1. Study Flow

Transmasculine and non-binary people with a cervix



Trans women and non-binary people assigned male at birth



*Participants will only collect vaginal samples if they have undergone vaginoplasty

1 **Introduction**

2

3 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

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6 6b Explanation for choice of comparators N/A

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8 Objectives 7 Specific objectives or hypotheses 6

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10 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

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14 **Methods: Participants, interventions, and outcomes**

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16 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

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19 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

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23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8-12

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26 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

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29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 12

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32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A

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34 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

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40 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

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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	<u>7</u>
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>7, 8, and 12</u>
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6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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	<u>N/A</u>
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16	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	<u>N/A</u>
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
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26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
28				
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31	Methods: Data collection, management, and analysis			
32				
33	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	<u>9-12</u>
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39		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	<u>11</u>
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1	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	<u>13</u>
2				
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4				
5	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	<u>13-14</u>
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>N/A</u>
9				
10		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)	<u>N/A</u>
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13				
14	Methods: Monitoring			
15				
16	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	<u>13</u>
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22		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	<u>N/A</u>
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25	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	<u>13</u>
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>13</u>
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>7</u>
35				
36				
37	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)	<u>7</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>7</u>
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>7</u>
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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	<u>12</u>
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>17</u>
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13	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	<u>13</u>
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17	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	<u>N/A</u>
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19				
20	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	<u>15-16</u>
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
32				
33				
34	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	<u>12-13 and Table 2</u>
35				
36				

*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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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Keywords:	Human Papillomavirus Viruses, Transgender Persons, Uterine Cervical Neoplasms, Health Equity

SCHOLARONE™
Manuscripts

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3 **Rationale and design of The Self-TI Study protocol: a cross-sectional human**
4 **papillomavirus self-testing pilot study among transgender adults in England**
5
6

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54 screening, cervical cancer, anal cancer
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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

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2
3 served as authors, collaborators, and members of the patient and public involvement
4 (PPI) group. Results of this study will be shared with the community prior to being
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6 published in peer-reviewed journals and the PPI group will help to design the results
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8 dissemination strategy. The evidence generated from this pilot study could be used to
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10 inform a larger, international study of HPV self-testing in the transgender and non-binary
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12 community.
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18 **Trial registration number:** NCT05883111
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20 21 **Strengths and Limitations**

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

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

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

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3 23 sexual practices, and are less likely to recommend screening.¹⁴ Further, TMNB patients
4
5 24 may be less likely to be vaccinated against HPV than cisgender women.¹⁶
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8 25 Transgender women and transfeminine non-binary (TWNB) adults (those who
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10 26 were registered male at birth and have a female or non-binary gender identity) may be
11
12 27 at increased risk of HPV infection compared to cisgender individuals. England began a
13
14 28 national HPV immunisation programme for adolescent girls with the bivalent HPV
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16 29 vaccine in 2008, switching to the quadrivalent in 2012 and the nonavalent in 2021.^{17 18}
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18
19 30 The UK implemented a gender-neutral vaccination program in 2019 with a catch-up
20
21 31 programme for people up to the age of 45 years who are considered high risk for HPV
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23 32 (e.g., men who have sex with men).¹⁹ Though transgender and non-binary people may
24
25 33 be eligible for vaccination through the catch-up programme, barriers to healthcare and
26
27 34 lack of perceived risk means that many TWNB adults may still be unvaccinated.²⁰
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29 35 Additionally, co-infection with HIV, which may be elevated among TWNB adults
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31 36 compared to the general population,²¹ increases the risk of persistent HPV infection²²⁻²⁴
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33 37 and HPV associated cancers.^{25 26} One small US study reported a study HPV prevalence
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35 38 of 89% in anal and 9% in oral specimens from TWNB adults.²⁷ A Brazilian study of 268
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37 39 transgender women reported a study prevalence to be 77% in anal, 34% in genital, and
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39 40 11% oral specimens.²⁸ Studies from both The Netherlands and Thailand estimate a
40
41 41 20% prevalence of neovaginal high-risk HPV, though these two studies had a high
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43 42 proportion of invalid HPV results, suggesting the true prevalence may be higher.^{29 30}
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45 43 The oncogenic potential of persistent high-risk HPV infection in the vagina of TWNB is
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47 44 poorly understood and current guidelines do not recommend screening for this
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3 45 population.³¹ Both low- and high-grade squamous intraepithelial lesions have been
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5 46 reported in the vagina of TWNB adults but incidence data is lacking.^{32 33}
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8 47 Prior research conducted in cisgender women (largely from high-income
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10 48 countries) has shown that self-sampling for HPV with PCR-based assays has
11
12 49 comparable performance to clinician-collected samples for the detection of cervical
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14 50 HPV.^{34 35} Limited research suggests that most TMNB patients may prefer HPV testing
15
16 51 by self-collection,^{36 37} though patients have expressed concern about the lack of
17
18 52 evidence-based guidelines specific to TMNB to inform their preference.^{36 38} Indeed, only
19
20 53 one small study³⁹ has compared the performance of clinician- and self-collected
21
22 54 samples in TMNB, showing good concordance; however more research is needed to
23
24 55 assess whether this is an acceptable approach for cervical screening in TMNB. Reisner
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26 56 *et al.*⁴⁰ found a study HPV prevalence of 16% among 130 TM participants and that HPV
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28 57 testing by self-sample showed good concordance with clinician-collected samples.
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31 58 Similarly, one US study that included TWNB adults found that people were more likely
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33 59 to engage in anal cancer screening with an at-home self-collection kit than attend a
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35 60 clinician-collected screening appointment.⁴¹
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40 61 We present the protocol for Self-TI, a pilot study whose objective is to assess the
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42 62 feasibility and acceptability of HPV self-testing at four body sites among TMNB and
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44 63 TWNB adults.
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46 64 **METHODS AND ANALYSIS**

47 65 **Study design and setting**

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49 66 The Self-TI Study (Self-TI) is a pilot study examining the acceptability and
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51 67 feasibility of HPV self-testing among transgender and non-binary people conducted in
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3 68 England (IRAS# 319364 and clinicaltrials.gov NCT05883111). The study received
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5 69 ethical approval from the Research Ethics Committee (REC) of Wales 4 (Wales REC 4,
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7 70 #23/WA/0266) and the Ethical Review Panel within the Division of Cancer Epidemiology
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9 71 and Genetics at the US National Cancer Institute (NCI) (#3G009-05). Amendments to
10
11 72 the protocol and study materials are approved by the REC and the protocol was last
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13 73 revised on January 23, 2024 (4th revision). Before taking part in this pilot study, all
14
15 74 participants provide informed written consent to participate to the study staff.
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17 75 Participants are asked if they consent to future use of their research specimens;
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19 76 otherwise specimens will be destroyed after the aims of the study protocol are met.
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24 77 **Study setting and participant recruitment**

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26 78 Enrolment began in February 2024 and will continue for one year. Self-TI seeks
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28 79 to enroll 50 participants who identify as TMNB with a cervix and 50 participants who
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30 80 identify as TWNB assigned male at birth. Participants are recruited at one of three
31
32 81 clinical sites in England: CliniQ or Ambrose Kings sexual health clinics in London, or
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34 82 Clinic-T in Brighton. These sites were chosen as they are in areas with large
35
36 83 transgender and non-binary populations, their providers are specialists in transgender
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38 84 and non-binary sexual health, and the clinic staff have experience conducting research
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40 85 studies. Participants can be recruited and pre-screened for study eligibility when they
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42 86 book an appointment for a cervical cancer screening (TMNB study group only) or a
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44 87 sexual health screening (TWNB study group only). Recruitment occurs through
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46 88 advertisement posters and banners placed in the clinics, and flyers placed in gender
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48 89 identity clinics and general practitioners' offices known to have transgender and non-
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50 90 binary patients. Self-TI has created a website (www.self-ti.com), which contains
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3 91 information on the study, HPV and cancer education, and links to contact the study sites
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5 92 to enrol. Self-TI also commissioned a well-known trans activist and artist in England, to
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7 93 record a 45 second advertisement video. This video is posted the activist's social media
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9 94 sites (Twitter, Instagram, and Tik Tok), other LGBTQ+ cancer charities in England, and
10
11 95 the Self-TI's website and social media sites. The Standard Protocol Items:
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14 96 Recommendations for Interventional Trials (SPIRIT) checklist is available as an online
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16 97 supplemental file.⁴²
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19 98 **Participants**

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21 99 Individuals who identify as TMNB with a cervix, aged 25–65, with at least one
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23 100 year of self-reported testosterone therapy, are eligible to participate in the TMNB study
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25 101 group. Testosterone exposure is a requirement of study participation as it is associated
26
27 102 with vaginal atrophy such that speculum and swab insertion to the recommended depth
28
29 103 could be painful, unpleasant, or necessitate additional lubricant affecting the accuracy
30
31 104 and acceptability of clinician- and self-collected HPV testing.^{9 40} Individuals who identify
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33 105 as TWNB, aged 18 and over, are eligible to participate in the TWNB study group. TWNB
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35 106 participants with a vagina are preferentially selected into the study, with the first three
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37 107 months of enrolment restricted to individuals who had undergone vaginoplasty. After
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39 108 three months, the study team will evaluate whether it is feasible to reach the targeted
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41 109 sample size with this restriction and if not, the eligibility criterion will be removed.
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43 110 Individuals with a vagina must have undergone vaginoplasty greater than one year prior
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45 111 to entering the study due to safety concerns over self-sampling on recently healed
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47 112 epithelium. All participants are given a participant information sheet, which is discussed
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49 113 with study staff as part of informed consent procedures.
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114 Data collection

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

Table 1. Study activities and timeline

Study procedure	Prior to Day 1		In Clinic Day 1		At Home ≤ 4 weeks (TWNB only)
	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

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123 Sampling

124 All participants are asked to self-collect samples in the clinic in the following
 125 order: oral rinse, urine, vagina, and anus (collection materials are provided in Table 2).
 126 Each participant will receive a self-sampling kit with written instructions for self-
 127 collection that includes a QR code linked to an instructional video. Study staff will also
 128 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)

129
 130 The participants use Scope mouthwash (Proctor and Gamble, US) to collect
 131 buccal cells and a Colli-pee® collection device (Novosanis, Belgium) to collect first void
 132 urine (Table 2). The Colli-pee® device was selected as it has been used successfully by
 133 sexual and gender minority participants in other studies and can accommodate a variety
 134 of genital anatomies.

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

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3 143 sample (Table 2). The choice of sampling methods was based on a review of previous
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5 144 studies that examined the same body sites and concordance between in-clinic and at-
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8 145 home sampling methods^{43 44}, though the mailing of dry swabs without transport media
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10 146 may affect anal specimen adequacy, especially if fecal matter is present.⁴⁵

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12 147 After the self-administered samples are collected, TMNB participants have a
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14 148 pelvic exam as part of the standard cervical cancer screening. In England, individuals
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17 149 with a cervix are invited to participate in the National Cervical Screening Programme
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19 150 (CSP) every 3 years for those between the ages of 25-49 and every 5 years for those
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21 151 between the ages of 50-65. Screening is conducted with a primary HPV test and if
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24 152 positive, a reflex cervical sample is sent for cytology. Self-TI is paired with the CSP so
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26 153 that TMNB individuals do not need to undergo pelvic exams more than once. In Self-TI,
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28 154 the clinician will take two cervical swabs; the first for the (CSP) sent to the National
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30 155 Health Service (NHS) laboratories, and the second for the clinician-collected sample for
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32 156 Self-TI using an endocervical broom (Hologic, US). The CSP sample is collected first so
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35 157 that if the participant declines further samples the standard of care is met.

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38 158 After TWNB participants collect their self-administered samples, they will be
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40 159 given a kit to complete a second vaginal (if applicable), anal, and oral rinse sampling at
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42 160 home. Once collected, the participant places the dry brushes and samples in the pre-
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44 161 addressed, postage paid mailer provided before dropping it in the post within one month
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47 162 of their first study visit. The kit includes written instructions with a QR code linked to an
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49 163 instructional video. Study staff follow up with TWNB study participants on a weekly
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51 164 basis for up to four weeks to ensure the return of their study samples.

52 53 54 165 **Self-administered online survey**

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3 166 After self-collection, participants take a self-administered online survey, which
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5 167 takes approximately 20–25 minutes to complete. The survey includes questions on
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7 168 based on previously validated surveys that capture sensitive demographic
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10 169 characteristics, acceptability of self-sampling (e.g., physical and emotional comfort,
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12 170 confidence in collection), comparing self-collected to clinician-collected sampling (TMNB
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14 171 study group only),³⁹ comparing self-collected sampling in the clinic to at-home collection
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16 172 (TWNB study group only), history of HPV vaccination, knowledge of HPV,³⁹ comparing
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18 173 self-collected to clinician-collected sampling (TMNB study group only), medical
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20 174 mistrust,⁴⁶ and sexual history.^{39 47} comparing self-collected sampling in the clinic to at-
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22 175 home collection (TWNB study group only), history of HPV vaccination, knowledge of
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24 176 HPV,¹⁵ medical mistrust,⁴⁶ and sexual history.⁴⁷ Participants receive a £20 gift card to a
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26 177 large online retailer, as remuneration for their participation in Self-TI.
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30 178 **Outcomes**

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33 179 The primary study outcomes are the acceptability and feasibility of self-sampling
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35 180 among participants that will inform a larger study. Acceptability is measured by the
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37 181 physical and emotional responses to self-sampling for each collection method using a 7-
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39 182 point Likert scale. Feasibility is measured by the proportion of specimens returned from
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41 183 self-collection in the clinic and those mailed from home.
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44 184 This pilot study will also estimate the study prevalence of HPV (positivity and
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46 185 genotype) and the correlation of HPV detection between the four self-collected samples.
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48 186 The concordance between the vaginal self-collected sample and clinician-collected
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50 187 cervical sample will be estimated among TMNB. Among TWNB, we will estimate the
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52 188 correlation between the samples collected by participants in the clinic with the samples
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3 189 collected at home. Finally, Self-TI will collect exploratory data on risk factors associated
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5 190 with HPV prevalence, which can be fully assessed in a larger trial.
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7 191 **HPV testing**

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10 192 The cervical, vaginal, and anal swabs are reconstituted in a plastic vial with
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12 193 PreservCyt transport medium (ThinPrep PreserveCyt Solution, Hologic, US) before
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14 194 freezing at -80°C. Oral and urine samples are placed directly into -80°C. Samples are
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17 195 shipped in batches to the Center for Genomic Research (CGR) at NCI. All samples will
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19 196 be tested using a next-generation sequencing based-assay (TypeSeq) developed by
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21
22 197 CGR, which generates a positive/negative result for 51 HPV genotypes.⁴⁸
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24 198 **Data management**

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26 199 Data management and project coordination is done at the Division of Cancer
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28 200 Epidemiology and Genetics at NCI. Study oversight and data management are led by
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30
31 201 the study chief investigator (AMB) and the statistician (SSJ). Research staff enter de-
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33 202 identified participant data into an electronic data capture system. All participant
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35 203 information (including laboratory data) is confidential and stored in a secure location.
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37 204 Only the personnel listed on the delegation log will have access to participant data; the
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39 205 statistician and laboratory personnel have access to deidentified data only. Participant
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42 206 data are checked at regular intervals for quality assurance. The number of AEs is
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44 207 expected to be very small and thus an independent Data Monitoring Committee was not
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46 208 appointed. However, all adverse events will be collected, and severe adverse events
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48 209 deemed by the chief investigator to be related to study procedures and unexpected, will
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51 210 be reported to the sponsor within 24 hours and to the REC within 15 days of learning of
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54 211 the event.
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212 **Statistical analysis**

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

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

229 **Patient and public involvement**

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

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3 235 individuals. Authors SSJ, SOC, and EW attended all meetings, which were led either by
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5 236 SOC or EW who are members of the transgender and non-binary community, and SOC
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7 237 is the founder of a cancer charity for lesbian, gay, bisexual, transgender, intersex, and
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9
10 238 queer individuals. PPI members reviewed the study protocol, data collection forms,
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12 239 online self-administered survey, advertisement and recruitment plan, instructional video,
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14 240 and results dissemination plan. Meetings were conducted over Zoom in the evenings to
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16 241 accommodate members' schedules and followed up via email to provide additional
17
18 242 opportunities for written feedback on materials. Online meetings included short
19
20 243 presentations on HPV-related cancer topics given by experts in the field to provide
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22 244 information exchange. PPI members were compensated for their time with multi-retailer
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24 245 gift cards to an amount in line with National Institute for Health Research guidelines.

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28 246 Several important suggestions were made by the PPI group and adopted into the
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30 247 study protocol. The standard Evalyn® brush is manufactured in a dark pink color, which
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32 248 was suggested could be off putting to our participants, so we worked with the
33
34 249 manufacturers to provide Self-TI with devices in a more neutral blue color. Though the
35
36 250 Evalyn® brush has several features that make it ideal for individuals who are not
37
38 251 familiar with self-sampling, one drawback is that it is slightly thicker than other swabs
39
40 252 used for vaginal sampling. Therefore, it was suggested by the PPI group that
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42 253 participants be provided with a slimmer swab upon request. Additionally, though it is
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44 254 preferred that TMNB participants complete the survey in the clinic after their exam, the
45
46 255 PPI group felt that participants should be given the option to complete the survey at
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48 256 home. This change was implemented and TMNB participants can scan or be emailed a
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50 257 QR code to the survey link after leaving the clinic if desired. The group felt that some
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3 258 participants would want to leave the clinic immediately after their speculum exam as it
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5 259 may result in increased feelings of dysphoria and can be uncomfortable or painful for
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8 260 some participants.
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10 261 **ETHICS AND DISSEMINATION**

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12 262 People with a male gender marker in their medical record are not invited to
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14 263 participate in the CSP and the laboratory may reject cervical samples from male
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16 264 patients. The chief investigator worked with the laboratories processing CSP samples
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18 265 for Self-TI participants to ensure samples would not be discarded prior to testing. Senior
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20 266 staff (AMB and SSJ) also consulted the US National Institutes of Health Bioethics group
21
22 267 about returning study results to the participants. Because the assay under study in Self-
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24 268 TI is a research test and not approved for clinical use in the UK, participants will not
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26 269 have their study results returned to them. Instead, TMNB participants should defer to
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28 270 the HPV result provided by the CSP, as applicable. Further, in cases where the HPV
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30 271 result from Self-TI conflicts with the CSP result or in the absence of a CSP result (as in
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32 272 the case of TWNB samples), senior study staff felt that providing participants with a
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34 273 result that could not be followed up with clinically could cause distress and would be
35
36 274 unethical. Only HPV positive results taken from samples as part of the CSP will warrant
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38 275 follow up under the NHS.
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41 276 Information gained from this study will be published in peer-reviewed journals
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43 277 and presented at national and international conferences. Prior to scientific
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45 278 dissemination, we will engage with the PPI group in writing the lay results, results
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47 279 dissemination strategy and final publication. The lay summary of the results will be
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49 280 posted to the Self-TI website, participating clinic websites, and the websites of charities
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3 281 and organisations supporting trans and non-binary people so that study participants and
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5 282 community members may be notified of the results first at the PPI group's request.
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8 283 Several online webinars are planned to disseminate the results and allow community
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10 284 members to engage in a discussion with the researchers. These webinars will be
11
12 285 recorded and posted on the Self-TI website. Finally, data from this pilot study will inform
13
14 286 a larger, multi-center, international study.

17 287 **DISCUSSION**

19 288 The overarching goal of this pilot study is to provide important insight into the
20
21 289 acceptability and feasibility of HPV self-sampling among transgender and gender
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23 290 diverse individuals for a larger study. The pilot study will provide essential data that will
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25 291 inform recruitment, study procedures, and sample size calculations for this larger study.

28 292 A major strength of our study is community involvement from conception to
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30 293 implementation. We included community voices at every stage of protocol development
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32 294 and have had a dedicated PPI group in addition to transgender and non-binary senior
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34 295 study staff advising our study throughout. This strategy has led to improved
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36 296 advertisements, study materials, and outreach efforts. Continued work with community
37
38 297 members will help us disseminate study results to a wider audience.

42 298 Potential study limitations include the inability to generalize our results to the
43
44 299 wider transgender population in England as we used sexual health clinics in two major
45
46 300 cities to recruit our participants. Compared to the general population of transgender
47
48 301 individuals, our study participants may be more engaged in care, have greater access to
49
50 302 care, and have higher health seeking behaviors. This recruitment strategy was chosen
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52 303 to maximize the proportion of positive HPV tests, to enable recruitment of a reasonable
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3 304 sample size in a short amount of time. Our decision to use dry swabs for anal sampling
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5 305 may affect acceptability as dry swabs were reported to cause pain in 19% of users⁴⁹ as
6
7 306 well as adequacy as the presence of feces was shown to inhibit HPV assays.⁴⁵ Finally,
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9
10 307 the implementation of HPV self-sampling methods and strategies may reduce barriers
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12 308 for transgender and non-binary people in high-resourced areas, but barriers will remain
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14 309 for individuals who live in areas where there is widespread discrimination resulting in a
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16
17 310 lack of access to culturally appropriate screening.
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3 **Authors' contributions:** AMB and SSJ conceived, designed, and supervised the study.
4
5 SSJ, CO, and AMB were responsible for costings, ethics approval, and study set-up.
6
7 AMB and SSJ are responsible for data management. SSJ drafted the manuscript. MC
8
9 supervised the HPV methylation assay and provided several methodological
10
11 contributions. SOC maintains the study website. SSJ, SOC, and EW oversaw the
12
13 coordination of the PPI group. AMB, SSJ, SOC, and EW were responsible for creating
14
15 the study survey. All authors revised the manuscript and approved the final draft.
16
17

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19
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21
22

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24
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47
48 Research Governance Operations Manager, Joint Research Management Office,
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50 research.governance@qmul.ac.uk
51
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53 **Sponsors references:** IRAS Number: 319364; Edge Number: 155220
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3 **Competing interest statement:** AMB is a trustee of OUTpatients, of which SOC is
4
5 CEO. None of the other authors have any conflicts to declare.
6

7
8 **Patient and public involvement:** Patients and the community were involved in the
9
10 design, conduct, and dissemination plans of this research. Refer to the Methods section
11
12 for further details.
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19 **Figure 1. Study flow diagram**
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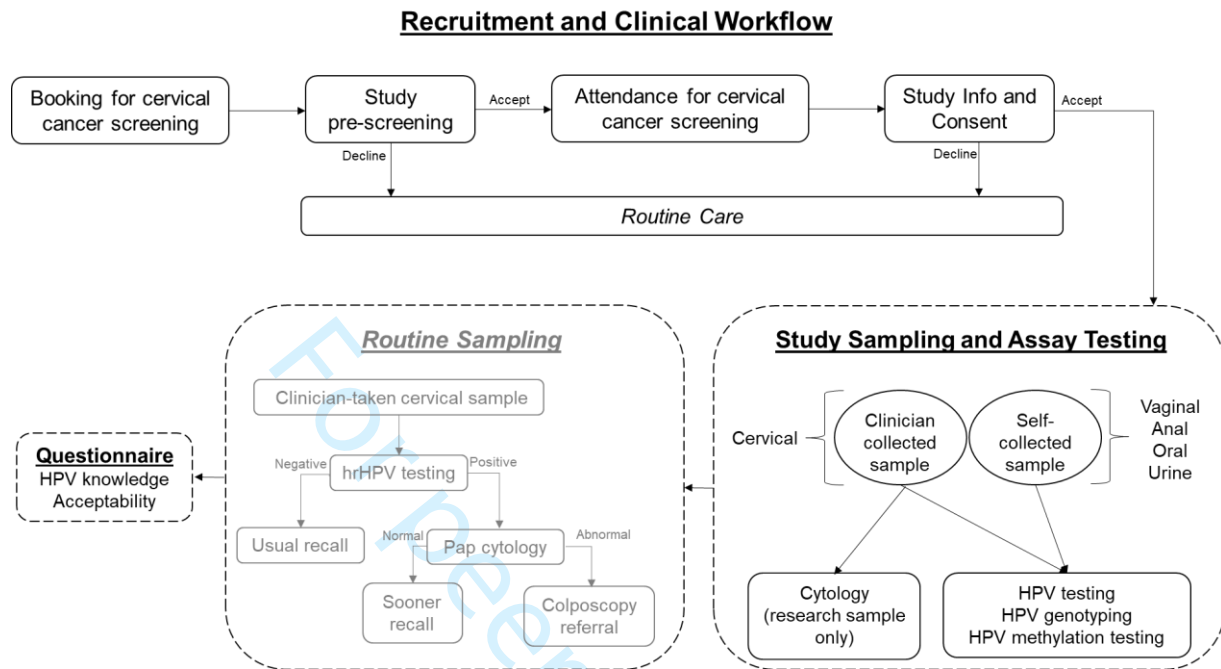
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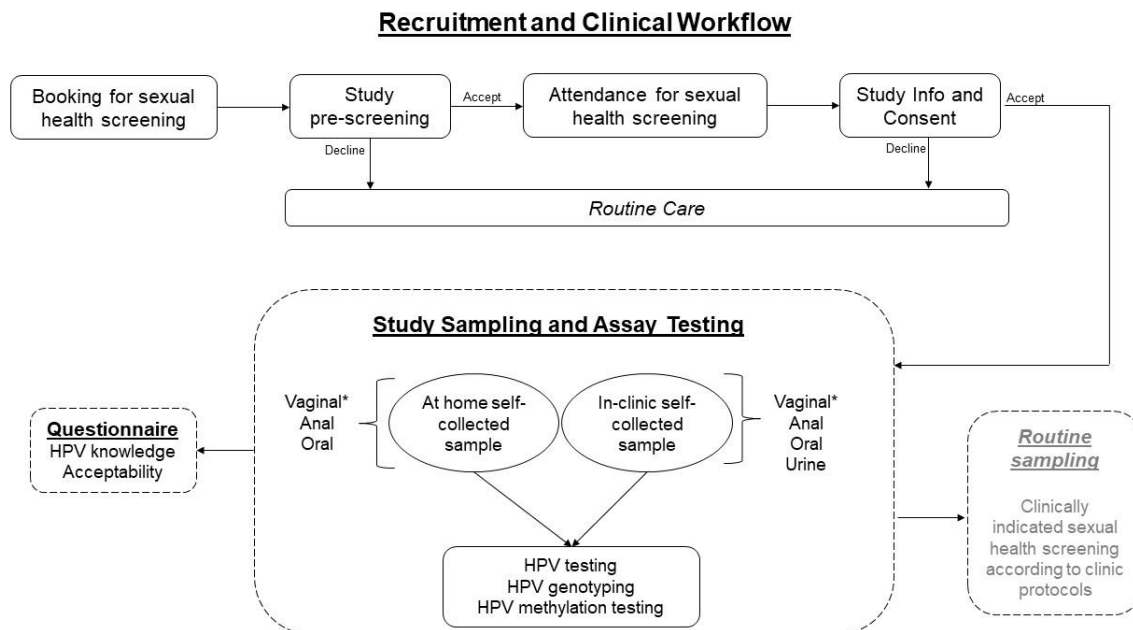
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Figure 1. Study Flow

Transmasculine and non-binary people with a cervix



Trans women and non-binary people assigned male at birth



*Participants will only collect vaginal samples if they have undergone vaginoplasty

1 **Introduction**

2

3 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

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6 6b Explanation for choice of comparators N/A

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8 Objectives 7 Specific objectives or hypotheses 6

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10 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

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14 **Methods: Participants, interventions, and outcomes**

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16 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

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19 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

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23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8-12

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26 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

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29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 12

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32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A

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34 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

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40 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

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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	<u>7</u>
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>7, 8, and 12</u>
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6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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	<u>N/A</u>
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16	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	<u>N/A</u>
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>N/A</u>
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>N/A</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>
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31	Methods: Data collection, management, and analysis			
32				
33	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	<u>9-12</u>
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39		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	<u>11</u>
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1	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	<u>13</u>
2				
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5	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	<u>13-14</u>
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>N/A</u>
9				
10		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)	<u>N/A</u>
11				
12				
13				
14	Methods: Monitoring			
15				
16	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	<u>13</u>
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22		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	<u>N/A</u>
23				
24				
25	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	<u>13</u>
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>13</u>
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>7</u>
35				
36				
37	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)	<u>7</u>
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>7</u>
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>7</u>
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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	<u>12</u>
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>17</u>
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13	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	<u>13</u>
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17	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	<u>N/A</u>
18				
19				
20	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	<u>15-16</u>
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
32				
33				
34	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	<u>12-13 and Table 2</u>
35				
36				

*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.